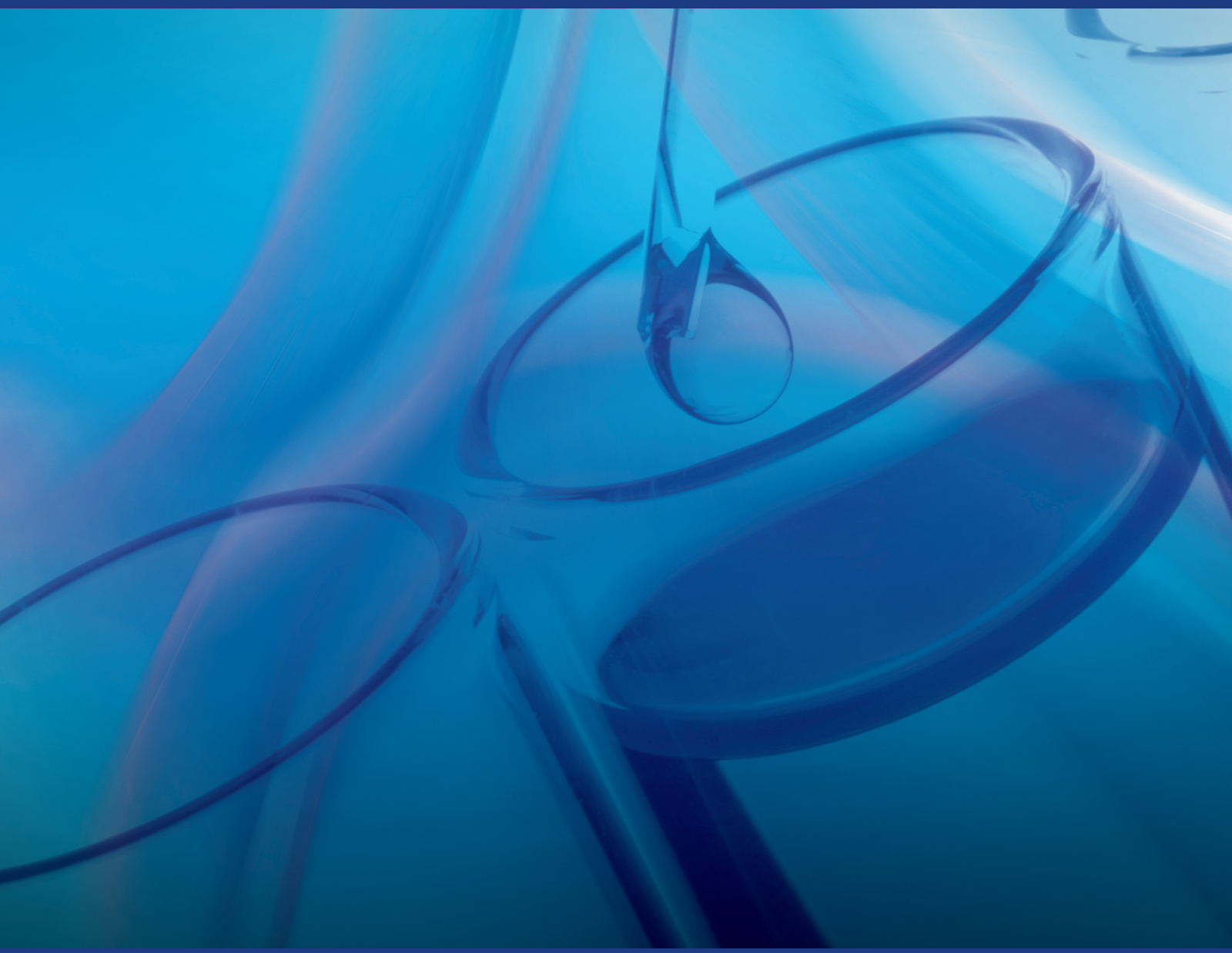
Advances in Urology

Germ Cell Tumors: Updates on Epidemiology, Biology, and Treatment Considerations

Lead Guest Editor: Aditya Bagrodia
Guest Editors: Constantine Albany and Timothy A. Masterson



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Editorial Board

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Editorial

Germ Cell Tumors: Updates on Epidemiology, Biology, and Treatment Considerations

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Germ cell tumors (GCTs) are the most common solid tumors in young men. GCTs represent a rare oncologic success story with 5-year cure rates exceeding 98% for early-stage tumors and 80% for patients with metastatic disease, attributable to the integration of surgery, cisplatin-based chemotherapy, and radiation therapy. Despite the excellent clinical outcomes in testicular GCTs, significant challenges and opportunities exist, as GCTs represent the most life years lost for nonpediatric malignancies [1].

There is certainly room for improvement in managing patients with germ cell tumors, and it is critical that the urology, oncology, and radio-oncology communities do not rest on the laurels of past successes. We must understand and modify socioeconomic differences that underpin germ cell tumor epidemiology and outcomes in order to narrow treatment gaps.

Special considerations for patients with pediatric and adolescent GCTs must also be recognized to improve outcomes among this subgroup. In this special issue, Amatruda et al. review the unique considerations of pediatric patients with GCTs, including demographic factors, histologic characteristics, treatment specifics, and emerging molecular data. Saltzman and Cost provide insights in treating adolescents with GCTs, including clinicopathologic outcomes, psychosocial support requirements, fertility and hypogonadism concerns, and transitional care needs.

Further, in this issue, considerable attention is appropriately dedicated to mitigating treatment-associated morbidity in patients with GCTs. Minimizing short, intermediate, and long-term treatment-related toxicity is mandatory for these young cancer survivors who have a whole life to live. Fung and colleagues comprehensively characterize complications associated with GCT treatment. The incidence and pathophysiology underlying common adverse effects such as cardiovascular disease, secondary malignancies, Raynaud's phenomenon, and neurotoxicity are reviewed, as are recent developments in understanding genetic predisposition for adverse consequences and ways to ameliorate them. Huddart and Reid describe the clinical experience with adjuvant chemotherapy for patients with high-risk Stage I nonseminomatous germ cell tumors. Supporting evidence for why one cycle of bleomycin, etoposide, and cisplatin (BEP) in the adjuvant setting is emerging as the optimal adjuvant chemotherapy regimen for patients with stage IB disease is provided in the context of preserving oncologic control and minimizing dose-dependent chemotherapy-associated adverse effects.

On the surgical end of the spectrum, Daneshmand and colleagues provide the rationale and early experience with retroperitoneal lymph node dissection (RPLND) for patients with small volume metastatic seminoma in an effort to avoid toxicities associated with either radiotherapy or chemotherapy, which are the treatment modalities typically used to manage these patients. In another effort dedicated to minimizing treatment-related morbidity, Pierarazio et al. describe the state of the literature concerning techniques and outcomes for robotic-assisted retroperitoneal lymph node dissection. Importantly, the authors note importance of ensuring oncologic outcomes is not compromised as this technology continues to develop. Cary and Masterson

delineate the role of modified template retroperitoneal lymph node dissection in the primary and post-chemotherapy setting, again demonstrating the commitment to avoid treatment toxicity, including retrograde ejaculation following RPLND while maintaining excellent cancer control. The authors review various templates and essential patient-selection characteristics, particularly when considering modified templates in the postchemotherapy setting.

Among patients with cisplatin-resistant disease, Feldman and colleagues discuss the ongoing clinical trial of conventional-dose salvage chemotherapy versus high-dose chemotherapy with stem cell support (NCT02375204) and the background literature supporting the need for this important trial. Chovanec and colleagues report on the preclinical work suggesting a role for immunotherapy in GCTs as well as early clinical experience in this exciting arena.

Last but certainly not least, Hamilton et al. describe their experience with risk-adapted surveillance in patients with GCT. This exciting research aims at individualizing the intensity of follow-up for patients with early-stage GCT to reduce both radiation exposure and costs associated with long-term surveillance.

In conclusion, it is our privilege to guest edit this special issue on germ cell tumors that highlights contemporary work in the field of GCTs. We are grateful to the experts in the field that provided their invaluable insight. This particular issue makes us optimistic that the future is bright for the optimal and refined management of patients with germ cell tumors.

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Review Article

A Review of Outcomes and Technique for the Robotic-Assisted Laparoscopic Retroperitoneal Lymph Node Dissection for Testicular Cancer

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Objectives. The robotic-assisted laparoscopic retroperitoneal lymph node dissection (R-RPLND) represents a new frontier in the surgical management of testicular cancer in the realm of minimally invasive urologic oncology. We aimed to review the early outcomes as compared to the laparoscopic and open approaches as well as describe the operative technique for the R-RPLND. *Materials and Methods*. We reviewed all the literature related to the R-RPLND based on an electronic PubMed search up until July 2017. *Results and Discussion*. Encouraged by favorable early oncologic and safety outcomes for treatment of clinical stage (CS) I nonseminomatous germ cell tumor (NSGCT), the R-RPLND affords the same recovery advantages as the laparoscopic retroperitoneal lymph node dissection (L-RPLND) while offering greater dexterity, superior visualization, and a theoretically shorter learning curve for the surgeon. While R-RPLND has a promising future in the management of patients with primary and-postchemotherapy NSGCT, larger and more vigorous prospective studies are needed before supplanting the open RPLND as the gold standard approach for primary low-stage NSGCT or becoming an equivalent surgical modality in the postchemotherapy setting.

1. Introduction

Testicular germ cell tumor (GCT) is the most common solid tumor in men between the ages of 20–44. Men diagnosed with GCT have excellent survival rates due to advances in the multimodal treatment paradigm of chemotherapy, radiation therapy, and surgery [1]. Retroperitoneal lymph node dissection (RPLND) remains an established treatment option for nonseminomatous GCT in the primary setting for low-stage (clinical stages (CSs) I and II) diseases and residual masses after chemotherapy [1]. Due to the excellent survival outcome, with a 5-year overall survival rate of 98%, there has been a greater emphasis on reducing morbidity and long-term toxicity for testicular cancer survivors. Open RPLND (O-RPLND) remains the gold standard approach for surgical management of the retroperitoneum for GCTs. It is, however, maximally invasive and can result in significant postoperative morbidity and prolonged hospitalizations [2–4].

For primary CS I and CS II NSGCT, minimally invasive RPLND has become a less morbid alternative to the O-RPLND while touting favorable early oncologic outcomes [5, 6]. Laparoscopic RPLND (L-RPLND), first reported in 1992, offered a reduced recovery time, less blood loss, and lower complication rates compared to O-RPLND [5, 7]. However, the operation had a very steep learning curve [8], a lower lymph node yield [9], and critics have pointed out that the L-RPLND's long-term oncologic outcomes have not been studied as rigorously as O-RPLND, which is partly related to the high rate of adjuvant chemotherapy given to patients with positive lymph nodes [10].

The natural evolution of minimally invasive urologic oncology from laparoscopy to robotics laid the foundation

for the first robotic-assisted laparoscopic RPLND (R-RPLND) to be performed in 2006 by Davol et al. [11]. The advantages of R-RPLND over L-RPLND were similar to other urologic operations that transitioned to a robotic approach: a reduced learning curve, three-dimensional visualization, and greater instrument dexterity from the wristed instruments. Boosted by early results demonstrating equivalence in oncologic and safety measures compared to open and laparoscopic approaches, the R-RPLND has become an excellent option for the treatment of CS I and CS II nonseminomatous GST (NSGCT) and is emerging as a feasible approach for post-chemotherapy RPLND [12]. In this article, we will review the technique and early outcomes of R-RPLND as compared to both O-RPLND and L-RPLND for the management of primary low-stage nonseminomatous and postchemotherapy GCT.

2. Materials and Methods

We performed an electronic PubMed search for all relevant publications regarding the outcomes and technique of the R-RPLND up until July 2017. We used the keywords robotic, retroperitoneal lymph node dissection, and testicular cancer, which resulted a total of 36 papers. All single and multi-institutional R-RPLND studies in adults with testicular cancer were included and reviewed in addition to studies investigating outcomes associated with O-RPLND and L-RPLND.

3. Results and Discussion

3.1. Primary Low-Stage Nonseminomatous Testicular Cancer

3.1.1. Role of RPLND in the Guideline-Directed Management of Low-Stage NSGCT. Patients diagnosed with CS I NSGCT, based on NCCN guidelines, have the option of active surveillance, platinum-based chemotherapy, or RPLND [1]. While each treatment option offers an excellent survival rate, each has its own respective drawbacks as well. Active surveillance offers the best opportunity to avoid unnecessary treatment and is the preferred treatment based on NCCN guidelines for CS IA disease; however, patients with recurrence are often subject to three or four cycles of platinum-based chemotherapy, and not all patients are willing to accept the anxieties associated with surveillance [13]. Adjuvant chemotherapy offers the best cure rate as a single modality, approaching 97%; however, it will overtreat a significant number of men and subject them to the known and unknown long-term toxicities of platinum-based chemotherapy [14]. These long-term toxicities include secondary malignancy, early cardiovascular disease, and a number of single-organ toxicities, including nephrotoxicity, pulmonary toxicity, ototoxicity, neurotoxicity, and hypogonadism [15]. Primary RPLND offers the ability to accurately stage the extent of disease while avoiding the significant toxicity of chemotherapy [16, 17] or the high relapse rate that is observed in 20–30% of patients who choose surveillance [13, 18]. While RPLND for CS I NSGCT may result in overtreatment for some patients, 25–35% of patients will harbor metastatic disease on presentation without radiographic evidence of pathologic retroperitoneal lymph nodes [19]. When RPLND is performed at a high-volume institution, the risk of recurrence is low (2%) with survival rates exceeding 95% [20]. From the open experience, RPLND alone is curative in 80–90% of patients with pN1 disease discovered in the retroperitoneum [21]. The disadvantages of RPLND are the risk of complications, which include ejaculatory dysfunction, blood loss, visceral injuries, ileus, and chylous ascites [4]. In the phase III randomized study of primary chemotherapy versus RPLND, the recurrence rate was higher in the RPLND group (8% versus 0.5%), but 37% of patients undergoing chemotherapy experienced a grade III or IV toxicity, compared to only 9% of RPLND patients [22].

4. Outcomes

4.1. Oncologic Outcomes. While the first use of the L-RPLND was for the purpose of staging alone, the intent of the R-RPLND is to match the oncologic efficacy of O-RPLND while providing the benefits of a minimally invasive approach. The largest R-RPLND series to date, a multi-institutional study of 47 CS I and 5 CS II patients which includes our patient experience, reported an excellent 2-year recurrence-free survival of 97% in the entire cohort [6]. Stepanian et al., with a median follow-up of 49 months, reported no retroperitoneal or distant recurrences in 19 patients undergoing robotic RPLND [23]. These results are summarized in Table 1. Impressively, 75% (6/8) of patients with positive retroperitoneal lymph nodes received no additional therapy while two patients with elements of embryonal carcinoma in their retroperitoneum on final pathology received chemotherapy. It is worth noting that three of these patients had teratoma who were definitively treated with surgery alone and were not candidates for chemotherapy. Pearce et al. reported that 62% (5/8) of patients with positive lymph nodes received chemotherapy with a single out-of-template recurrence of teratoma after chemotherapy [6]. These oncologic results compare favorably to O-RPLND and L-RPLND which, based on the findings from a large meta-analysis of >800 patients, experience recurrence-free rates of 92.5% and 95.4%, respectively [9]. While the results are promising, the low rates of positive lymph nodes in these series, ranging from 17% to 42%, and the use of adjuvant chemotherapy for node-positive patients make drawing conclusions, regarding comparative efficacy to O-RPLND and L-RPLND, a challenge. Furthermore, the majority of these studies investigating R-RPLND have short follow-up and varying surgical techniques, which further complicates their collective analysis.

Lymph node yield, a correlate for the extent of node dissection, can provide valuable information regarding the staging and therapeutic benefit of R-RPLND. Importantly, their reported median lymph node yield (LNY) of 26 nodes (IQR I8-32) outperformed the LNY reported in a contemporary meta-analysis of L-RPLND, which reported a median of 16 lymph nodes [9]. R-RPLND, however, appears to be similar to LNY observed in O-RPLND, which ranges from 28–33 [24, 25]. Conversely, in a separate head-to-head comparison from our institution of 16 R-RPLNDs and 21 L-RPLNDs from a single-surgeon experience, no difference

Table 1: Summary of perioperative outcomes from notable series for primary and postchemotherapy R-RPLND.

Primary RPLND													
Group	Year	*N*	CS I	CS II	Operative time (mins)	EBL (ml)	Lymph node yield	LOS (days)	Complication rate (%)	Positive lymph nodes (%)	Recurrence-free rate (%)	Antegrade ejaculation (%)	Follow-up (months)
Harris et al. [26]	2015	16	16	0	294	75	22	—	6.3	12.5	—	100	13.5
Cheney et al. [32]	2015	10	9	1	311	100	22	2.75	—	30	80	91	22
Stepanian et al. [23]	2016	16	11	5	293	50	19.5	1	5	38	100	90	49
Pearce et al. [6]	2017	47	42	5	235	50	26	1	14	17	97	96	16
Postchemo RPLND													
Group	Year	*N*	CS I	CS II	Operative time (mins)	EBL (ml)	Lymph node yield	LOS (days)	Complication rate (%)	Positive lymph nodes (%)	Recurrence-free rate (%)	Antegrade ejaculation (%)	Follow-up (months)
Cheney et al. [32]	2015	8	7	1	369	313	18	2.2	—	62.5	100	—	22
Stepanian et al. [23]	2016	4	1	3	324	150	22	1.5	—	50	100	100	41
Kamel et al. [12]	2016	12	6	6	312	475	22	3	25	50	100	66.7	31

LOS = length of stay; EBL = estimated blood loss; CS = clinical stage.

in the LNY was found [26]. To date, no prospective R-RPLND series has been published, and long-term oncologic and survival outcomes have yet to be reported in a large series. While the early results are promising and appear to suggest favorable recurrence rates and LNY compared to L-RPLND and O-RPLND in the hands of experienced robotic surgeons, determining oncologic equivalency to O-RPLND and L-RPLND will require larger, prospective series with longer follow-up.

Furthermore, though the oncologic outcomes of the primary RPLND for the management of low-stage NSGCT are often deliberated, there is considerable agreement that RPLNDs should be performed exclusively by experienced high-volume surgeons at experienced institutions, which result in fewer complications and superior oncologic outcomes [20, 27]. The early published oncologic outcomes of the R-RPLND, it is worth noting, are from experienced robotic surgeons in high-volume academic centers.

4.2. Perioperative Outcomes. As in other minimally invasive surgeries in urologic oncology, the R-RPLND affords a reduced blood loss and shorter recovery time, both of which translate into shorter hospital stays [28]. Blood loss is minimized for R-RPLND primarily due to the tamponading effects of pneumoperitoneum on venous bleeding. For R-RPLND, Harris et al. demonstrated equivalent blood loss (75 mL, IQR 50–100 mL) and operative time (270.5 minutes (mins), IQR 236–299 mins) compared to L-RPLND [26]. Similarly, two other series reported a median blood loss of 50 mL [6, 23], significantly less than the reported 184–450 mL blood loss for open primary RPLND [4, 29–31].

Perhaps, the most significant advantage that is afforded by the R-RPLND is the shorter recovery time compared to O-RPLND that translates into a shorter hospital length of stay (LOS). Pearce et al. and Stepanian et al. both reported a median LOS of 1 day which was far superior to both L-RPLND and O-RPLND (3.3 days and 6.6 days, resp.) [6, 9, 23]. Cheney et al., in a smaller series of 10 patients with low-stage NSGCT who received a R-RPLND, experienced a similarly short 2.7 day LOS [32]. Some O-RPLND series at experienced high-volume centers, however, have managed to reduce the difference in LOS compared to minimally invasive approaches. Syan-Bhanvadia et al. via the extraperitoneal open approach and Beck et al. of Indiana University have reported a mean LOS of 2.8 to 3 days [30, 31]. The dramatically reduced hospitalization of R-RPLND is likely explained by both the less morbid incision compared to O-RPLND and the lower rates of postoperative ileus. Together, this translates into a shorter convalescence due to less pain, earlier ambulation, and earlier return of bowel function.

Minimally invasive approaches for RPLND, however, are limited by a greater operative time compared to O-RPLND, which persists even beyond the learning curve [9]. In a large meta-analysis, L-RPLND performed by experienced surgeons had significantly greater operative time compared with O-RPLND (204 mins versus 186 mins) [9]. A similar trend applies to R-RPLND, reporting greater operative times ranging from 239 to 311 minutes [6, 26, 32]. While there are no studies investigating costs associated with R-RPLND, prior studies have demonstrated that the reduced LOS associated with L-RPLND drove its reduced cost relative to O-RPLND [33]. While the cost of robotic technology may be high relative to laparoscopy, cost savings for R-RPLND may be achieved through shorter length of stays and reduced complication rates, as was shown for laparoscopic versus robotic partial nephrectomy [34].

4.3. Complications. As part of the rationale for primary RPLND to avoid the long-term toxicities of chemotherapy, surgical complications need to be minimized at all costs. O-RPLND, however, has traditionally experienced relatively high intraoperative and postoperative complication rates at 5–7% and 24–33%, respectively [2, 4]. More contemporary O-RPLND series, however, report lower overall complication rates as low as 7% for primary RPLND [35]. The majority of serious intraoperative complications represent visceral injury or bleeding from lumbar veins or the great vessels which may require transfusions or, rarely, open conversion. Pearce et al. reported only two (4.3%) intraoperative complications, one of which was due to an aortic injury requiring open conversion for vascular repair. Conversion rates reported in the literature for L-RPLND are similarly rare (3.7%, range 1–5.4%) [9].

Postoperative complication rates are similarly low for R-RPLND compared to open and laparoscopic approaches. Pearce et al. reported only two Clavien Grade 1 complications and two Clavien Grade 3 complications for a postoperative complication rate of 8.5% [6]. While making direct comparisons is challenging, it appears that postoperative complications for R-RPLND are congruent to large series of L-RPLND and O-RPLND, reporting complication rates of 15.5% [9] and 7–33% [4, 35], respectively. Of note, R-RPLND experienced dramatically fewer instances of postoperative ileus compared to open series (2% versus 18%) [4, 6]. This is likely related to differences in the technique of bowel mobilization. Interestingly, two of four complications reported by Pearce et al. were chylous ascites (4.3%), which is significantly greater than the 0.4%–1.7% rate reported in a primary open series [4, 9, 36]. This complication includes only two patients and may represent a statistical anomaly due to the small cohort size or the early learning curve; however, it cannot be ignored and it warrants further consideration in future R-RPLND series. The rate of chylous ascites for R-RPLND, however, appears to be an improvement over L-RPLND, which has published rates as high as 6.6% [9, 37]. Proponents of R-RPLND believe that the improved dexterity and visualization facilitates superior ligation of lymphatics relative to L-RPLND.

The vast majority of low-stage NSGCT patients should obtain a nerve-sparing procedure to preserve antegrade ejaculation for reducing the morbidity of long-term sexual dysfunction. Pearce et al. reported 100% preservation of antegrade ejaculation [6]. Similar excellent functional outcomes are reported in the smaller R-RPLND series. In a comparative series to L-RPLND, 11% of patients who underwent a laparoscopic

procedure experienced ejaculatory dysfunction compared to 0% in the robotic cohort [26]. Cheney et al. also reported a preservation of antegrade ejaculation in 10 of 11 patients [32].

5. Primary RPLND Technique

5.1. Intraoperative Technique. R-RPLND for primary CS I NSGCT involves a transperitoneal approach with the patient typically positioned in the modified flank position with a slightly flexed table. After pneumoperitoneum is achieved with a Veress needle, a 12 mm camera port and three 8 mm robotic ports are placed in a standard linear fashion to triangulate the retroperitoneum. Typically, a 12 mm AirSeal and a 5 mm blunt assistant port are also placed. Others have described a supine or dorsal lithotomy positioning with the patient placed in Trendelenburg and robotic docking occurring over the patient's left shoulder for the daVinci Si or alongside the patient for the daVinci Xi using a four-port linear configuration [23]. A major advantage to supine positioning is a more convenient shift to a bilateral template without repositioning the patient upon either identifying positive LNs on frozen sectioning for primary RPLNDs or in the postchemotherapy setting. A modified node template dissection, including nerve sparing, is performed as previously described [38–40]. A unilateral template may be performed for CS I disease, and a bilateral template is recommended for CS II disease [41]. After reflection of the ipsilateral colon to reveal the retroperitoneum, dissection is performed following boundaries of the renal vein superiorly, the ureter laterally, and the iliac bifurcation inferiorly. The gonadal vein is identified and ligated at the level of its origin, and the remaining portion of the ipsilateral spermatic cord is dissected free from the inguinal ring. For a left-sided template, lymph node packets are removed from the left common iliac nodes, preaortic, paraaortic, and retroaortic areas. Right sided-templates include lymph nodes from the paracaval, interaortocaval, and preaortic spaces. The sympathetic chain and postganglionic nerve fibers are identified and preserved. Hem-o-lok clips are placed on lymph node packets for preventing postoperative lymphatic leak as well as for control of lumbar vessels. Retrocaval and retroaortic lymph node packets can be more challenging to manage and require special consideration to ensure a complete lymph node dissection. Lumbar vessels are ligated using a variety of techniques, including surgical clips, ties, or suture ligation. The dexterity of robotic instruments allows for complete control of the great vessel to ensure dissection of all retrocaval or retroaortic tissue. In addition, the magnified view facilitates nerve dissection and preservation; the camera angle often allows a unique view of retrocaval and retroaortic structures. After hemostasis is achieved, a fibrin sealant may be applied to the lymphatic beds to prevent lymphatic leaks. A drain is typically not placed.

5.2. Postoperative Care. Patients are transferred to the floor where their diet is advanced from clear liquids on the night of surgery to a fat-free regular diet on the day after surgery. It is our practice to follow a low-fat diet that is regularly advanced over four weeks to minimize the risk of chyle leak. There is a paucity of data regarding the efficacy of this approach; however, we have not experienced a chyle leak in our institutional experience with minimally invasive RPLND following this protocol. Patients receive education from a nutritionist regarding a low-fat diet (≤20 g fat/day), which they will continue for 4 weeks postoperatively. Patients are usually discharged home on postoperative day 1 after they are tolerating a regular diet and have successfully ambulated and voided with adequate pain control. Patients usually return to school or work within 2 weeks.

6. Postchemotherapy RPLND

Postchemotherapy RPLND (PC-RPLND) for patients with residual tumors after chemotherapy represents a far more challenging surgery compared to the primary RPLND setting. Desmoplasia from the therapeutic action of chemotherapy can fuse normal tissue planes and add complexity to dissection of tissues and, if needed, repair of vascular injuries. The risk-benefit ratio of cancer cure and morbidity of surgery makes justification of an investigational, minimally invasive technique more challenging. However, select surgeons and centers report perioperative outcomes supporting minimally invasive PC-RPLND as a safe surgery. In addition, perioperative outcomes and complications, including the preservation of antegrade ejaculation, are significantly worse due to the need for a bilateral template and the treatment effect of chemotherapy on the retroperitoneal tissue [3, 4]. Based on the favorable outcomes of L-RPLND in the postchemotherapy setting [42], the natural evolution of the R-RPLND has included attempts by experienced robotic surgeons to perform postchemotherapy R-RPLND (PC-RPLND) in selected patients. To date, only two smaller series have demonstrated early feasibility [12, 32]. The Mayo Clinic R-RPLND experience included nine patients who were postchemotherapy. Notably, their median LNY (18 nodes), blood loss (313 mL), and LOS (2.2 days) were not significantly different from their primary R-RPLND patients; however, their PC-RPLND patients experienced significantly greater operative time (369 mins versus 311 mins, $p = 0.03$). Notably, two patients required open conversion in the postchemotherapy group, which represents a conversion rate of 22.3%. At a median follow-up of 22 months, there were no retroperitoneal recurrences. Kamel et al., in a series of 12 patients, experienced a 91.7% completion rate with only a single open conversion due to what the author considered poor patient selection [12]. It is also worth mentioning that Stepanian et al. included four robotic PC-RPLNDs with no conversions [23]. At a median follow-up of 31 months, there were no recurrences. Currently, the literature on robotic PC-RPLND outcomes is immature and requires larger series before conclusions regarding oncologic and safety performance can be made. From these smaller series, we can conclude that R-RPLND in the postchemotherapy setting is feasible with an understandably higher rate of open conversion. Postchemotherapy RPLND has inherent objectives that are different from the primary RPLND setting, and incomplete control of the

retroperitoneum or an incomplete resection during RPLND is a predictor of worse survival in the postchemotherapy setting [43]. Therefore, it is our position that oncologic outcomes remain the priority in the postchemotherapy setting, and oncologic outcomes should not be leveraged against perioperative outcomes. As larger, multi-institutional cohorts are published, we can hopefully better evaluate the merits and technique of a robotic PC-RPLND.

7. Conclusion

The first L-RPLND performed in 1992 and the first R-RPLND performed in 2006 marked the beginnings of a minimally invasive era to reduce the treatment morbidity for testicular cancer survivors. Early results from expert robotic surgeons at high-volume academic institutions have demonstrated both feasibility as well as favorable early oncologic outcomes and complication rates in the primary RPLND setting compared to O-RPLND and L-RPLND. Larger, prospective studies are required to better evaluate long-term oncologic outcomes and complication rates in both the primary and postchemotherapy settings.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

The Use of Modified Templates in Early and Advanced Stage Nonseminomatous Germ Cell Tumor

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The surgical management of both early and advanced stage germ cell tumors of the testis remains a complex process of surgical decision making to maximize oncologic control while minimizing morbidity. Over the past 5 decades, the evolution of the surgical template for retroperitoneal lymphadenectomy (RPLND) has resulted in important modifications to achieve these goals. In this review, we will characterize the historical motivating factors that led to the modified template, outline patient and clinical factors in selecting these approaches in both early and advanced stage disease, and briefly discuss future horizons for their implementation.

1. Introduction

Few topics generate more discussion and consideration than the extent and laterality of the surgical template when managing the retroperitoneum (RP) in germ cell tumor (GCT) patients. The implications of limiting the surgical template inappropriately leave patients at risk for RP relapses. Conversely, extending the template beyond necessary boundaries increases the risk of surgical complications and long-term side effects. Several modifications have been incorporated that allow for an optimization between functional and oncologic outcomes. Understanding the historical rationale for these alterations and the clinical scenarios in which implementation of a limited dissection can be safely integrated is imperative. For the purposes of this review, our goal is to highlight the motivating factors and clinical experience that led to changes in the surgical boundaries for retroperitoneal lymph node dissection (RPLND).

2. Historical Perspectives and Rationale for Template Modifications

Prior to effective chemotherapy for metastatic GCT, wide surgical resection of retroperitoneal (RP) disease was necessary to provide patients their only chance for durable, cancer-free survival. Additionally, cross-sectional imaging was unavailable and staging of disease limited. Accordingly, the burden of disease in this era was great; therefore, suprahilar and bilateral retroperitoneal dissections were routinely performed. With the development of curative, platinum-based chemotherapy regimens [1] along with the introduction of cross-sectional imaging of the abdomen with computed tomography [2] and discovery of serum tumor markers (STM) [3], the management of testicular cancer patients shifted. Surgery was associated with significant morbidity, with the loss of ejaculatory function representing the most pressing issue for young men and their fertility, occurring in roughly 90% of patients undergoing bilateral template dissections. Surveillance protocols were implemented for patients without detectable metastatic disease (CSI) to avoid this morbidity, utilizing chemotherapy in those that relapsed or failed observation. Limitations of surveillance protocols included the inaccuracies of clinical staging in roughly 30% of patients [4] and the greater burden of surveillance imaging and salvage treatments at the time of relapse.

Several surgical advancements improved our understanding of nodal dissemination of disease to the RP and neural pathways that impacted ejaculatory function were discovered, setting the stage for surgical modifications and refinement. Preceded by cadaveric and lymphangiographic

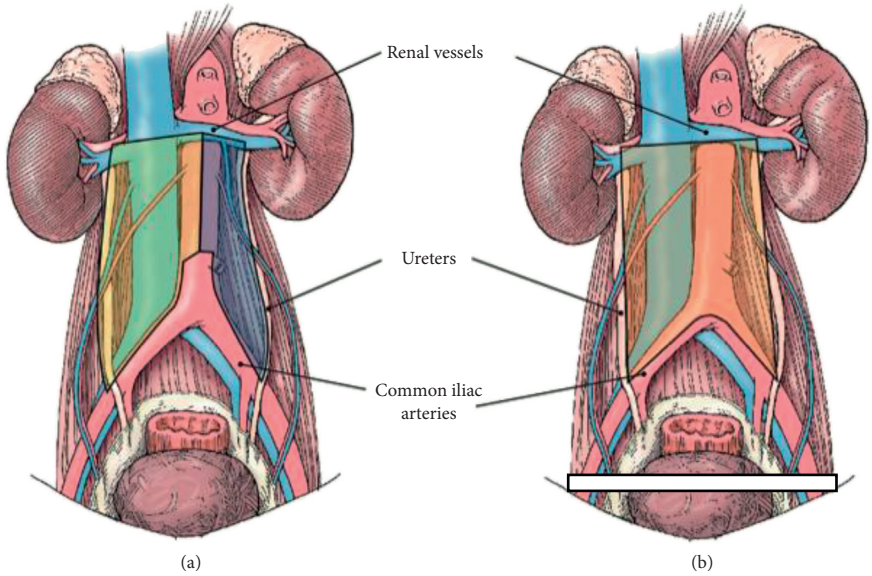

Figure 1: Template boundaries for left and right modified RPLND (a) and bilateral template rPLND (b).

studies elucidating the primary and secondary lymphatic drainage of the testicle [5–10], Ray et al. presented their nearly 30-year experience with bilateral, infrahilar RPLND in 283 patients [11]. Among the 122 patients with resectable metastatic disease, they characterized distinct patterns of spread based upon the laterality of the testicular primary. The authors noted the absence of crossover relative to the primary landing zones among patients with solitary metastases of the right or left testes. In 1982, Donohue et al. reported their findings among 104 patients with node-positive disease who were not previously treated with chemotherapy and underwent routine full bilateral dissections, including the suprahilar regions [12]. This study confirmed the predictable patterns of disease spread as reported by Ray et al. and provided pathologic rationale for the safe omission of suprahilar, interiliac, and contralateral RP dissections in low-volume disease. These modifications resulted in a reduction in the risk of postoperative chylous ascites, renovascular injury, pancreatic complications, and improved preservation of antegrade ejaculation.

Weissbach and Boedefeld reported on a prospective, multi-institutional trial of 214 consecutive patients undergoing a bilateral dissection for clinical stage II disease [13]. The goals of this study were to determine the localization and distribution of solitary and multiple lymph node metastases. These authors again confirmed the uncommon occurrence of contralateral disease relative to the aorta in the setting of early stage tumors, defined as solitary metastases measuring 5 cm or less. More importantly, when a limited template was compared prospectively by this same group among patients with CSI disease, no differences were seen regarding relapse rates or perioperative complications, while preservation of ejaculatory function was noted in 74% undergoing a modified dissection as compared to 34% subjected to a radical (bilateral) dissection [14].

Despite data from several published series, incorporation of these template modifications into clinical guidelines has remained controversial. Patient selection remains key for maximizing the cancer control and limiting the morbidity. In the primary setting, the risk of contralateral spread increases with increasing tumor burden. For patients with residual disease after chemotherapy, locations of disease both pre- and postchemotherapy, IGCCCG risk classification, along with tumor size have been suggested as criteria to consider when selecting patients for template modifications. Included in Figure 1 are the current templates utilized at our institution for right and left modified boundaries (A), in addition to bilateral template surgery (B). The following sections report on the current data and guidelines.

3. Outcomes in Early Stage NSGCT

Several institutions have assessed oncologic and functional outcomes with modifications in the surgical template over time. While significant variability exists among groups as to the type of modifications made to the template, outcomes regarding RP relapse rate, and recovery of ejaculatory function are uniformly reported. In one of the earliest studies out of Italy, Pizzocaro et al. reported on 61 CSI patients, of which 10 experienced relapse in the absence of adjuvant therapy. None of these occurred in the RP and 87% reported preservation of antegrade ejaculation with template modification alone [15]. Similar findings were seen in a cohort of 85 CSI patients from Brigham & Women's Hospital in Boston, again with no RP recurrences identified and 94% recovering antegrade ejaculation [16]. Donohue et al. from Indiana published their experience with unilateral template modifications, this time with ipsilateral nerve-sparing [17]. In this series of 75 patients published in 1990, 73 of which were CSI and 2 patients had low-volume CSIIa disease.

One RP recurrence was reported and later salvaged. When assessing survival outcomes across all studies, cancer specific and overall survival approaches 100%.

Proponents of bilateral, infrahilar dissections with unilateral or bilateral nerve-sparing have suggested that limited templates subject patients to higher rates of unresected disease in the RP, leaving them at greater risk for late relapse, higher burdens of chemotherapy, and potentially a greater risk of death. Eggener et al. reported upon 191 cases of pathologic node-positive cases undergoing primary RPLND for early stage NSGCT [18]. Comparing published templates to the distribution of disease mapped within their cohort, they estimate that 3% to 23% of patients with unilaterally modified dissections would have nodal disease outside of the field of surgery. A couple points are worth further discussion in this study. Interestingly, there were 136 patients with clinical stage IIA disease; however, only 80 (58%) were found to have pathologic disease. Further, there were 20 patients with elevated tumor markers at the time of RPLND. In the only prospective trial comparing outcomes between surgical approaches, no difference in oncologic outcomes was identified, and a twofold increase in functional outcomes was reported with the unilateral template (Weissbach). To date, no randomized trials have compared template modifications to full bilateral dissections for difference in cancer control, 90-day morbidity, and long-term functional outcomes regarding ejaculatory function. Additionally, the Eggener study omits any consideration for intraoperative findings that may influence the judgment of the surgeon to expand the dissection. Nevertheless, improving upon the oncologic and functional outcomes reported among these open series when template modifications are performed at high-volume centers with therapeutic intent would be difficult to accomplish.

4. Postchemotherapy RPLND Template Outcomes

Early experience in using full bilateral templates following cisplatin-based chemotherapy was reported by Donohue et al. in 1982 [19]. Given the uncertainties of frozen section pathologic evaluation in the postchemotherapy setting and bulky disease with what is now considered suboptimal chemotherapy, the authors supported the use of complete bilateral RPLND. Since that time, several centers have investigated the oncologic safety of modified unilateral templates in appropriately selected individuals in contemporary series. In 2007, Beck et al. evaluated 100 patients who underwent a modified dissection with a median follow-up of 31.9 months [20]. Patient selection criteria were: nonseminomatous GCT's with normal serum tumors markers after cisplatin-based chemotherapy and tumors limited to the primary landing zone both before and after chemotherapy. There were 4 recurrences during follow-up, all of which were outside the boundaries of a full bilateral template. This study was recently updated with 10-year follow-up data with an additional 3 patients demonstrating a recurrence [21]. Again, no recurrences were within the bounds of a full bilateral template with the majority of recurrences being in the chest. An additional series of 102 patients from the Austrian group also evaluated the safety of template surgery in the post-chemotherapy setting [22]. The inclusion criteria in this series were normal serum tumor markers after first-line cisplatin-based chemotherapy with stage II disease. All patients underwent template surgery based on the location of the primary tumor. There was 1 recurrence in the RP within the boundary of a full bilateral template for a recurrence rate of 0.9% at a median follow-up of 8.5 years. The majority (73%) of these patients demonstrated a complete response to chemotherapy with residual masses <1 cm. Heidenreich et al. described the German experience in 98 patients who underwent a modified template RPLND [23]. The inclusion criteria in this series were similar to the prior studies and also limited the residual mass to ≤5 cm in diameter. One patient developed a RP recurrence in this series for a 1% recurrence rate at 3 years of follow-up. These studies in combination demonstrate a risk of RP recurrence of 0.6% in approximately 300 patients.

Others have published on the pathologic findings of disease outside the boundary of a modified template. For example, Carver et al. published the results of 269 patients who had a full bilateral template performed and described the pathologic findings outside the bounds of a modified template [24]. They demonstrate that extra-template disease was present in 7% to 32% depending on the boundaries used for template dissections. However, the inclusion criteria in this study were quite different than other published reports. In the Carver et al. study, unselected patients with bulky disease, significant receipt of salvage chemotherapy regimens, elevated STMs at the time of surgery, and positive preoperative imaging outside the modified template boundaries were included. These factors limit the relevance of this study in determining the utility of template surgery in the post-chemotherapy setting.

5. Functional Outcomes with Template Modifications

Historical comparisons for bilateral RPLND are associated with loss of seminal emission and ejaculation in the majority of patients. With the incorporation of unilateral templates, preservation of antegrade ejaculation was attributable to the exclusion of any dissection or disruption of the contralateral efferent, postganglionic sympathetic nerve fibers as they course to the hypogastric plexus. Donohue reported ejaculatory rates of 90% with modified, unilateral templates without any compromise in oncologic efficacy [4]. Similar rates of preservation were reported from the Italian group among 61 CSI patients [15]. In the only prospective trial assessing functional and oncologic outcomes among patients undergoing either a unilateral template compared to the standard bilateral template, the modified template was associated with a twofold improvement in ejaculatory rates without any greater risk of in field relapse [14]. With further modifications to include ipsilateral nerve-sparing within the surgical template, rates of ejaculatory preservation were improved. Jewett et al. demonstrated feasibility in a series of 30 patients, with 18 of 20 patients in whom successful nerve-sparing was accomplished ultimately recovering function [25]. The Indiana group published their experience combining

unilateral template modifications with ipsilateral nerve-sparing in 1990. In this cohort of 75 early-staged patients, 100% were able to achieve successful antegrade ejaculation [17]. In a more contemporary series of 135 men undergoing nerve-sparing primary RPLND at Indiana, 134 achieve normal function, and nearly 75% were able to conceive [26].

While data exist describing the safety of template surgery in the postchemotherapy setting from an oncologic standpoint, functional data also support an improved ejaculatory status in modified template surgery. In the Indiana series with 10-year follow-up data, antegrade ejaculation occurred in 97.7% of patients, who were contacted [21]. Additionally, Heidenreich et al. evaluated the likelihood of being able to perform nerve-sparing surgery and found that 74.5% versus 55.5% of patients could undergo preservation of the postganglionic sympathetic nerve fibers in modified template versus bilateral template surgery, respectively [23]. Furthermore, antegrade ejaculation occurred in 85% of modified template resections versus 25% of full bilateral resections in their series, ($p < 0.001$). Additional clinical outcomes are also improved with a modified template dissection in the appropriately selected patient, such as shorter operative times, less blood loss, less transfusions, and fewer postoperative complications [23].

6. Future Directions

The majority of the current data supports the oncologic safety of modified template surgery in strictly defined cohorts. Efforts to determine the safety in other patient populations such as poor-risk disease and late relapse offer areas of potential study. These studies would require meticulous design to ensure patient safety. For example, patients with a late relapse 10 years following their primary tumor with a small solitary recurrence in the ipsilateral landing zone could be reasonable to apply modified template principles. The assumption here would be that the disease has declared itself to the ipsilateral landing zone of the primary tumor and there has been a 10-year lag time to monitor the contralateral side with no recurrence.

Data surrounding the use of minimally invasive surgery and template dissection is limited particularly in the postchemotherapy setting, but this should and will be held to the same standards of the open approach. Oncologic outcomes regarding the therapeutic value of template surgery in laparoscopic and robot-assisted primary RPLND are significantly lacking due to small numbers of patients, even smaller numbers with true pathologic disease, and the majority of patients with pathologic stage II disease receiving adjuvant chemotherapy. While some early reports of nerve-sparing success in the robotic settings are promising in the primary RPLND setting [27], this is not consistent across studies with some series demonstrating lower antegrade ejaculation rates with the robotic approach [28, 29]. Others have shown inferior ejaculatory rates in clinical stage I patients with the laparoscopic technique compared to robotic techniques [30]. Ejaculatory outcomes in the postchemotherapy setting with minimally invasive techniques are unclear. Overall, the high bar of 99% ejaculatory success [26] and subsequent fertility in open primary RPLND using modified templates cannot be compromised by incorporating a robotic approach.

7. Conclusions

With more than 35 years of experience, several studies have confirmed the safety of modified templates for RPLND both in the primary and postchemotherapy setting. Benefits include limiting the morbidity of surgery, without compromising the therapeutic impact among appropriately selected patients. Expansion of its use within other patient populations warrants exploration but must be integrated in a thoughtful manner to ensure patient outcomes are not compromised.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Adjuvant Therapy for Stage IB Germ Cell Tumors: One versus Two Cycles of BEP

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Testicular germ cell tumours are the commonest tumours of young men and are broadly managed either as pure seminomas or as 'nonseminomas'. The management of Stage 1 nonseminomatous germ cell tumours (NSGCTs), beyond surgical removal of the primary tumour at orchidectomy, is somewhat controversial. Cancer-specific survival rates in these patients are in the order of 99% regardless of whether surveillance, retroperitoneal lymph node dissection, or adjuvant chemotherapy is employed. However, the toxicities of these treatment modalities differ. Undertreating those destined to relapse exposes them to the potentially significant toxicities of 3-4 cycles of bleomycin, etoposide, and cisplatin (BEP) chemotherapy. Conversely, giving adjuvant chemotherapy to all patients following orchidectomy results in overtreatment of a significant proportion. Therefore, the challenge lies in delineating the patient population who require adjuvant chemotherapy and in determining how much chemotherapy to give to adequately reduce relapse risk. This chapter reviews the factors to be considered when adopting a risk-adapted strategy for giving adjuvant chemotherapy in Stage 1B NSGCT sand discusses the data regarding the number of BEP cycles to administer.

1. Background

Testicular germ cell tumours (TGCTs) are the commonest tumours of young men aged between 20 and 35 years. They are divided into those of pure seminoma subtype (that histologically resemble primordial germ cells) and those with elements that resemble extra embryonic tissue (with or without seminoma components), generally termed "nonseminomas." Nonseminomatous germ cell tumours (NSGCT) make up roughly 50% of cases and are common in a younger age group than seminomas (median age around 25 years). A characteristic of TGCT is their sensitivity to cisplatin-based chemotherapy which means that, in contrast to most solid tumours, patients with metastasis are usually cured. The most commonly used schedule is "BEP," consisting of bleomycin, etoposide, and cisplatin. This is highly successful chemotherapy and will cure around 85–90% of patients with metastatic disease and over 95% of those with good prognostic features (i.e., absence of visceral metastasis and low tumour markers) [1]. The cost of this is the risk of significant toxicity, both acute and late (e.g., renal damage, peripheral neuropathy, hearing damage, increased risk of cardiovascular disease, and second cancer; summarised in Table 1). Management of these patients is supported by monitoring tumour markers such as alpha fetoprotein (AFP) and human chorionic gonadotrophin (HCG), which are elevated in patients with metastatic NSGCT in around two-thirds of cases [2].

Around 75–80% of patients diagnosed with NSGCT present with no other clinical evidence of disease outside the testis on examination, imaging, or on tumour markers. These patients are termed Stage I and have excellent outcomes, with 5-year disease-specific survival over 98% [3]. Without additional treatment though, relapse occurs in around 30%.

Histopathological markers have been used to help predict the risk of recurrence. The best validated of these prognostic markers has been the presence or absence of lymphovascular invasion (LVI). Patients without LVI have around 15–20% risk of relapse, and if LVI is present, there is a 40–50% risk of recurrence [4]. This finding has been consistent across

Table 1: Toxicities of BEP chemotherapy.

Dose-related toxicities of BEP	Non dose related	Unknown relationship to dose
Infertility	Febrile neutropenia	Second malignancy
Peripheral neuropathy	Alopecia	Cardiovascular disease
Ototoxicity	Nausea/vomiting	
Raynaud's phenomena		
Fatigue		
Skin toxicity		
Avascular necrosis hip		
Pneumonitis/lung fibrosis		
Renal damage		
Anaemia		
Metabolic syndrome		

a number of large studies and is current standard of care in dividing patients into higher risk groups despite the modest predictive power; that is, even in low-risk group, 15–20% of patients will relapse and 50% of high-risk patients will remain in remission [1].

Other markers such as proportion of embryonal carcinoma (EC), rete testis invasion, and MIB-1 staining have been proposed, but results have not been fully validated. Tumours with no embryonal components generally have a low rate of recurrence [5–7]. Absence of undifferentiated embryonal carcinoma was one of the original MRC risk factors identified in the first MRC surveillance studies [6]. Some studies have suggested that the proportion of embryonal carcinoma may increase relapse risk [4, 8] though this does correlate with LVI and so has not been fully validated. MIB-1 has also been suggested to be associated with increased relapse risk, but in a recent study [8], an association could not be validated. Recently, CXCL12 expression has been proposed as a prognostic marker and validated in two data sets. On the basis of this marker and vascular invasion, three risk groups have been proposed including low (10% risk), intermediate (30–40% risk), and high (70%) risk groups though this remains to be validated.

A number of different approaches have been utilised in this patient group. In the past, removing the retroperitoneal lymph nodes has been practiced particularly in the United States and parts of Europe. Patients who are node negative (pN0) have a lower rate of subsequent recurrence (~10–15%). Node-positive patients (pN1) may be cured by this approach but continue to have a significant rate of recurrence (~30%). These patients have often been offered subsequent adjuvant chemotherapy (see below). Though undoubtedly some patients may avoid chemotherapy, this is at the cost of a major surgical procedure with the risk of attendant morbidity both immediate and long term. Patients still require follow-up as there remains a significant risk of relapse even in the pN0 group, and even without the use of adjuvant chemotherapy, a substantial number of patients will still be exposed to chemotherapy.

An alternative approach, based on pioneering work of Peckham and colleagues and subsequent MRC trials is to watch patients closely a policy termed active surveillance. This approach watches carefully with the aim of early relapse detection and treatment of recurrence by BEP chemotherapy. This approach has the virtue of avoiding treatment (and its attendant toxicities) except when necessary. The use of surveillance has grown over the years but is not necessarily trouble free. Patients who relapse require the use of full-dose chemotherapy [3]. The surveillance phase can cause psychological stress and can make it difficult for some patients to return to a normal lifestyle for fear of recurrence. Finally, there remains a concern regarding compliance. Several studies have shown a degree of noncompliance with follow-up in GCT patients. The fear is that noncompliers can relapse with more advanced disease with a poorer prognosis. This is a concern as a priori identification of noncompliance is difficult. For these reasons, the role of adjuvant chemotherapy has been explored especially in those at high risk of recurrence.

2. Adjuvant BEP Chemotherapy

An alternative approach to surveillance is to use adjuvant chemotherapy following treatment. This was first explored in the early 1990s after the success of using BEP chemotherapy in metastatic disease. It was argued that using more limited chemotherapy in those at high risk would restrict exposure to chemotherapy and prevent relapse. The key study of this approach was the MRC TE05 study. 114 patients were recruited with a predicted recurrence risk based on MRC risk factors of >50% [9]. Two patients recurred but one patient on histology review was proven to have a non-germ cell cancer, so in the 108 patients with centrally reviewed NSGCT, 1 relapsed and the 95% CI excluded a risk of relapse of 5%. This study was supported by similar smaller studies from Bern and Vienna [10, 11]. These data have been replicated in a number of reported studies totalling almost 1000 patients and a combined risk of relapse of <2% (summarised in Table 2). Most of the studies have used BEP for adjuvant treatment though a few studies have used variants of BEP. MD Anderson reported on substituting carboplatin for cisplatin [12], and the MRC replaced etoposide with vincristine [13], both achieving results similar to that achieved by BEP. The lower efficacy of carboplatin in metastatic disease and concerns regarding neurotoxicity, respectively, has meant that these approaches have not been adopted.

Following this work, adjuvant BEP has become an option for high-risk stage 1 NSGCT. Its use has been the subject of

Table 2: Studies of 2 cycles of adjuvant chemotherapy in testicular nonseminomatous germ cell tumours.

Study	Institution	Chemotherapy	Eligibility	Median follow-up (months)	*N*	Number of malignant relapses (all relapses)
Cullen et al. [9]	MRC, UK	BEP	MRC >50% risk	NS	104	1 (1)
Pont et al. [11]	Vienna	BEP	VI	79 (range, 27 to 119)	40	1 (2)
Bohlen et al. [10]	Berne	BEP/PVB	≥pT2/EC	93 (range 32 to 146).	58	0 (1)
Germa-Lluch et al. [14]	Spanish germ cell group	BEP (90%)	≥pT2	NS	168	1
Chevreau et al. [15]	Toulouse	BEP	VI or EC	113.2 (range 63–189)	40	0
Oliver et al. [16]	Anglia, UK	BEP BOP	MRC >30% risk	NS	28 74	1 (1) 2 (2)
Amato et al. [12]	MD Anderson	CEB	*MDA high risk	38	68	0 (1)
Guney et al. [17]	Istanbul	BEP	*MDA high risk	26 (range 10–60)	71	3 (4)
Dearnaley et al. [13]	MRC, UK	BOP	VI	70	115	2 (2)
Bamias et al. [18]	Hellenic germ cell group	BEP	≥pT2/EC	79	142	1 (1)
Mezvrishvili and Managadze [19]	Tbilisi	BEP/EP	VI	NS	41	0 (1)
Total					949	12 (17) 1.3% (1.8%)

*MDA high risk: pre-op AFP > 80 ng/ml, VI or >pT2. Chemotherapy drugs: B, bleomycin; C, carboplatin; E, etoposide; O, vincristine; P, cisplatin; V, vinblastine. MRC, Medical Research Council; VI, lymphovascular invasion present; EC, embryonal carcinoma.

much debate. This is centered on the issue of late toxicity from BEP. The acute toxicities of BEP (Table 1) have been recognised for many years. Over the last decade, the risk of long-term effects have been better appreciated especially neuropathy, cardiovascular disease, and second malignancy. This has meant that opponents of adjuvant chemotherapy have advocated avoiding exposure of patients to the hazards of chemotherapy unless there is evidence of defined disease. On the other hand, proponents of adjuvant chemotherapy point to the lower doses used, and assuming this means less risk of toxicity. They also note the benefit of lower use of retroperitoneal lymph node surgery. Originally, the 2 cycles of BEP used adjuvantly was half of the dose of that used for metastatic disease. So, with a ~50% relapse risk, the total number of cycles of chemotherapy needed to be delivered ("burden" of chemotherapy) was similar with either approach, though distributed differently in the population. However, with a MRC/EORTC randomised trial [12] showing that 3 cycles of BEP was sufficient for most patients, the balance in terms of burden of chemotherapy was in favour of a surveillance approach (i.e., assuming a 50% relapse risk); for every 100 adjuvant patients, 200 cycles of BEP would be delivered compared to 150 cycles for 100 surveillance patients undergoing 50 relapses. This has led to the exploration as to whether less adjuvant chemotherapy may be sufficient.

3. Single-Cycle Adjuvant BEP

At the Royal Marsden, we initially investigated a single cycle of BEP in patients with intermediate risk of recurrence. In 22 patients with approximately 20% risk of recurrence (i.e., 4-5 patients expected to recur), no active recurrences were noted though 1 patient required resection for teratoma differentiated [20]. In a similar higher risk group (defined as presence of vascular invasion or predominant embryonal carcinoma) in 42 patients, Westermann and colleagues reported a single active relapse compared to an expected rate of around 15 patients [21] (updated in [22]).

This approach has now been tested in 3 larger studies (Table 3). In the first of these, Albers and colleagues in the German germ cell cancer study group conducted a randomised trial comparing a single cycle of BEP versus RPLND [23]. In 191 patients randomised to BEP, 2 relapses were seen (1 of which was mature teratoma). In the RPLND arm, 32/173 patients were node positive and received adjuvant chemotherapy, and 15 node-negative patients relapsed (equating to 47 patients with active disease, 27%). The Scandinavian Swenoteca [24] group adopted a single cycle of BEP for intermediate- and high-risk patients as a population-based treatment protocol. In their latest report on 571 patients and a median follow-up of 7.9 years, 3.2% of patients with lymphovascular invasion ($n = 258$) and 1.6% patients with no lymphovascular invasion ($n = 255$) have relapsed with only one patient dying of multiply relapsed TGCT.

The latest study to report is the UK 111 study [25]. This large prospective nonrandomised study was designed to specifically exclude a relapse risk of over 5% after a single cycle of BEP. This study recruited 246 patients and reported after a median follow-up of 39.9 months and with a minimum follow-up of 2 years in 91% of patients. Four patients have had a malignant recurrence and 3 a TD recurrence. The primary end point was 2-year malignant recurrence rate which was 1.3% (95% CI 0.4–4.0%) and thus met its aim to exclude a 2-year recurrence rate of 5%. A full publication is awaited.

Table 3: Summary of studies of single-cycle adjuvant BEP chemotherapy.

Study	Eligibility	Median follow-up (months)	*N*	Number of malignant relapses (all relapses)	Predicted relapse risk	Predicted number of relapses
Gilbert (RMH) [20]	1 or 2 MRC RF	120	22	0 (1)	20%	4
Westermann (Switzerland) [21]	VI+	99	13	1	30%	13
	>50% EC		29			
Albers (GCSCG) [23]	Any	56	191	1 (2)	26%	50
Tandstad [24] (SWENOTECA)	VI+	95	258	7 (8)	42%	108
	VI–		255	3 (4)	12%	31
111 study [25]	VI+	40	236	4 (7)	42%	99
Total			**1004**	**16 (23)** **1.6% (2.3%)**		**305***

*23/305 equals 7.5% of predicted relapses.

4. Current Perspectives

It is our opinion that the data discussed are now robust enough to conclude that 1 cycle of BEP can successfully reduce the risk of recurrence to less than 5%. The additional benefit of adding a second cycle in terms of risk reduction of relapse is small and, in our judgement, is not sufficient to justify the additional toxicity. Using a single cycle of BEP would reduce the overall use of chemotherapy in the "high-risk" vascular invasion population. Using the model described above, treating 100 patients with single-cycle adjuvant BEP would give 100 cycles to this population compared to 150 cycles if it is assumed that 50% relapse on surveillance. In addition to amount of chemotherapy, the balance of who receives is very different either spread across the whole population or concentrating, with greater exposure, in those with proven disease. There is no evidence in any of the studies of adjuvant chemotherapy or surveillance that use of either approach affects overall survival. This has prompted a vigorous debate between supporters [26–28] of adjuvant chemotherapy and surveillance as to the optimal approach, both in seminoma and nonseminoma. To our mind, to exclusively offer either approach, given lack of survival difference, is inappropriate. We attempt to present a balanced argument of the pros and cons of the two approaches stressing the impact on relapse and discussing what is known regarding immediate- and long-term toxicity (including risk of cardiovascular disease and second malignancy). The idea of adjuvant toxicity seems intrinsically attractive to many, with the wish to get treatment over with and avoid future uncertainty of relapse as common levers for deciding on adjuvant chemotherapy.

4.1. Future Approaches. Adjuvant chemotherapy has usually been used for patients found to be at higher risk of recurrence. The adoption of single-cycle adjuvant chemotherapy raises the question of whether patients with lower risk should be offered this treatment. The Swenoteca group allowed patients with lower risk of recurrence to receive adjuvant BEP in their protocols and reported a less than 2% relapse risk [24]. We do not offer this approach routinely as this would expose 80% or more of patients to BEP who would not have relapsed and increases the overall burden of chemotherapy. There may be exceptional instances such as when surveillance or full course of BEP would be difficult when it might be considered.

The landscape of adjuvant therapy could be changed if there was better prognostication. We recently reported a new prognostic index that could split stage 1 NSGCT patients into 3 broad groups based on vascular invasion and whether they had expression of CXCL12 or had near 100% embryonal content [8]. Using these criteria, we identified a small group (10–15%) with a very high recurrence risk (>70%) and a significant group (~40–50%) with a low risk of recurrence (~10%) with the remainder having a 30–40% recurrence risk. This index needs further validation but may have implications for decision making regarding adjuvant therapy. We believe most clinicians would agree the low-risk group should be surveyed and the high-risk group would benefit from adjuvant therapy. The intermediate group may be more controversial. The total burden of chemotherapy for surveillance and adjuvant chemotherapy would be roughly similar. These patients might reasonably be surveyed but many may consider the risk high enough to justify adjuvant chemotherapy if a single cycle of BEP is used.

This landscape is not static. More sophisticated genetic profiling may be on the horizon [29], and whilst data are emerging, that microRNA analysis may be a sensitive indicator of subclinical disease [2, 30]. Any impact on prognostication may affect the balance between surveillance and adjuvant therapy.

It is possible that the increasing confidence in the use of adjuvant BEP could change the treatment algorithm in other areas. For instance, could single-cycle BEP with less-invasive surgical techniques lead to a resurgence of surgical management of low-volume (stage 2) NSGCT [31]?

5. Conclusion

Single-cycle BEP is effective at reducing the risk of recurrence of stage 1 NSGCT to less than 5% and should be the preferred over two cycles of BEP if adjuvant therapy is chosen rather than surveillance. However, surveillance approaches can legitimately still be offered to all patients.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Conventional-Dose versus High-Dose Chemotherapy for Relapsed Germ Cell Tumors

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The majority of metastatic germ cell tumors (GCTs) are cured with cisplatin-based chemotherapy, but 20–30% of patients will relapse after first-line chemotherapy and require additional salvage strategies. The two major salvage approaches in this scenario are high-dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT) or conventional-dose chemotherapy (CDCT). Both CDCT and HDCT have curative potential in the management of relapsed/refractory GCT. However, due to a lack of conclusive randomized trials, it remains unknown whether sequential HDCT or CDCT represents the optimal initial salvage approach, with practice varying between tertiary institutions. This represents the most pressing question remaining for defining GCT treatment standards and optimizing outcomes. The authors review prognostic factors in the initial salvage setting as well as the major studies assessing the efficacy of CDCT, HDCT, or both, describing the strengths and weaknesses that formed the rationale behind the ongoing international phase III "TIGER" trial.

1. Background

Germ cell tumors (GCTs), comprising 1% of male cancers and 5% of male genitourinary malignancies, are the most common tumor in young men. Most patients with advanced disease are cured with platinum-based chemotherapy; however, 20–30% patients will fail to achieve a durable response and require salvage treatment [1]. Unfortunately, the majority of patients requiring salvage chemotherapy will ultimately die, with death from GCT accounting for the greatest number of average life years lost of any non-childhood malignancy [2]. Presently, the two major salvage approaches include conventional-dose chemotherapy (CDCT) and high-dose chemotherapy (HDCT) with autologous stem cell transplant (ASCT).

Due to inconsistencies between retrospective and randomized data comparing these two strategies and the rarity of the patient population, a universally recommended approach in the initial salvage setting is lacking. As such, practices vary widely throughout the world and patients are highly encouraged to participate in clinical trials. The objective of this review is to outline the prognostic factors that affect outcome in the salvage setting, the data supporting both salvage chemotherapy strategies (CDCT and HDCT), and an ongoing randomized clinical trial that seeks to definitively establish one of these approaches as the standard of care in the initial salvage setting.

2. Prognostic Factors for Salvage Chemotherapy

For patients with metastatic GCT, prognostic factors at initial diagnosis are universally accepted with the International Germ Cell Cancer Cooperative Group (IGCCCG) classification used to guide first-line chemotherapy. Patients experiencing treatment failure with cisplatin-based first-line chemotherapy, however, represent a highly heterogeneous population. Traditionally, separate prognostic factor analyses were performed for patients undergoing CDCT and HDCT, respectively. Factors consistently associated with favorable outcome to salvage CDCT regimens across

multiple series included gonadal primary tumor site, complete response (CR) to first-line chemotherapy, and disease-free interval after first-line chemotherapy of at least several months, whereas burden of disease and tumor marker levels at the time of salvage chemotherapy demonstrated prognostic importance in some but not all series [3–6].

Prognostic factors for outcome to salvage HDCT were initially reported on small number of patients at individual centers treated with one specific regimen limiting the generalizability of the findings. Beyer et al. were the first to develop a multicenter prognostic model for HDCT derived from 310 patients treated with various HDCT regimens at 4 different centers in Europe and the United States. Factors associated with an adverse outcome included primary mediastinal nonseminomatous germ cell tumor (PM-NSGCT), HCG ≥ 1,000 IU/L, progressive disease prior to HDCT, and platinum-refractory disease. A point value was assigned to each of these factors and used to calculate a cumulative score which separated patients into good, intermediate, and poor-risk groups with failure-free survival rates of 51%, 27%, and 5%, respectively.

In a retrospective study of 184 patients with gonadal or retroperitoneal primary GCTs (PM-NSGCT patients were excluded) treated with salvage high-dose carboplatin and etoposide at Indiana University (IU), Einhorn and colleagues identified platinum-refractory disease, IGCCCG poor-risk classification at first-line chemotherapy, and receipt of HDCT as third-line or later to be associated with adverse outcome [7]. Feldman et al. reported on 107 patients treated with salvage HDCT as part of a phase I/II study of the TI-CE regimen at Memorial Sloan Kettering Cancer Center (MSKCC) and observed PM-NSGCT, receipt of HDCT as third-line or later, presence of lung metastases, HCG ≥ 1,000 IU/L, ≥3 metastatic sites and IGCCCG intermediate- or poor-risk classification at first-line chemotherapy as associated with poor outcome [8]. A more recent study from IU of 364 patients treated with high-dose carboplatin and etoposide identified use of HDCT as third-line or later therapy ($n = 61$, 17%), platinum-refractory disease ($n = 122$, 34%), PM-NSGCT ($n = 20$, 5%), nonseminoma histology ($n = 285$, 78%), IGCCCG intermediate- or poor-risk disease ($n = 213$, 59%) and HCG ≥ 1000 mIU/ml at HDCT initiation ($n = 90$, 25%) as associated with adverse progression-free survival (PFS) [9].

Given the variation in prognostic factors reported in these and other studies, the separate focus on CDCT and HDCT, the limited number of patients from which these models were derived, and the small number of chemotherapy (particularly HDCT) regimens used, a collaborative effort, known as the International Prognostic Factor Study Group (IPFSG), was formed to develop a universally accepted prognostic model prior to initial salvage chemotherapy. The IPFSG collected data from a retrospective cohort of nearly 1,600 patients treated in 13 countries who progressed after initial cisplatin-based chemotherapy [10]. Fifty-one percent of these patients received HDCT, justifying the use of the classifier in this population. Prognostic variables on multivariate analysis applicable to the entire population independent of treatment approach (CDCT or HDCT) included primary tumor site, response to first-line treatment, progression-free interval between first-line therapy and relapse, tumor markers at relapse (AFP and HCG), and presence of liver, bone, or brain metastases at relapse. Each of these risk factors was assigned a numerical point value depending on its prognostic significance, with the sum total score (maximum of 10) used to segregate patients into five risk groups (very low, low, intermediate, high, and very high). Two-year PFS varied significantly according to risk group (very low risk: 91%, low risk: 64%, intermediate risk: 53%, high risk: 33%, and very high risk: 22%). Overall survival (OS) was also significantly different across the groups.

3. Salvage Conventional-Dose Chemotherapy

Cisplatin plus ifosfamide-containing regimens form the backbone of salvage CDCT, with studies testing a variety of third drugs to add to this combination. In the 1980s when the combination of cisplatin, vinblastine, and bleomycin (PVB) was the standard first-line regimen, the combination of etoposide, ifosfamide, and cisplatin (VIP) was the most common salvage regimen since it included two drugs not administered in the first-line setting. Once etoposide plus cisplatin (EP) and bleomycin plus EP (BEP) supplanted PVB as standard first-line treatment regimens, vinblastine, ifosfamide, and cisplatin (VeIP) became the most popular salvage regimen. Numerous studies reported on salvage VIP, VeIP, or both used in heterogeneous populations of patients including in the second-, third-, and even later-line setting. CR rates approximated 25–35% with durable remission rates of 5–15% [11–13]. Once activity was demonstrated, VeIP and VIP were moved forward for evaluation in the initial salvage setting with improvement in CR rates to approximately 40–50% and durable remission rates to approximately 25% (Table 1) [4, 5]. In the largest study evaluating VeIP as initial salvage treatment, Loehrer and colleagues treated 135 patients who experienced progressive GCT after first-line chemotherapy but who had remained disease-free for at least 3 weeks from their last chemotherapy dose and observed a CR rate of 50% and durable remission rate of 24% [5].

A subsequent phase I/II study at Memorial Sloan Kettering Cancer Center (MSKCC) evaluated the addition of paclitaxel to ifosfamide plus cisplatin (TIP) as initial salvage treatment of 46 patients [14]. This trial limited eligibility to patients with features predicting a favorable outcome to salvage CDCT including gonadal primary tumor site and either a CR to first-line chemotherapy or a partial response with negative tumor markers (PR-negative markers) lasting ≥6 months. The CR rate was 70%, 2-year PFS rate was 65%, and 63% of patients remained continuously disease-free with median follow-up of nearly 7 years. These significantly improved outcomes compared to initial salvage VeIP can be partially explained by favorable patient selection and a small number of patients included with metastatic disease in the setting of a second gonadal primary GCT. However, the study also included 14 (30%) patients with late relapse (>2

Table 1: Prospective studies examining the use of initial salvage conventional-dose chemotherapy.

Author (year)	N	CDCT Regimen(s)	Notable inclusion or exclusion criteria	EP/BEP as first-line therapy	CR/PR to first-line therapy	IR to first-line therapy	CR	Median f/u (months)	Durable remission
McCaffrey et al. [4]	56	VeIP or VIP	None	53%	36%	64%	36%	52	23%
Loehrerr et al. [5]	135	VeIP	Cisplatin-refractory patients excluded[a]	100%	100%	0%	50%	72[b]	24%
Kondagunta et al. [14]	46	TIP	Included only patients with CR- or PR-negative marker to first line, gonadal primary, and <6 cycles of cisplatin in first line	74%	100%	0%	70%	69	63%
Fizazi et al. [17]	37	GIP	Included only patients with CR or PR-negative marker to first line, gonadal primary, and <6 cycles of cisplatin in first line	86%	100%	0%	54%	53	51%

CDCT, conventional-dose chemotherapy; EP, etoposide plus cisplatin; BEP; bleomycin, etoposide, and cisplatin; IR; incomplete response; CR, complete response; f/u, follow-up; VIP, etoposide, ifosfamide, and cisplatin; VeIP, vinblastine, ifosfamide, and cisplatin; GIP, gemcitabine, ifosfamide, and cisplatin; [a]progression at <3 weeks after completion of first-line chemotherapy; [b]minimal (not median) follow-up.

years from the end of prior chemotherapy), a group with historically poor outcome to salvage CDCT, with 7 achieving durable remissions. TIP has also been studied as salvage therapy in series with less restrictive eligibility criteria and using a lower dose of paclitaxel and in some cases, also ifosfamide [15, 16]. Not surprisingly, these studies did not duplicate the high CR and durable remission rates achieved in the MSKCC TIP series, although Mardiak observed a 65% objective response rate (ORR), 41% CR rate, and 47% 2-year PFS rate, all of which still compare favorably to VeIP [15].

More recently, Fizazi et al. reported on a phase II trial combining gemcitabine with ifosfamide and cisplatin (GIP) in the initial salvage treatment of 37 patients with GCT and the favorable criteria used in the MSKCC TIP study [17]. Although this trial did not reach its primary endpoint of a 65% CR rate, GIP still demonstrated activity with favorable response (e.g., CR or PR-negative markers), CR, and 2-year PFS rates of 78%, 54%, and 51%, respectively. The authors suggested GIP exhibited similar efficacy as TIP in this favorable-risk population but with less febrile neutropenia (22% versus 48%) and severe neurotoxicity (0% versus 7%). However, the durable remission rate was lower with GIP even though none of the patients had experienced a late relapse.

Given the traditional ifosfamide-cisplatin backbone of curative salvage CDCT regimens, use of VIP as an alternative to BEP for first-line treatment of intermediate- and poor-risk patients can make selecting an initial salvage CDCT regimen difficult. This is particularly applicable to patients > 50 years old or those with pulmonary compromise at diagnosis, groups with increased susceptibility to bleomycin lung toxicity in whom bleomycin is often avoided. Potential options include PVB (if patients are now candidates for bleomycin) given neither vinblastine nor bleomycin was used in the first-line setting, or the combination of gemcitabine, oxaliplatin, and paclitaxel (GOP), which can also result in some durable CRs [18]. However, a more common approach seems to be initial salvage HDCT with ASCT.

A lack of phase III studies demonstrating the superiority of any one conventional-dose regimen has led to variation in practice. Nevertheless, TIP appears to be the most commonly used regimen, perhaps because no study has yet to report a higher durable remission rate than the MSKCC TIP series and given the study of GIP did not meet its primary endpoint [17].

4. Salvage High-Dose Chemotherapy

The concept of HDCT stemmed from work in the 1980s, demonstrating that tumor cell resistance acquired after therapy with alkylating agents could be overcome by dose intensification (e.g., increase in dose by multiples of 5–10). To avoid the need for direct bone marrow harvest, growth factor support, typically G-CSF with or without chemotherapy, is used to disrupt adhesions between hematopoietic stem cells (HSCs) and stromal cells in the bone marrow, releasing HSCs into the vasculature for collection.

An early report by Nichols et al. demonstrated the potential for HDCT to salvage some patients with relapsed GCT but at the cost of significant toxicity, including treatment-related mortality (TRM) [19]. With improved supportive care measures, four modern studies provide robust evidence of clinical benefit with salvage HDCT with limited TRM (Table 2) [7–9, 20]. In a retrospective study at IU [7], 184 consecutive patients with testicular or retroperitoneal primary GCT underwent two cycles of high-dose carboplatin and etoposide, each followed by ASCT. Carboplatin dose was calculated using body surface area (BSA), and patients in remission after HDCT received adjuvant oral etoposide for 3 months. At median follow-up of 48 months, 116 (63%) patients had a durable CR with 5-year OS of 65%. Notably, patients with PM-NSGCT and late relapse were excluded from this series.

MSKCC investigators reported outcomes with the TI-CE regimen within a prospective phase I/II trial of 107 patients with relapsed/refractory GCT and unfavorable

Table 2: Studies examining the use of high-dose chemotherapy as initial (or later) salvage therapy.

Author (Year)	Study design	N	Notable I/E criteria	Median f/u (m)	HDCT as initial salvage	HDCT regimen	Cycles	Durable CR	OS
Einhorn et al. [7]	Retrospective	184	I: None E: PM-NSGCT and late relapse	48	73%	Carboplatin 700 mg/m^2 (d 1–3) Etoposide 750 mg/m^2 (d 1–3)	2	58% 2-year DFS	65% at 5 years
Feldman et al. [8]	Prospective, phase I/II	107	I: ≥1 adverse prognostic feature for salvage CDCT[a] E: None	61	76%	Part A (TI): Paclitaxel 200 mg/m^2 (d 1) Ifosfamide 2000 mg/m^2 (d 1–3) Part B (CE): Carboplatin AUC 7-8 (d 1–3) Etoposide 400 mg/m^2 (d 1–3)	2 3	48% 5-year DFS	52% at 5 years
Lorch et al. [20]	Prospective, randomized phase III	211	I: None E: None	90	86%	Arm A: VIP Carboplatin 500 mg/m^2 (d 1–3) Etoposide 500 mg/m^2 (d 1–3) Arm B: VIP Carboplatin 550 mg/m^2 (d 1–4) Etoposide 600 mg/m^2 (d 1–4) Cyclophosphamide 1600 mg/m^2 (d 1–4)	1 3 3 1	52% 2-year PFS 47% 2-year PFS	50% at 5 years 40% at 5 years
Adra et al. [9]	Retrospective	364	I: None E: Late relapse	40	83%	Carboplatin 700 mg/m^2 (d 1–3) Etoposide 750 mg/m^2 (d 1–3)	2	60% 2-year PFS	66% at 2 years

I, inclusion; E, exclusion; HDCT, high-dose chemotherapy; f/u, follow-up; m, months; CR, complete response; OS, overall survival; PM-NSGCT, primary mediastinal nonseminomatous germ cell tumor; d, day; DFS, disease-free survival; AUC, area under the curve; PFS, progression-free survival; VIP, etoposide, ifosfamide, and cisplatin; [a]extragonadal primary site, incomplete response (IR) to first-line therapy, and PD after a salvage CDCT (cisplatin plus ifosfamide-based) regimen.

features for achieving a durable remission to CDCT including an extragonadal primary site, incomplete response to initial therapy or relapse/incomplete response to salvage CDCT [8]. Patients received two cycles of paclitaxel with ifosfamide every two weeks, followed by 3 cycles of high-dose carboplatin and etoposide every three weeks. In contrast to the IU study, carboplatin dose was based on area under the curve (AUC) instead of BSA and patients with late relapses and PM-NSGCT were eligible. Fifty percent ($n = 54$) of patients achieved a CR and 8% ($n = 8$) achieved a PR-negative marker response. At median follow-up of 61 months, 5-year disease-free survival (DFS) and 5-year OS were 47% and 52%, respectively. When only patients who would have met the criteria for HDCT at Indiana University were considered, the 5-year DFS and OS improved to 57% and 62%, respectively [8]. In addition, the data demonstrated that patients with late relapse and PM-NSGCT remain potentially curable with salvage HDCT, albeit with a lower probability.

The IU group recently reported on another 364 patients treated with salvage HDCT and ASCT between 2004 and 2014 [9]. A notable difference from their prior series was inclusion of patients with PM-NSGCT; patients with late relapse were still excluded. Treatment was identical to the prior IU series with two consecutive courses of 700 mg/m^2 carboplatin and 750 mg/m^2 etoposide daily for 3 consecutive days, followed by ASCT. Maintenance oral etoposide was administered to 134 patients who achieved a CR, of whom 105 received three cycles. With median follow-up of 3.3 years, the 2-year PFS and OS were 60% and 66%, respectively. Of 9 treatment-related deaths (2.5%), 6 occurred within 30 days of HDCT completion and three resulted from secondary leukemia. The authors acknowledged the potential for selection bias that is inherent within studies of HDCT-eligible populations.

The German Testicular Cancer Study Group compared sequential HDCT with single HDCT in 211 patients with relapsed or refractory GCT. Patients were randomized to one cycle of VIP plus three cycles of high-dose carboplatin and etoposide (arm A) or three cycles of VIP plus one cycle of high-dose carboplatin, etoposide, and cyclophosphamide (arm B), followed by ASCT. At a median of 7.5 years of follow-up, 5-year PFS and OS rates were 48% versus 46% and 50% versus 40%, respectively, for sequential and single HDCT, respectively. The 10% difference in 5-year OS, which almost reached statistical significance ($p = 0.057$) was attributed to the fewer treatment-related deaths in the sequential HDCT arm (4% versus 16%). When IPFSG scores were applied, the improved outcome with sequential HDCT was most prominent in IPFSG high-risk patients treated in the first salvage setting (3-year OS 56% versus 11%) and those attempting HDCT as second salvage (3-year OS 40% versus 20%) [20].

5. HDCT versus CDCT as First Salvage Therapy

Given the efficacy of both CDCT and HDCT in the salvage setting and in particular, the excellent outcomes with HDCT for patients with unfavorable features, several

Table 3: Studies comparing the use of conventional-dose chemotherapy with high-dose chemotherapy as initial salvage therapy.

Author (Year)	Study design	Notable I/E criteria	Treatment regimen	NCDCT versus HDCT	Median f/u	PFS/EFS	OS
Beyer et al. [21]	Retrospective matched-pair analysis[a]	I: NSGCT only E: Pure seminoma	CDCT: Any HDCT: VIP × 2–3 then 1 cycle ICE	55[b] 55[b]	7.5y & 9y[c] 5y	HR 0.72–0.84[d]	HR 0.77–0.83[d]
Pico et al. [24]	Phase III randomized (IT-94)	I: none E: IR to first-line therapy; pure seminoma treated with carboplatin	CDCT: VIP or VeIP × 4 HDCT: VIP or VeIP × 3 then CarboPEC × 1	128 135	45 months	35% at 3y 42% at 3y	47% 47%
Lorch et al. [20]	Retrospective, including IPFSG subgroup analyses	I: ≥3 cycles of EP-based CT E: cisplatin-refractory disease[e]	CDCT: Any HDCT: ≥1 cycle carboplatin + etoposide ± ifosfamide, thiotepa, or cyclophosphamide	773 821	58 months	HR 0.44[d]	HR 0.65[d]

I, inclusion; E, exclusion; CDCT, conventional-dose chemotherapy; HDCT, high-dose chemotherapy; f/u, follow-up; PFS, progression-free survival; EFS, event-free survival; OS, overall survival; NSGCT, nonseminomatous germ cell tumor; VIP, etoposide, ifosfamide, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; y, years; HR, hazard ratio; CarboPEC, carboplatin, etoposide, and cyclophosphamide; IPFSG, International Prognostic Factor Study Group; [a]matching factors: primary tumor location, response to first-line treatment, duration of response, HCG and AFP levels; [b]fifty-five pairs of patients had full matches on >4 of 5 factors; [c]median follow-up for patients treated at Medical Research Council and Munich, respectively; [d]hazard ratio(s) favoring HDCT; [e]progression within 4 weeks of the first-line cisplatin-based regimen.

studies have attempted to compare these two strategies to establish the optimal initial salvage approach (Table 3). In the first study to address this question, Beyer et al. conducted a retrospective, matched pair analysis comparing initial salvage HDCT and CDCT [21]. Fifty-five pairs of patients with relapsed/refractory NSGCT treated with either initial salvage CDCT or HDCT between 1981 and 1995 had full matches on at least 4 of 5 selected prognostic factors (primary tumor location, response to first-line treatment, duration of response, and serum AFP and serum HCG). Hazard ratios favored HDCT for both event-free survival (EFS; 0.72–0.84) and OS (0.77–0.83). Results remained consistent when restricting analysis to those who received both etoposide and cisplatin as initial therapy. Limitations were acknowledged, including the fact that CDCT patients were treated at multiple institutions as part of a cooperative group trial and from earlier time points, in contrast to HDCT, where patients were treated at a single center and more recently. These differences were previously demonstrated to be of prognostic significance [22, 23]. Furthermore, 18% of CDCT patients did not receive etoposide in their first-line regimen and not all patients received ifosfamide during salvage CDCT. Finally, selection bias leading to patients with better performance status or fewer comorbidities receiving initial salvage HDCT could not be excluded. Collectively, these weaknesses may overinflate the differences favoring HDCT.

In the only randomized phase III study to address this question, a multi-institutional European trial (IT-94) compared four cycles of VIP or VeIP (arm A) with three such cycles followed by one cycle of high-dose carboplatin, etoposide, and cyclophosphamide with ASCT (arm B) [24]. Of 263 eligible patients, 128 and 135 patients were randomized to arms A and B, respectively, with 103 (80%) and 98 (73%) receiving all four chemotherapy cycles, respectively. Among evaluable patients, objective response (OR) rates after 4 cycles were 67% versus 75% ($p = 0.23$). At median follow-up of 45 months, there was no significant difference in EFS or OS, though there was a significant difference in 3-year EFS (55% versus 75%) favoring HDCT among patients achieving a CR. Although the authors concluded that IT-94 demonstrated no clinical benefit with initial salvage HDCT, there are several notable limitations of this study. Accrual was lower than expected with early stoppage of the study negatively impacting the statistical power. Only a single (rather than sequential) HDCT cycle was administered as part of arm B and 27% of patients randomized to HDCT did not receive the fourth (high-dose) cycle. Mortality was also higher than expected at 7% for Arm B (versus 3% for Arm A), potentially obscuring any benefit with HDCT. Furthermore, patients with incomplete response to initial therapy were excluded, a group more likely to benefit from HDCT given historically poor outcomes with salvage CDCT.

In light of these limitations and the small size of the prior Beyer-matched pairs analysis, Lorch et al. used the IPFSG database to retrospectively compare initial salvage HDCT and CDCT among 1594 patients with progression after at least three cisplatin-based cycles in the first-line setting. Two-year PFS was significantly superior after HDCT ($n = 821$) compared with CDCT ($n = 773$), both overall (50% versus 28%, $p < 0.001$) and within each IPFSG risk category. There was also a significant improvement in 5-year OS (53% versus 41%, $p < 0.001$) favoring initial salvage HDCT, overall, and within each IPFSG subgroup with the exception of low-risk patients. Despite the benefit observed for HDCT, numerous biases were acknowledged including patient selection bias (given the nonrandom treatment allocation) potentially favoring HDCT, wide variation in the CDCT regimens used, with some possibly inferior to others (e.g., TIP), and potential investigator bias in considering patients to progress earlier with CDCT than HDCT. Given the inherent methodological limitations of this retrospective, albeit large analysis, this study does not definitively prove the superiority of HDCT over CDCT, but rather underscores the

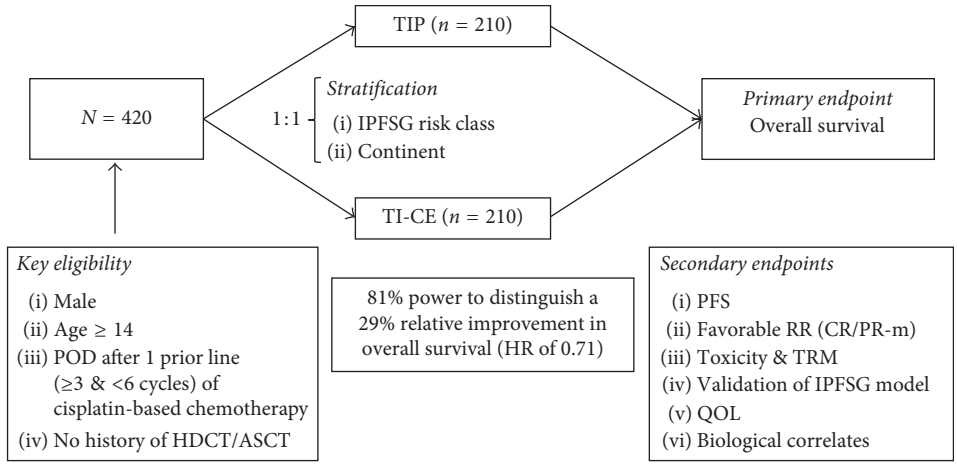

Figure 1: Study design of the TIGER trial (Alliance 0311012; EORTC 1407). POD, progression of disease; HDCT/ASCT, high-dose chemotherapy with autologous stem cell transplant; TIP, paclitaxel, ifosfamide, and cisplatin; TI-CE, paclitaxel and ifosfamide followed by high-dose carboplatin and etoposide; IPFSG, International Prognostic Factors Study Group; PFS, progression-free survival; response rate; CR, complete response; PR-m, partial response with normal tumor markers; TRM, treatment-related mortality; QOL, quality of life.

need for a prospective randomized trial to compare a highly effective CDCT regimen (TIP) to a sequential HDCT regimen (TI-CE), and this ultimately formed the foundation of the TIGER trial.

6. The TIGER Trial

The TIGER trial (A031102, E1407) is an international collaboration among many centers in North America, Europe, and Australia with the goal of determining the optimal initial salvage chemotherapy approach in patients with advanced GCT. Patients with unequivocal disease progression after a minimum of 3 and no more than 6 cisplatin-based chemotherapy cycles, administered in the first-line setting, are randomized 1:1 to receive CDCT with TIP (control arm) or HDCT using TI-CE (experimental arm) as illustrated in Figure 1. The primary endpoint is OS, with secondary endpoints including PFS, favorable response rate, toxicity, quality of life, and biological correlates. Patients will be stratified by a modification of their IPFSG category into low-, intermediate-, and high-risk groups, with prospective evaluation of outcomes by risk group. With a target accrual of 420 patients, the study is powered to detect a 29% difference in OS between the two arms. The study is ongoing and as of 11/1/2017 has accrued 67 (16%) patients. Results are anxiously awaited and will hopefully definitively establish either HDCT or CDCT as the standard of care in the initial salvage setting.

7. Conclusion

Both CDCT and HDCT have curative potential in the salvage management of relapsed/refractory GCT. Common salvage CDCT regimens include VeIP, TIP, and GIP, with no randomized data establishing one clearly superior regimen, although the best results reported to date are with TIP, albeit in a favorably selected patient population. Salvage HDCT regimens can achieve durable remissions even in patients with unfavorable characteristics with low TRM. As a result of conflicting data from retrospective series suggesting improved outcomes with HDCT and the IT-94 randomized study demonstrating no benefit to HDCT over CDCT, the optimal initial salvage approach remains unclear with practices varying widely around the world. The global cooperative group-led TIGER trial (A031102, E1407) is testing TIP versus TI-CE in this setting and seeks to definitively answer this important question.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Immune-Related Concepts in Biology and Treatment of Germ-Cell Tumors

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Germ-cell tumors (GCTs) are highly curable with chemotherapy. Salvage chemotherapy or surgery can cure a proportion of patients, but the ones failing these treatments will die of their disease in the young age. Immune checkpoint pathways are emerging as powerful targetable biomarkers, and a significant preclinical and clinical research is underway to widen our knowledge and expand the treatment possibilities with immune therapy. The concept of immune modulation that was currently adopted in many solid tumors is understudied in GCTs. Herein, we summarize the current knowledge of published literature discussing the immune mechanisms and immune therapy in GCTs.

1. Introduction

The success story of curing germ-cell tumors (GCTs) established a cisplatin-based chemotherapy as a mainstay for achieving >95% relative overall survival rate [1]. Unfortunately, chemotherapy is not a universal cure for all patients with metastatic disease. About 40–80% of patients with relapse after initial chemotherapy will fail the salvage treatment, and their prognosis is dismal [2–4]. Researchers have spent limitless effort to further advance the anticancer treatment with the most recent substantial achievement being the discovery of modern immune therapy in numerous solid cancers. GCTs are traditionally referred to as "a model for cure" with chemotherapy; however, a scientific inquiry has risen, whether the immune mechanisms may be as important in GCTs as it is in melanoma, lung cancer, kidney cancer, or others. The failure of chemotherapy in substantial proportion of GCT patients creates a therapeutic dilemma for many decades with no major advancement since the introduction of the salvage chemotherapy. Therefore, the question whether immunity plays a significant role in the pathogenesis of GCTs is critical to answer, allowing to derive implications for future development in the treatment of this unique solid malignancy. Herein, we summarize the current knowledge of the literature to provide the insights into the immune biology of GCTs.

2. Literature Search

We performed a literature search of the PubMed/Medline database and meeting libraries of American Society of Clinical Oncology (ASCO) and ASCO Genitourinary Cancers Symposium for publications with the terms "testicular germ cell tumors," "immunity," "immune," "immunotherapy," "tumor infiltrating lymphocytes," "TIL," "inflammation," "cytokines," "check-point." Combinations of these key words were used for comprehensive search as outlined in Figure 1. The search of literature was performed on September 1, 2017. Original full-text articles published in English were reviewed, and the reference lists of key articles were further evaluated. We did not limit our search by the years of publication. Our search was conducted according to the Preferred Reporting Items for

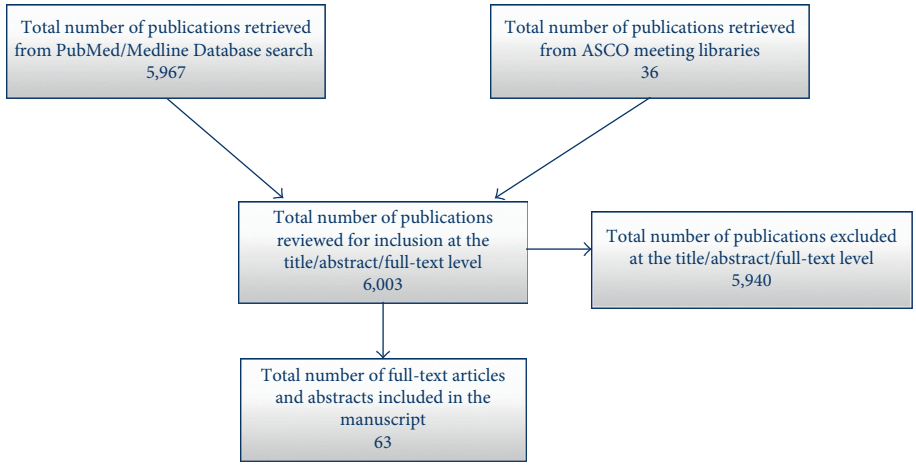

Figure 1

Systematic Review and Meta-Analysis (PRISMA) statement. Identified reports were reviewed according to the Consolidated Standards of Reporting Trials (CONSORT) criteria. The search resulted in overall 6003 publications. Sixty-three publications were selected for inclusion in our review article. The outline of the literature search is summarized in Figure 1.

3. Immune-Cell Infiltration, Cytokine Signaling, and Genomic Underpinnings

The observation of immune reaction induced by GCTs evidenced by lymphocytic and granulomatous intratumoral infiltrates dates as early as 1964 and was published by Marshal and Dayan from Bernhard Baron Institute of Pathology in London [5]. Rich infiltration with immune cells in testicular GCTs, particularly in seminomas, was observed by number of other earlier studies [6–11], suggesting an involvement of the immune system in GCT biology. The immune-cell characterization of seminoma by Bols et al. has shown tumor infiltrating lymphocytes (TILs) that included CD3+ and T-memory cell populations, while B-cells and plasma cells were present less frequently. Seminoma in situ (germ-cell neoplasia in situ adjacent to seminoma) was infiltrated mainly by CD4+ and CD8+ TILs and then followed by B-cells, dendritic cells, NKcells, and macrophages. This study was also among the first ones to provide data about prognostic significance of TILs, where authors showed that lower TIL count was associated with the risk of relapse [9]. Hvarness et al. provided similar observation of immune microenvironment in germ-cell neoplasia in situ describing macrophages, CD8+T-cells, CD450R0+ T-cells, and B-cells present in the GCNIS tissue [12]. T-lymphocytes and macrophages were also documented in an embryonal carcinoma [8]. Further observations presented data of characteristic cytokine signaling encompassing tumor tissue with immune-cell infiltrates. Klein and colleagues observed a presence of B-cells and dendritic cells in GCNIS, accompanied by high level of transcripts of several proinflammatory (IL6, IL-1β, and TNF-α), anti-inflammatory (TGF-β1), Th1-driven (IL-2 and IFN-γ) cytokines, and chemokines (CXCL-13, CXCL-10, and CCL-5) [13]. In vitro experiments were conducted on seminoma-derived T-cam2 and peripheral blood mononuclear cell (PBMC) coculture. PBMC exhibited a robust increase in the production of IL1β, TNF-α, TGF-β, and CCL5 transcript levels after direct, but not after indirect, contact with T-cam2 cells. PBMC previously stimulated with the mitogen phytohemaglutinin also exhibited significantly higher expression of IL-1β, IL-6, and IFN-γ. Moreover, authors provided surprising observation of the natural production of IL-6 by T-cam2 cell lines [14]. A specific cytokine signature was also observed as a response to murine testicular teratoma. Two cytokines, IL-6 and IL-10, were the most abundant allowing for subsequent promotion of humoral immune response [15]. Cytokine signatures observed to date position IL-6 signalling as one of the proposed central proinflammatory mechanisms in GCTs. Furthermore, a study by Purdue et al. that evaluated single nucleotide polymorphisms (SNPs) in immune function genes uncovered that SNPs in *TGFB*1, *LTA/TNF*, and others (*IL2*, *IFNGR*2, and *IL*10) may be responsible for an increase in the susceptibility for GCTs [16]. Recent study described distinct molecular signatures of immune cells specifically for seminoma showing elevation of expression signatures for B-cells, cytotoxic T-cells, Th17 cells, and T-regulatory cells (T-reg). This increase was associated with an increase in specific cytokines and immune checkpoints (CTLA4, LAG3, and PD-L1). Interestingly, there was no correlation between immune cells and load of mutations, neoantigens, or detected viruses, which confirms observations obtained from TCGA (The Cancer Genome Atlas) datasets [17–19]. The strongest association of growth in immune-cell populations was observed with activating mutations in *KIT* together with increased expression profiles of *KIT* and *MHC class I* and *II* genes [17]. Another in vitro study tried to address IFN-γ produced by GCT cells (NTERA and NCCIT cell lines) as a potential treatment target by a specific blocking antibody but found that autocrine production of IFN-γ was insufficient to utilize the signaling blockade in favor of the cell inhibition [20].

However, the question of the specific role of immune surveillance in GCT development remains open. Authors from Denmark assessed the immune-cell infiltrate phenotype

in GCNIS versus normal tissue and infertile testicular tissue and did not find differences in immune infiltrating cells in this region. Authors, thus, speculated that immune surveillance is not the critical factor for germ-cell development [12]. According to another study evaluating canine seminomas, T-reg TILs did not prove the critical role in the immune response in canine seminoma [21]. Androgen receptor mutation specific to Sertoli cells was discovered to result in loss of testicular immune privilege, a physiological barrier to prevent an immune response against germ-cell antigens. The experiment was performed on Sertoli cell-specific androgen receptor mutant mice, who exhibited higher intratesticular levels of IgG as compared with nonmutant mice, subsequently resulting into infertility [22]. It is not clear how this observation may fit into pathogenesis of GCTs. However, assessing the androgen-receptor associated signaling in patients with GCTs may shed more light into immune surveillance and its errors in patients with metastatic disease. Interesting observations were done in several studies showing that the incidence of GCTs significantly increases in the population of acquired immunodeficiency syndrome (AIDS) patients [23–25]. The number of events from these studies prevents from the conclusion whether acquired immunodeficiency alters GCT-specific survival in this patient population. Nevertheless, the raise in incidence of GCTs may provide indirect indications of the role of overall immune health in this disease development.

4. Immune-Related Biomarkers in GCTs

Despite the fact that we are not able to clearly assess the role of the immune surveillance in the development of GCTs, the prognostic role of TILs is clear. Data regarding new biomarkers, such as immune checkpoints, started to emerge recently as a result of astonishing clinical achievements of immune checkpoint inhibition in various malignancies.

Kersemaekers et al. suggested that FAS/FASL apoptotic signaling in GCT TILs may be a contributing factor to GCT development [26]. Another similar study by Schmelz, however, failed to replicate these results [27]. One of the new promising targets in different types of tumors is programmed-death-1 receptor (PD-1; CD279) and its ligand (PD-L1; B7-H1; CD274), which deliver inhibitory signals that regulate the balance between T-cell activation, tolerance, and immune-mediated tissue damage [28]. PD-1 is a member of the immunoglobulin superfamily and is expressed on double-negative T cells in thymus and on activated CD4+ T-cells, CD8+ T-cells, natural killer cells, B-cells, and monocytes [29]. It is primarily involved in modulating T-cell activity in peripheral tissues through interaction with its ligands PD-L1 and PD-L2 [9]. PD-L1 is expressed in different organs, including placenta, heart, lung, and liver as well as on activated T-cells, B-cells, dendritic cells, macrophages, and mesenchymal stem cells [30].

PD-L1 is expressed also on various tumor cells [29]. Expression of PD-L1 is an important process by which tumor cells suppress antitumor immunity in the tumor microenvironment [31]. Prognostic significance of PD-L1 expression on tumor cells was described in various malignancies [32–37], and the inhibition of PD-1/PD-L1 interaction has become an important landmark in cancer treatment. PD-1 and PD-L1 blocking antibodies have demonstrated clinical activity in several types of cancer including melanoma, nonsmall-cell lung cancer, renal cell cancer, ovarian cancer, and head and neck cancers [38].

The discovery of the PD-1 receptor and its ligand inspired Fankhauser et al. to conduct the first study in GCTs, which described the abundant expression of PD-L1 in seminoma and nonseminoma [39]. Our study explored the prognostic significance of PD-1/PD-L1 pathway in 140 patients with GCTs. We observed abundant expression of PD-L1 but not PD-1 on tumor cells and TILs (expressed in reverse manner on tumor and TILs) that correlated with poor risk clinical characteristics and survival. The low versus high expression of PD-L1 in tumor was associated with better survival (HR = 0.43; 95% CI 0.15–1.23; $P = 0.04$ for OS) [40]. In contrast, high PD-L1 on TILs correlated with better survival (HR = 0.08; 95% CI 0.04–0.16; $P = 0.001$ for OS). Based on these results, we developed a prognostic tool using PD-L1 on tumors and TILs independently of International Germ Cell Cancer Collaborative Group (IGCCCG) criteria [41]. Siska et al. performed a deep exploration of immune infiltrates in GCTs by immunohistochemistry and gene expression profiling and identified that activated T-cell infiltration correlated with seminoma and good prognosis. Advanced GCTs were associated with decreased T-cell and NK-cell signatures, while T-regs, mastocytes, and macrophages proved to be activated in patients with advanced stage disease. Authors also observed increased PD-L1 signalling in seminomas compared with nonseminomas using immunohistochemistry [42]. A study conducted on 102 patients from Japan evaluated the prognostic role of tumor-infiltrating neutrophils (TIN) by assessing CD66b+ TIN and found that they correlated with nodal and distant metastases, S stage, and nonseminoma histology. CD66b+ TIN were prognostic for progression-free and overall survival ($P < 0.05$ for both) [43]. The presence of inflammation in the cancer microenvironment may be identified with a simple clinical tool, the systemic immune inflammation index (SII), calculated as platelets × neutrophils/lymphocytes from the peripheral blood smear. SII proved to predict prognosis in several malignancies [18–22]. Chovanec et al. assessed the prognostic significance of SII in 240 GCT patients and discovered statistically significant differences in PFS and OS. Patients with lower levels of systemic inflammation, represented by lower SII, had significantly better prognosis compared with patients with high SII [44]. Preclinical research initiative by Terayama et al. aimed to evaluate testicular germ-cell specific autoimmunogenic antigens (AIs) in experimental mice with autoimmune orchitis. Authors immunized the serum of these mice with germ cells (nonmalignant), observing 11 specific AIs as a result. The results led to a speculation that these testis-specific AIs may provide a substrate for future research in targeting GCT novel targets [45]. The discovery of toll-like receptors (TLRs) has contributed to the expanding knowledge about the innate immune system. TLRs were proposed to contribute to cancer development [46]. TLRs 2, 3, 4, and 9 are expressed in testicular and GCT tissues; however, the expression in cancer tissue is significantly stronger [7]. Lin et al. published findings from a preclinical therapeutic

trial in a mouse model using a conjugate of toll-like receptor 7 (TLR7) and OCT4. Mice were immunized with this novel agent and were subsequently challenged with the mouse embryonal carcinoma. Treatment with the conjugate resulted in significant release of IL12 and IFN-γ in vitro, and the significant increase in CD3+/CD8+ T cells occurred in vivo. Moreover, the rate of cytotoxicity in immunized mice was significantly higher, while the tumor growth decreased by 90% compared to the controls treated with OCT4 or TLR7 alone [47]. While experiments with animal models including animal cancer are difficult to interpret in the context of human biology, this study provides a pilot data of GCT immunogenicity. Vaccination with inhibin alpha was assessed and was effective against stromal cell tumors in preclinical in vitro and autochtonous mouse models but did not exhibit efficacy in GCTs [48]. Schreck et al. published an interesting observation of the loss of activation-induced cytidine deaminase (AID) in GCNIS and GCTs compared to the normal spermatocytes [49]. AID is normally involved in class-switch recombination of immunoglobulin genes in antigen-dependent B-cell maturation, suggesting that immune escape may be a mechanism participating in GCT development. This interpretation, however, may be biased and more studies are needed for validation.

5. Patterns in Cytokine and Immune-Cell Response to GCT and Its Treatment

Our research initiative investigated the patterns of cytokine signalling in peripheral blood in 79 patients with GCTs unveiling specific patterns in seminoma versus non-seminoma, nonpulmonary visceral metastases, and cerebral metastases and administered chemotherapy corresponded with the decline in the proinflammatory signature [50, 51]. These patterns generally suggest the tumor proangiogenic activity, the inhibition of immune response by low T- and NK-cell stimulation, the inhibition of T- and B-cell maturation, and the inhibition of chemoattraction and phagocytosis. The simultaneous immune stimulation and immune inhibition observed in our study was also described previously [51–53]. Further research has shown that increased pre-chemotherapy levels of cytokines promoting angiogenesis, tumorigenesis, immune stimulation, and chemoattraction correlated with shorter PFS and OS in 92 GCT patients [54]. Investigators from the University of Birmingham also observed a spontaneous CD4+ and CD8+ T-cell responses against cancer testis antigen in peripheral blood of patients with GCTs. The frequency of these T-cells substantially declined (by 89%) following orchiectomy for stage I GCTs [55].

6. Immune Therapy Efficacy and Clinical Trials

Early immunotherapy trials date to 1970s and 1980s. Undeniable efficacy of high-dose (HD) IL2 and HD IFN-α in selected patient population led to establishment of these treatments in malignant melanoma and kidney cancer. Anecdotal evidence existing in GCT patients is included in these clinical trials. The review summarized by Rosenberg et al. mentions 1 patient treated with HD IL2 + IFN- α and 1 patient treated with HD IL2 + lymphokine activated killer cells. No response was observed in either of them [56]. The concept of immune therapy has been abandoned or has never truly arisen because the excellent sensitivity of cisplatin-based chemotherapy provided substantially more powerful treatment results compared to other solid malignancies. Recent development of new biomarkers and novel immune therapies, however, raised questions, whether refractory GCTs may be candidates for immune checkpoint inhibition. A single-arm phase II study by Adra et al. from Indiana University recruited 12 patients with refractory GCTs to be treated with anti-PD1 inhibitor pembrolizumab. Although transient declines in tumor markers were noted in few cases, none of the patients had a radiographic response or a stable disease with this treatment [57]. Contradictory data to this trial exist from several case reports with platinum refractory GCTs treated with anti-PD1 agents (pembrolizumab or nivolumab) after salvage HD chemotherapy. These case reports describe possible responses in 3 out of 7 patients [58–60]. However, the interpretation of anti-PD1 treatment efficacy in these cases may be biased, as one of the patients received concomitant etoposide and the other two had only a short-term response to nivolumab. A single case report by Chi et al. provided evidence of ongoing partial remission with marker stabilization after treatment with nivolumab [61]. Based on the data from biomarker studies mentioned earlier in the article, we hypothesize that anti-PD-L1 treatment is more promising for patients with refractory GCTs and phase II trial with anti-PD-L1 inhibitor avelumab is being currently opened in Slovakia (NCT number not assigned yet). Another mechanism may be involved in immune regulation of GCTs, as proposed by Albany et al., who assessed guadecitabine, a demethylation agent, combined with cisplatin to reestablish a platinum sensitivity. A genome-wide analysis from their preclinical findings has shown that response to treatment was accompanied by activation of p53 together with the presence of immune-related pathways [62]. A phase I/II clinical study evaluating guadecitabine plus cisplatin in refractory GCTs is currently underway (NCT02429466).

7. Conclusion

GCTs and the immunity remains an understudied area. Existing evidence suggests active participation of immune system in the response to the presence of GCT and a certain level of evidence suggests its involvement in GCT development as well. Powerful biomarkers, such as PD-L1, TILs, and TLRs, are perhaps among first key elements to provide deep insight into GCT immune regulation and may certainly serve as reasonable treatment targets for future clinical trials.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Review Article

Dissecting the Evolving Risk of Relapse over Time in Surveillance for Testicular Cancer

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Testicular cancer is the most common malignancy in young men, and the incidence is increasing in most countries worldwide. The vast majority of patients present with clinical stage I disease, and surveillance is being increasingly adopted as the preferred management strategy. At the time of diagnosis, patients on surveillance are often counselled about their risk of relapse based on risk factors present at diagnosis, but this risk estimate becomes less informative in patients that have survived a period of time without experiencing relapse. Conditional survival estimates, on the other hand, provide information on a patient's evolving risk of relapse over time. In this review, we describe the concept of conditional survival and its applications for surveillance of clinical stage I seminoma and nonseminoma germ cell tumours. These estimates can be used to tailor surveillance protocols based on future risk of relapse within risk subgroups of seminoma and nonseminoma, which may reduce the burden of follow-up for some patients, physicians, and the health care system. Furthermore, conditional survival estimates provide patients with a meaningful, evolving risk estimate and may be helpful to reassure patients and reduce potential anxiety of being on surveillance.

1. Testicular Cancer Epidemiology

Testicular cancer is the most common malignancy in men aged 20–34 years, with an estimated 8850 new cases being diagnosed in the United States in 2017 [1]. The incidence of testicular cancer is increasing worldwide and is thought to be related to improved detection, better collection of information in databases, and increased exposure to environmental carcinogens [2]. Germ cell tumours comprise the predominant histology in testicular cancer [3] and are broadly categorized into seminoma and nonseminomatous germ cell tumours (NSGCT) due to differences in management and prognosis. The vast majority of patients with germ cell tumours present with localized disease (stage I), defined as disease without retroperitoneal or distant metastasis [4]. The 5-year cause-specific survival for patients with stage I seminoma or NSGCT is over 99% [5, 6]. Given the excellent cure rates, the emphasis on managing stage I disease has shifted towards reducing treatment-related burden.

2. Progression following Orchiectomy for Clinical Stage I Germ Cell Tumours

Approximately 70% and 85% of patients with clinical stage I NSGCT and seminoma, respectively, will be cured by orchiectomy alone [6–8]. However, given the potential for disease progression, some advocate primary adjuvant treatment and highlight the benefit of avoiding a more intense salvage regimen in those that do relapse. Conversely, others advocate surveillance and emphasize that the majority of patients can be spared the potential short- and long-term complications of primary adjuvant treatment. As this debate continues, some have adopted a risk-adapted approach, and in this section, we review factors associated with disease progression on surveillance.

The largest series to date evaluating surveillance for clinical stage I NSGCT is a population-based cohort study from Denmark [7]. This study by Daugaard et al. included 1226 patients; however, data were complete in only 499

patients. They performed a multivariable analysis that only included variables found to be significant at the 5% level in the univariate analysis, which were elevation of hCG, presence of vascular invasion, invasion of rete testis, tunica albuginea, or epididymis, and presence of embryonal carcinoma, yolk sac tumour, choriocarcinoma, or teratoma. In patients with complete data, they found that the presence of embryonal carcinoma (hazard ratio 3.85, 95% confidence interval 2.03 to 7.32), lymphovascular invasion (hazard ratio 2.20, 95% confidence interval 1.64 to 2.99), which stages a patient at T2 and clinical stage IB as opposed to T1 and IA, and rete testis invasion (hazard ratio 1.47, 95% confidence interval 1.10 to 1.98) was significantly associated with relapse-free survival. Several other studies have demonstrated the prognostic significance of lymphovascular invasion [6, 9–11] and embryonal carcinoma, though for the latter, it is controversial whether only the presence is necessary [7] or whether it needs to be predominant [11] or pure embryonal carcinoma [9]. There has been concern regarding the generalizability of using predominant embryonal carcinoma as a prognostic factor, given the potential for interobserver and tumour sampling differences [9]. Conversely, rete testis invasion has not been identified as a prognostic factor in other studies, and further studies are needed to validate the findings of Daugaard et al.

In surveillance for clinical stage I seminoma, tumour size has been identified as a risk factor for disease relapse, though this is not considered as validated as lymphovascular invasion is for NSGCT. A study that pooled data from four institutions used changes in the statistical model fit by evaluating the likelihood ratio statistic to select variables for the final multivariable model [12]. This study did not explicitly state which variables were included in the final multivariable model; however, candidate variables included age, tumour size, rete testis invasion, small vessel invasion, and histologic subtype (classical versus anaplastic). In the multivariable analysis of the 453 patients with complete data, this study found that tumour size > 4 cm in greatest diameter (hazard ratio 2.0, 95% confidence interval 1.3 to 3.2) and rete testis invasion (hazard ratio 1.7, 95% confidence interval 1.1 to 2.6) were independent prognostic factors for relapse on surveillance. The 4 cm cut point was based on the median tumour size in this patient population.

A subsequent study [13] sought to validate prognostic factors in surveillance for clinical stage I seminoma and used data from three institutions, two of which were not part of the prior study. The median tumour size in this study was 3 cm. This study does not explicitly describe which variables or the number of patients that were included in the multivariable model; however, they found that tumour size ≥ 3 cm (hazard ratio 1.87, 95% confidence interval 1.15 to 3.06) was associated with relapse, but rete testis invasion was not (hazard ratio 1.36, 95% confidence interval 0.81 to 2.28). As such, the independent role of rete testis invasion for disease relapse in clinical stage I seminoma remains controversial, while tumour size has generally become accepted as a risk factor. While dichotomizing tumour size facilitates categorizing patients into risk subgroups, the association of tumour size on relapse likely represents a continuum of risk. Indeed, the same study provides a table demonstrating the rising risk of relapse with increasing tumour sizes. Interestingly, the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual now stratifies T1 seminoma based on tumour size ≥ 3 cm [14], and this stratification was not present in prior editions [15].

3. Guideline Recommendations for Management of Clinical Stage I Germ Cell Tumours

Several guidelines describe treatment options for clinical stage I germ cell tumours, including those from the Canadian Urological Association [16], the European Association of Urology [17], the National Cancer Comprehensive Network [18], the European Society of Medical Oncology [19], and others [20–23]. To date, there are no guidelines from the American Urological Association on the management of testicular cancer. Although guidelines exist from other societies, in this section, we focus on these select few from major urologic and oncology groups.

For stage I seminoma, the Canadian Urological Association guidelines were published in 2010 and recommend surveillance as the preferred option for all patients [16]. When adjuvant therapy is chosen, radiotherapy and chemotherapy are options. A risk-adapted approach is not endorsed by the Canadian Urological Association guidelines. Conversely, the European Association of Urology guidelines [17], which are updated regularly with the most recent version published in 2017, describe that surveillance can be offered to all patients but go further and describe that patients without any risk factors for relapse, described in these guidelines as tumour size < 4 cm and no rete testis invasion, should not be offered adjuvant therapy. When adjuvant therapy is used, chemotherapy is an option, while radiotherapy should not be used. The National Cancer Comprehensive Network guidelines [18] are also updated regularly, most recently in 2017, and describe surveillance as the preferred option for patients with pT1–T3 clinical stage I seminoma, but specific recommendations are not given for pT4 tumours. The guidelines do not provide specific factors or scenarios to indicate when surveillance is not appropriate but mention that if adjuvant treatment is desired, either chemotherapy or radiotherapy is an option. A risk-adapted approach based on tumour size or rete testis invasion is explicitly not supported by the National Cancer Comprehensive Network guidelines. Finally, the European Society for Medical Oncology guidelines [19] were published in 2013 and describe a risk-adapted strategy based on tumour size > 4 cm and rete testis invasion, whereby high-risk patients, those with either risk factor, should preferentially be treated with surveillance or primary chemotherapy, with radiotherapy as an alternative, and low-risk patients should be preferentially treated with surveillance with chemotherapy and radiotherapy as alternatives.

For clinical stage I NSGCT, the Canadian guidelines [16] support surveillance for all risk groups. When adjuvant treatment is selected, retroperitoneal lymph node dissection (RPLND) and chemotherapy are options. The European

guidelines [17] describe a risk-adapted approach, whereby patients at low risk for progression (without lymphovascular invasion) should be preferentially offered surveillance, with chemotherapy as an alternative. For high-risk patients, chemotherapy should be used preferentially, with surveillance as an alternative. The role of primary RPLND in the European guidelines is restricted to highly selected patients such as those with a contraindication to adjuvant chemotherapy or unwilling to accept surveillance. A risk-adapted approach is also adopted by the National Cancer Comprehensive Network guidelines [18]; in patients without lymphovascular invasion, surveillance is the preferred approach with RPLND as an alternative. In patients with lymphovascular invasion, RPLND and chemotherapy are the preferred options, with surveillance not being recommended in this group of patients. The European Society for Medical Oncology guidelines [19] prefer surveillance for low-risk disease (absence of lymphovascular invasion), with chemotherapy and RPLND as alternatives, while for high-risk disease, surveillance and chemotherapy are preferred options, reserving RPLND for patients with contraindications to the previously described options.

Overall, there is clearly significant heterogeneity between the guidelines on the recommended management of clinical stage I germ cell tumours. While surveillance is generally either preferred or accepted for low-risk disease, the role of surveillance in high-risk disease falls along a spectrum ranging from outright recommendation for surveillance in high-risk patients (Canadian guidelines) [16] to discouraging surveillance in these patients (National Cancer Comprehensive Network guidelines) [18]. Nonetheless, all guidelines describe the importance of informing patients regarding the risks and benefits of the various treatment options, and ultimately, the patient should make the informed choice regarding the preferred management strategy.

4. Variations in Surveillance Schedules

From the guidelines described above, only those from the European Association of Urology [17] and the National Cancer Comprehensive Network [18] suggest schedules for surveillance.

For seminoma surveillance, the European Association of Urology guidelines [17] recommend tumour markers with or without a physician visit two times a year in years 1 to 3 and once a year in years 4 and 5. Abdominal imaging with CT or MRI is recommended two times a year in years 1 and 2, once at 36 months, and once at 60 months. Beyond 5 years, management is according to the survivorship care plan which should address lifestyle recommendations and recurrence risk, among other patient-specific factors.

The guidelines from the National Cancer Comprehensive Network [18] recommend a history and physical every three months in year 1 and every six months thereafter until year 5. In contrast to the European guidelines, tumour markers are considered optional. In terms of imaging, a chest X-ray is recommended every six months for the first 2 years. Abdominal imaging with CT is recommended at 3, 6, and 12 months and then annually in years 2 and 3. Follow-up after 5 years is at the discretion of the physician.

Neither guidelines from the European Association of Urology nor National Cancer Comprehensive Network recommend risk-adapted surveillance for seminoma.

Given the higher risk of progression for stage I NSGCT, both the European Association of Urology and the National Cancer Comprehensive Network recommend more intense follow-up on surveillance. The European Association of Urology guidelines [17] recommend tumour markers with or without a physician visit 4 times a year in years 1 and 2, two times a year in year 3, and one to two times a year in years 4 and 5. A chest X-ray is recommended two times a year in the first two years, and an abdominal CT scan or MRI is recommended two times in year 1 and at 24 months. There is debate as to whether additional abdominal imaging is needed later in follow-up, with 50% of the consensus group members supporting such imaging at 36 and 60 months. Although seminoma schedules were not risk adapted in the European guidelines, for nonseminoma with lymphovascular invasion, more intense surveillance is considered through more frequent assessments of tumour markers, physician visits, and chest and abdominal imaging. Beyond 5 years, further management is according to the survivorship care plan.

Similar to the European guidelines [17], the National Cancer Comprehensive Network guidelines also describe risk-adapted surveillance for nonseminoma [18], which is also based on the presence or absence of lymphovascular invasion. In both risk groups, the physician visits and tumour marker assessments are identical, being done every two months in year 1, every three months in year 2, every four to six months in year 3, every 6 months in year 4, and annually in year 5. Imaging, however, is more intense in those with lymphovascular invasion with a chest X-ray every two months in year 1, every three months in year 2, every four to six months in year 3, every six months in year 4, and annually in year 5, while in those without lymphovascular invasion, this schedule is at 4 and 12 months and then annually until year 5. Abdominal imaging is also more intense in the lymphovascular invasion group with imaging every four months in year 1, every four to six months in year 2, every six months in year 3, and annually in year 4. In those without lymphovascular invasion, this schedule is every four to six months in year 1, every six to twelve months in year 2, and annually in year 3. Follow-up after 5 years is at the discretion of the physician.

Some other differences between the European Association of Urology and National Cancer Comprehensive Network are worth noting. For example, the National Cancer Comprehensive Network guidelines consider pelvic imaging as optional, whereas it is recommended in the European Association of Urology guidelines. Furthermore, the use of magnetic resonance imaging is described as an alternative to computed tomography in the European Association of Urology guidelines but is not described in the National Cancer Comprehensive Network guidelines.

Not only are there differences between the guidelines on the intensity of surveillance schedules, but there even seems

to be a difference of opinions within members of the guideline consensus groups [17]. This is not surprising, given that there is minimal level 1 evidence supporting these recommendations. To date, there has been only one randomized study evaluating surveillance intensity for germ cell tumours. This study randomized 414 patients with clinical stage I NSGCT, with or without lymphovascular invasion, managed with surveillance to chest and abdominal CT scans at 3 and 12 months versus scans at 3, 6, 9, 12, and 24 months [24]. With a median follow-up of 40 months, there was no significant difference in relapse-free survival or disease-risk stage at relapse. A subgroup analysis in those with lymphovascular invasion demonstrated no significant difference in relapse-free survival between 2 versus 5 scans, but only approximately 10% of the population had this adverse prognostic factor, and the authors were cautious to conclude whether 2 scans were sufficient in this high-risk group.

Given the lack of level 1 evidence to guide surveillance schedules, observational studies on surveillance for clinical stage I germ cell tumours are the predominant source for recommendations. As described, risk-adapted surveillance schedules are supported by both the European and National Cancer Comprehensive Network guidelines for nonseminoma, but neither guideline adopts a risk-adapted approach for seminoma. Risk-adapted follow-up based on surgical pathology is commonly accepted in nonmuscle invasive bladder carcinoma, upper urinary tract urothelial cell carcinoma, and renal cell carcinoma [25–27]; similar strategies are feasible and should be implemented for clinical stage I germ cell tumours if the risk of relapse over time differs between risk groups.

5. Conditional Survival

At the time of diagnosis, patients are typically presented with their risk of experiencing an outcome, which can be described as a static, baseline risk. Though not often specified, this baseline risk should be associated with a specific time frame. To illustrate this concept (Figure 1), suppose two outcomes are considered, A and B, both of which occur in 40% of patients at 5 years. Outcome A occurs early with all events occurring within the first year, while outcome B only occurs after 3 years. While the baseline risk for outcomes at 5 years is equivalent, the baseline risk for outcomes at 2 years is 40% and 0% for outcomes A and B, respectively. This example demonstrates the importance of the time frame associated with outcome probabilities in survival models.

Conditional survival uses the timing of events to estimate the probability of the outcome, given that a patient has survived a period of time without experiencing the outcome of interest. In the same theoretical example, an individual who has not experienced outcome A by 2 years of follow-up can be considered to have a negligible risk for outcome A thereafter. Conversely, at 2 years, an individual is still at risk for outcome B. As illustrated, the relative importance of observing for outcome A or B changes over time, and it becomes evident that the static, baseline risk of relapse is not meaningful to a patient that has survived a time period without the outcome. Conditional survival is a more informative risk of the outcome that changes over time, given that a patient has not yet experienced the outcome and can be considered a dynamic risk prediction [28]. The methods to estimate conditional survival have been described elsewhere [28].

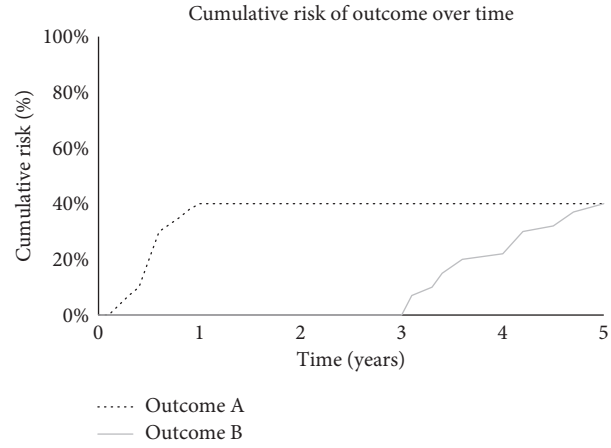

Figure 1: Timing of events and risk prediction. At baseline, the cumulative risk of outcomes A and B at 5 years is equivalent. However, the corresponding risk at 2 years is different, and this relates to the timing of events. Similarly, a patient that has survived 2 years without experiencing outcome A is at negligible risk of this outcome, given that this outcome does not occur after this time point. Conversely, at 2 years, they continue to be at risk for outcome B, demonstrating that the relative importance of observing for outcomes A and B changes over time.

Conditional survival has been described for various malignancies such as ovarian cancer [29], head and neck squamous cell carcinoma [30], gastric cancer [31], colorectal cancer [32], and melanoma [33]. In testicular cancer, a Canadian population-based study found that the 5-year conditional overall survival at diagnosis was 95% and increased to 99% at 3 years [34]. A European study using cancer registries found that conditional overall survival estimates in testicular cancer patients were comparable across age groups and became similar to those of the general population after the first year of diagnosis [35]. While these estimates attest to the excellent cure rates in testicular cancer, they are difficult to apply in clinical practice as they do not take into account disease histology and, more importantly, disease stage.

A recent multicenter, international, retrospective cohort study by Ko et al. evaluated conditional survival in 942 men presenting with stage II or III metastatic germ cell tumours and treated with first-line curative therapy [36]. The vast majority (93%) received first-line chemotherapy, with most patients receiving bleomycin, etoposide, and cisplatin. This study found that the 2-year conditional overall survival increased from 92% at baseline (0 months) to 98% at 24 months, and the 2-year conditional disease-free survival increased from 83% at baseline to 98% at 24 months. Translated into patient-relatable terms, a patient in this study population would be informed at the time of diagnosis that their risk of disease progression at baseline is 17%; however, a patient without evidence of disease progression at the 24-month visit could be told that their risk of progression

in the following 2 years is only 2%. In subgroup analyses by International Germ Cell Cancer Collaborative Group risk stratification, the improvement in conditional survival depended on the risk category, with the poor-risk category experiencing the most improvement, followed by the intermediate group. Indeed, this has been noted by others where the group at highest risk has the greatest improvement in conditional survival compared to the lowest risk group [29, 31, 32]. This can be understood conceptually based on the description mentioned above, whereby the timing of the outcome is likely to occur earlier in the high-risk category compared to the low-risk category. The study by Ko et al. also compared conditional overall and disease-free survival estimates between seminoma and NSGCT and found no significant difference between disease histologies. While these estimates are important to counsel patients presenting with stage II or III germ cell tumours receiving first-line curative therapy, they are not applicable to the majority of patients with germ cell tumours as most patients present with clinical stage I disease [4].

6. Conditional Survival on Surveillance for Clinical Stage I Germ Cell Tumours

In a recent study, we evaluated conditional risk of relapse on surveillance for clinical stage I germ cell tumours [37]. This was a single-center, retrospective cohort study of 1355 patients in which we evaluated 2- and 5-year conditional risk of relapse. To avoid confusion, it is worth noting that the Ko et al. study [36] described conditional survival probabilities of not having the outcome, whereas we described the conditional risk of having the outcome. In our study, patients were stratified based on disease histology as well as risk factors for relapse on surveillance (lymphovascular invasion and pure embryonal carcinoma in NSGCT and tumour stage (T1b versus T1a) for seminoma). For NSGCT, we found that the baseline risk of relapse at 2 years in patients with both risk factors for progression was 42% and those without either risk factor was 16%. This difference in baseline risk based on risk factors has been described previously [7]. At 24 months, the conditional risk of relapse was 0% in patients with both risk factors and 1% in those without either risk factor. Consistent with previous studies [29, 31, 32, 36], the greatest change in conditional survival was in the high-risk group. In those with a single risk factor, the conditional risk of relapse at 24 months was 3–6%.

These data demonstrate several clinically important concepts: (1) the baseline risk of relapse at 2 years is different among risk subgroups, (2) the timing of relapses differs among risk subgroups; in those with both risk factors, all relapsed occur early and the risk of relapse after 2 years was negligible compared to patients without risk factors who have a continued small chance of relapse, and (3) taken together, the first two notions suggest that surveillance protocols should be directed based on future risk of relapse, rather than the baseline risk. Similar observations were noted for our clinical stage I seminoma patients on surveillance.

Although our preliminary findings suggest that clinical stage I NSGCT patients with lymphovascular invasion and pure embryonal carcinoma may not need follow-up after 2 years given the negligible risk of relapse, our study was limited by the lack of its generalizability as it relied on our single-center's data. Furthermore, the sample size limited the number of relapses observed.

In a subsequent study presented at the 2017 American Urological Association Meeting [38], we combined our data with population-level data from Denmark. The most notable difference between this study and our prior one was that there continued to be relapses in NSGCT patients with both risk factors, suggesting that continued follow-up is warranted in this risk group. This difference was likely due to an increase in follow-up time and hence number of relapses and demonstrates the importance of collaborative studies, particularly in relatively uncommon diseases with few events of interest.

7. The Value of Conditional Survival Estimates for Surveillance of Clinical Stage I Germ Cell Tumours

Given the excellent cure rates, the focus in testicular cancer care has become reducing treatment burden and improving survivorship. In this section, we highlight how conditional survival estimates facilitate this goal, though the value of conditional survival estimates presented here also applies to other applications in clinical care.

Our understanding of the natural progression of testicular cancer has modified how we treat the disease. Surveillance for clinical stage I germ cell tumours attests to this notion as most patients were historically treated with adjuvant treatment following orchiectomy; however, realizing that the vast majority were being overtreated, surveillance had become increasingly adopted. In surveillance, the intensity and duration of follow-up have also changed over time. For example, we previously reported our institution's surveillance protocol for clinical stage I NSGCT in 1999, and this included a physician visit with tumour markers and a chest X-ray every two months in years 1 and 2, every four months in year 3, every six months in year 4, and at 60 months and CT scans every 4 months in years 1 and 2 [39]. Our group and others have subsequently reported patterns of relapse detection on surveillance for clinical stage I NSGCT [6, 7, 9], and the results of these studies have prompted changes in the intensity to our surveillance protocol; in our review of 371 clinical stage I NSGCT patients with a median follow-up of 6.3 years, we found that chest X-ray was never the only modality to identify disease progression [40]. As such, our current surveillance protocol for clinical stage I NSGCT no longer includes chest X-rays. Though the radiation exposure from a chest X-ray is relatively low, this change in our surveillance protocol reduces both the burden and costs to the health care system associated with surveillance. CT scans, on the other hand, are associated with significant radiation exposure, and every scan increases the lifetime attributable risk for secondary malignancy [41], which is a particularly important concern in testicular cancer patients, given the relatively young age of diagnosis. Our protocol reported in 1999 included 6 CT scans in the first two years, whereas our current protocol includes 4 over the same

period of time. Of note, our current protocol now includes a scan at 5 years, given our improved understanding of the progression and detection of relapse beyond two years. Furthermore, we now use low-dose CT scans as these provide diagnostically acceptable images for at least 99% of patients on surveillance for clinical stage I germ cell tumours and achieve a mean dose reduction of 55% compared to the standard dose protocol [42]. Similar changes to our seminoma protocol [37, 43] have also been reported and are also based on our improved understanding of the disease [6, 44]. Conditional survival estimates are useful in this context as they provide a clear estimate of the future risk of relapse, and surveillance protocols can be tailored accordingly. This may reduce physician visits which may improve worker productivity and reduce unnecessary tests which may decrease costs to the health care system and the potential risks of complications from testing.

A patient's quality of life is likely to be improved by reducing physician visits and testing, and patients may also benefit from being informed about their decreasing risk of relapse at each clinic visit. Studies have shown that long-term testicular cancer survivors experience increased anxiety compared to the general population [45, 46], and an Internet search will reveal many forums where patients discuss their anxiety related to being managed with surveillance, though anxiety has not yet been studied formally in the setting of testicular cancer surveillance. The potential for anxiety is not surprising, given that some patients have a risk of relapse as high as 40% within two years of diagnosis. Providing patients without relapse with an evolving, decreasing risk of relapse at each follow-up visit should help decrease some of the anxiety associated with surveillance, and our early clinical experience supports this. Furthermore, patients with this information can plan for the future in terms of family and career, and the information can be useful in obtaining medical and life insurance. Therefore, conditional survival estimates are both informative and useful for physicians and patients and can reduce the overall burden of surveillance on the health care system.

8. Conclusion

In this review, we highlight the role of conditional survival analyses in the context of surveillance for clinical stage I germ cell tumours. Conditional survival estimates can be used to tailor surveillance protocols which will reduce physician visits and tests, thereby reducing treatment burden and costs, and are important for patients to understand their evolving risk of relapse, which will reduce anxiety and assist in life planning. Future studies should evaluate whether applying conditional survival estimates in clinical practice reduces treatment burden and improves quality of life, without compromising survival outcomes.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Toxicities Associated with Cisplatin-Based Chemotherapy and Radiotherapy in Long-Term Testicular Cancer Survivors

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Testicular cancer has become the paradigm of adult-onset cancer survivorship, due to the young age at diagnosis and 10-year relative survival of 95%. This clinical review presents the current status of various treatment-related complications experienced by long-term testicular cancer survivors (TCS) free of disease for 5 or more years after primary treatment. Cardiovascular disease and second malignant neoplasms represent the most common potentially life-threatening late effects. Other long-term adverse outcomes include neuro- and ototoxicity, pulmonary complications, nephrotoxicity, hypogonadism, infertility, and avascular necrosis. Future research efforts should focus on delineation of the genetic underpinning of these long-term toxicities to understand their biologic basis and etiopathogenetic pathways, with the goal of developing targeted prevention and intervention strategies to optimize risk-based care and minimize chronic morbidities. In the interim, health care providers should advise TCS to adhere to national guidelines for the management of cardiovascular disease risk factors, as well as to adopt behaviors consistent with a healthy lifestyle, including smoking cessation, a balanced diet, and a moderate to vigorous intensity exercise program. TCS should also follow national guidelines for cancer screening as currently applied to the general population.

1. Introduction

Testicular cancer (TC) is the most common cancer, affecting young men aged 18–39 years [1]. Due to effective cisplatin-based chemotherapy introduced in the 1970s [2], TC is highly curable with a 10-year relative survival approaching 95% [3, 4]. However, treatment-related complications, including cardiovascular disease (CVD), second malignant neoplasms (SMN), neuro- and ototoxicity, pulmonary complications, nephrotoxicity, hypogonadism, infertility, avascular necrosis, cognitive impairment, anxiety/depression, and chronic cancer-related fatigue, accompany these remarkable successes [5–7]. These adverse outcomes of TC and its therapy have emerged as important issues for this young cohort of survivors. In this review article, we will focus on toxicities due to cisplatin-based chemotherapy and radiotherapy experienced by long-term survivors of TC, which are defined as individuals who are disease-free 5 years or more after primary treatment [8]. Due to sparse data, the risks of long-term toxicities after single-dose carboplatin for stage I seminoma or one to two cycles of bleomycin, etoposide, and cisplatin (BEP) for stage I nonseminoma will not be reviewed.

2. Cardiovascular Disease and Raynaud Phenomenon

A few hypotheses have been proposed to explain the pathophysiology of CVD in TC survivors (TCS), including the direct vascular damage hypothesis, the indirect hypothesis, and more recently the multiple-hit hypothesis [9, 10]. The direct vascular damage hypothesis proposes that cisplatin-based chemotherapy causes direct damage to the vascular endothelium [9]. In vitro exposure of endothelial cells to cisplatin or bleomycin causes cytokine release and cytotoxicity [11, 12]. Von Willebrand factor, an inflammatory

marker released by endothelial cells in response to vascular damage, increases in TC patients during chemotherapy [13]. Other markers of inflammation and endothelial dysfunction are also evident after cisplatin-based chemotherapy, including fibrinogen, tissue-type plasminogen activator, and high-sensitivity C-reactive protein [14, 15]. Microalbuminuria is present in an increased number of TC patients treated with cisplatin-based chemotherapy [14, 16], which is a clinical manifestation of systemic vascular dysfunction that independently predicts for vascular events, including stroke and myocardial infarction (MI) [17]. In one study, microalbuminuria persisted in 22% of TCS treated with cisplatin-based chemotherapy after a median follow-up of 14 years [16].

A prior investigation [15] showed that the carotid intimal medial thickness of TC patients, which correlates with increased risk of cerebrovascular accidents and MI [18], significantly increased during a 3.5-month course of cisplatin-based chemotherapy. This rate of increase was significantly higher than the annual change observed in carotid intimal medial thickness in the general population. Acute alterations in diastolic heart function were reported in a study [19] of 14 TC patients three months after initiation of 3 to 4 cycles of chemotherapy with BEP; these included significant decreases in the left ventricular end-diastolic and stroke volumes. Other suggested mechanisms of direct vascular damage include cisplatin-induced vasospasm due to hypomagnesemia [20–23] and increased formation of procoagulant endothelial microparticles released by endothelial cells, triggering thrombin generation and hypercoagulability [24, 25].

Raynaud phenomenon is another clinical manifestation of vascular damage and is estimated to be present in approximately 25% to 61% of TCS [26–30]. The onset of symptoms from Raynaud phenomenon generally begins within 4 to 12 months of chemotherapy, with 25% experiencing these symptoms up to 20 years [14]. Bleomycin is strongly associated with the development of Raynaud phenomenon. In a randomized study [31] of 395 patients with good-risk metastatic nonseminoma, 8% of patients randomized to BEP developed Raynaud phenomenon compared to none undergoing etoposide and cisplatin (EP). Vinblastine and cisplatin are other chemotherapeutic agents that may contribute to this toxicity [28–30, 32].

The indirect hypothesis postulates that cisplatin-based chemotherapy increases the prevalence of CVD risk factors in TCS, resulting in increased CVD events [9]. Multiple studies [14, 16, 30, 33–40] have reported increased frequency of hyperlipidemia, hypertension, diabetes, insulin resistance, and metabolic syndrome among TC patients after treatment with chemotherapy compared to surgery-only comparison groups or controls derived from the general population (Table 1). Although several studies [36, 38, 41] showed that metabolic syndrome and its individual components are associated with testosterone deficiency and hypogonadism, most TCS with CVD risk factors have normal testosterone levels [33]. Decreased testosterone levels may cause endothelial dysfunction, impair vascular smooth muscle reactivity, increase intima and media thickness of vessels, and increase synthesis of proinflammatory cytokines [42–44]. In an investigation by Haugnes et al. [33], relationships with both hypogonadism and cumulative dose of cisplatin and metabolic syndrome were evaluated among 1135 Norwegian TCS. Compared to the surgery group, TCS who received a cumulative dose of cisplatin >850 mg had a significant 2.8-fold increased odds of metabolic syndrome, with both total serum testosterone and smoking history (≥20 pack-years) being independent predictive factors in multiple regression models.

A multiple-hit hypothesis that encompasses both the direct and indirect hypotheses has recently been proposed to explain the elevated risk of CVD among TCS [10, 45]. This model hypothesizes that multiple factors interact synergistically to increase the risks of CVD among TCS, including orchiectomy-derived subclinical hypogonadism, chemotherapy-induced vascular injury, chemotherapy-related disturbance of metabolic homeostasis, and other TC treatment-related toxicities [10].

The relative risk of CVD among TCS treated with chemotherapy is 1.4- to 7.1-fold significantly higher compared to the general population or to those managed with surveillance only [16, 34, 35, 46, 47]. A British study [35] of 390 TCS treated with chemotherapy between 1982 and 1992 at a median follow-up of 9.7 years showed a 7% incidence of angina, MI or sudden cardiac death, with an elevated age-adjusted relative risk (RR) of 2.6 (95% confidence interval (CI) 1.2–5.8) when compared with TC patients treated with surgery alone. In a retrospective study [46] of a nationwide cohort of 2707 5-year TCS in the Netherlands (1965–1995) after a median follow-up of 17.6 years, cisplatin-based chemotherapy (cisplatin, vinblastine, bleomycin (PVB) or BEP) increased the risk of CVD by 1.7-fold (95% CI 1.1–2.5) when compared with age and sex-matched data in the general Dutch population.

To determine CVD risk after modern-era cisplatin-based chemotherapy in TC patients, Haugnes et al. [34] evaluated the prevalence of cardiovascular risk factors and long-term incidence of CVD among 990 5-year TC survivors (median follow-up: 19 years). All cytotoxic treatment groups (radiation only, chemotherapy only, and combined radiation/chemotherapy) had significantly increased prevalence of usage of antihypertensive medications compared with age-matched male controls in the general population. The odds of diabetes were higher in the radiation (odds ratio (OR) 2.3; 95% CI 1.5–3.7) and radiation/chemotherapy groups (OR 3.9; 95% CI 1.4–10.9) compared to controls [34]. Using age-adjusted Cox regression analyses, increased risks of atherosclerotic disease were reported in the radiation only (hazard ratio (HR) 2.3; 95% CI 1.04–5.3), chemotherapy only (HR 2.6; 95% CI 1.1–5.9), and combined radiation/chemotherapy cohorts (HR 4.8; 95% CI 1.6–14.4) compared to those managed with surgery only [34]. Treatment with BEP alone increased the risk of coronary artery disease by 5.7-fold (95% CI 1.9–17.1) compared with surgery only, while the risk for MI increased by 3.1-fold (95% CI 1.2–7.7) compared with age-matched male controls [34].

Using age-adjusted Cox regression analyses, increased risks of atherosclerotic disease were reported after radiation only (HR 2.3; 95% CI 1.04–5.3), chemotherapy only (HR 2.6;

Table 1: Prevalence of cardiovascular disease risk factors in chemotherapy-treated patients in select studies since 2000.

						Prevalence of cardiovascular risk factors versus Controls[b] (%)				
Author (year)	N[a]	Treatment dates	Median length of follow-up (range)	Median age at follow-up (range)	Control group (N)	HTN (definition)	Increased lipids[c] (definition)	DM (definition)	Obesity (definition)	Metabolic syndrome (definition)
Meinardi et al. (2000) [16]	62	Before 1987	14 y (10–20 y)	42 y (30–50 y)	Stage I TC (40)	39 versus 13 (SBP > 150 mmHg, DBP > 95 mmHg)	79 versus 53 (TC ≥ 201 mg/dL)	NA	21 versus 28[d] (BMI > 27.8)	NA
Strumberg et al. (2002) [30]	32	1977–1981	15 y (13–17 y)	40 y (30–59 y)	None	25 versus NA (DBP > 95 mmHg)	81 versus NA (TC ≥ 200 mg/dL)	NA	48 versus NA (BMI ≥ 25)	NA
Huddart et al. (2003) [35]	390	1982–1992	10 y (0–20 y)	41 y (23–72 y)	Stage I TC (242)	13 versus 9[d] (antihypertension medication)	1 versus 2[d] (lipid-lowering medication)	NA	NA	NA
Nuver et al. (2004) [14]	90	1988–1999	7 y (NA)	37 y (20–65 y)	Stage I TC (44) and healthy patients (47)	22 versus 23 versus 11[d] (SBP ≥ 135 mmHg, DBP ≥ 85 mmHg)	71 versus 59 versus 45[e] (LDL > 131 mg/dL)	NA	22 versus 27 versus 11[e] (BMI ≥ 30)	NA
Nuver et al. (2005) [36]	86	1988–1999	7 y (3–13 y)	37 y (20–65 y)	Stage I TC (44) and healthy patients (47)	NA	NA	NA	NA	26 versus 36 versus 9[e] (≥3 factors per NCEP definition [163])
Sagstuen et al. (2005) [37]	500	1980–1994	11 y (4–22 y)	44 y (23–75 y)	Surgery-only[f] (242)[g]	50 versus 39 (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or antihypertension medication)	NA	NA	18 versus 13[h] (BMI ≥ 30)	NA
Haugnes et al. (2007) [33]	464	1980–1994	11 y (5–22 y)	43 y (15–52 y)	Surgery-only[f] (225) and healthy population (1150)	45 versus 34 versus 50[i] (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg or antihypertension medication)	68 versus 67 versus 84[d] (TC ≥ 201 mg/dL)	3 versus 2 versus 3[d] (by patient self-report)	18 versus 13 versus 21[d] (BMI ≥ 30)	9 versus 7 versus 15[h] (≥3 factors per NCEP definition [163])
Haugnes et al. (2010) [34]	364	1980–1994	19 y (13–28 y)	49 y (31–69 y)	Surgery-only[f] (206) and healthy population (990)	26 versus 12 versus 13 (antihypertension medication)	14 versus 14 versus 9[e] (lipid-lowering medication)	5 versus 4 versus 4[d] (by patient self-report or fasting glucose ≥ 198 mg/dL)	17 versus 19 versus 23[d] (BMI ≥ 30)	NA

Table 1: Continued.

						Prevalence of cardiovascular risk factors versus Controls[b] (%)				
Author (year)	N[a]	Treatment dates	Median length of follow-up (range)	Median age at follow-up (range)	Control group (N)	HTN (definition)	Increased lipids[c] (definition)	DM (definition)	Obesity (definition)	Metabolic syndrome (definition)
Willemse et al. (2013) [38]	194[j]	1977–2008	7.8 y (0.1–30 y)	39.6 y (18–70 y)	Surgery-only (57) and healthy population (360)	29 versus 14 versus 22.5[k] (per NCEP definition [163])	NA	NA	29 versus 18 versus 19[k] (per NCEP definition [163])	16 versus 9 versus 8[k] (per NCEP definition [163])
de Haas et al. (2013) [39]	173	1977–2004	5 y (3–20 y)	37 y (19–59 y)	Healthy population (1085)	59 versus NA (SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or antihypertension medication) (AHA/NHLBI definition)	44 versus NA (HDL <1.03 mmol/l or lipid-lowering medication) (AHA/NHLBI definition)	14 versus NA (fasting glucose ≥5.6 mmol/l or medication) (AHA/NHLBI definition)	17 versus NA (waist circumference ≥ 102 cm) (AHA/NHLBI definition)	25 versus NA (≥3 factors per AHA/NHLBI definition)
Fung et al. (2017) [40]	952	1979–2015	4.3 y (1.0–29.9)	37 y (19–68 y)	NHANES matched controls (952)	16.8 versus 19.4[d] ever diagnosed with high blood pressure and current use of antihypertension medication	10.5 versus NA[l] current use of cholesterol lowering medication	3.1 versus NA[l] diabetes requiring insulin or diabetes requiring medication	31.3 versus 35.4[k] BMI ≥ 30	NA

*Adapted with permission from Feldman et al. [9] (Table 2). AHA: American Heart Association; BMI: body mass index; DBP: diastolic blood pressure; DM: diabetes mellitus; NHLBI: National Heart, Lung, and Blood Institute; NHANES: National Health and Nutrition Examination Survey; TC: testicular cancer; HTN: hypertension; LDL: low-density lipoprotein; NA: not available; NCEP: National Cholesterol Education Program; SBP: systolic blood pressure; TC: total cholesterol. (a) N varies slightly for individual factors due to missing data in papers for some variables. (b) Definitions of individual factors vary by study. Comparisons of chemotherapy group to controls significant unless otherwise stated; percentages vary slightly due to missing data for individual factors. (c) Cholesterol and fasting glucose values in definitions were converted from mml/L to mg/dL, where necessary for uniformity. (d) Not significant. (e) Significant versus healthy population controls but not versus surgery patients. (f) Includes both orchiectomy and primary retroperitoneal lymph node dissection patients. (g) A healthy population control group was also included in this study, but prevalence rates of cardiovascular risk factors were not reported for this control group, and therefore these data are not included in the table. (h) Significant only for patients who received >850 mg of cisplatin. (i) Significant versus surgery patients but not versus healthy controls. (j) 20 patients received carboplatin and 174 patients received combination chemotherapy. (k) Significant for patients who received combination chemotherapy compared to healthy population. (l) Significance versus controls not tested.

95% CI 1.1–5.9), and combined radiation/chemotherapy (HR 4.8; 95% CI 1.6–14.4) compared with surgery only (P-trend = 0.02) [34]. In particular, treatment with BEP alone increased CAD risk by 5.7-fold (95% CI 1.9–17.1) compared with surgery only and increased MI risk by 3.1-fold (95% CI 1.2–7.7) compared with age-matched male controls [34].

Several studies [48–50] have examined the extent to which increased CVD mortality might result from TC treatment. In an international population-based study [48] of 38,907 TCS (1943–2002) at a median follow-up of 10 years, a 1.6-fold (95% CI 1.3–2.0) increased risk of mortality from all circulatory diseases was reported for those treated with chemotherapy after 1975. Another population-based study [49] using the SEER program (1973–2008) found that patients with either mediastinal or nonmediastinal extragonadal GCT had significantly increased 4.5-fold and 2.8-fold risks of CVD mortality, respectively, compared to patients with primary testicular GCT. The increased number of cycles of primary chemotherapy and additional salvage chemotherapy typically required to treat extragonadal TC were hypothesized to contribute to this higher risk, although detailed chemotherapy data were not available [49]. Recently, Fung et al. [50] reported a significant 5.3-fold increase in CVD mortality during the first year after chemotherapy in a population-based study of 15,006 TCS managed initially with either chemotherapy or surgery alone without radiotherapy during 1980–2010. In contrast, excess CVD mortality was not observed more than one year after chemotherapy, likely due to advances in cardiovascular disease management, as reflected in the 31% decline in US cardiovascular death rates from 2000 to 2010 [51]. In multivariable analyses, increased CVD mortality after chemotherapy was confined to the first year after TC diagnosis (HR 4.86; 95% CI, 1.25–32); distant disease ($P < 0.05$) and older age at diagnosis ($P < 0.01$) were independent risk factors [50].

Currently, there are no established evidence-based CVD screening recommendations developed specifically for TCS. In November 2013, the American College of Cardiology and the American Heart Association released guidelines for the assessment of cardiovascular disease risk, the management of elevated cholesterol and increased body weight, and lifestyle modifications to reduce CVD risk in adults in the general population [52]. Health care professionals should monitor and modify cardiovascular risk factors of TCS by referring to these guidelines [52] and by leveraging TC diagnosis as a teachable moment to promote lifestyle changes, including smoking cessation, optimal nutrition, and a nonsedentary lifestyle [7, 53].

3. Second Malignant Neoplasms

Syndromic, cancer treatment, and shared etiologic exposures are the major causative factors of SMN [54]. Figure 1 shows the influence of lifestyle factors, genetic susceptibility, environmental exposures, host effects, and a combination of influences, including gene-environment interactions in the development of SMN. Age at exposure and attained age are modifiers for the risks of selected SMN [55].

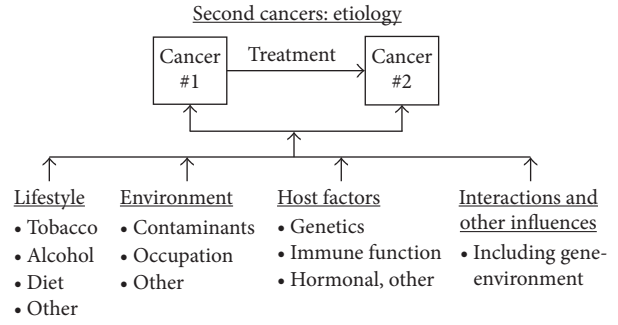

Figure 1: Risk factors for second primary cancer (refer to text). Many influences some of which are diagrammed here may contribute to the development of multiple primary cancers, including interactions between exposures. *Adapted with permission from Travis [169].

After receiving radiotherapy for TC treatment, TCS have significantly increased risks of leukemia [56] and solid cancers [46, 55, 57–59] (Table 2). An international population-based study of 18,567 TCS reported a significantly 3-fold increased risk of leukemia after abdominal and pelvic radiotherapy with a mean dose of 10.9 Gy to active bone marrow [56]. The median latency for leukemia was 5.0 years with a quarter of survivors developing leukemia more than one decade later (maximum latency: 17.3 years) [56]. After radiation treatment, long-term TCS also have significantly 1.4 to 1.9-fold increased risks of second solid cancers compared to the general population (Table 2) [46, 55, 57]. An international population-based investigation of 10-year TCS reported that the RR of SMN at sites included in typical infradiaphragmatic radiotherapy fields were significantly larger than risks at unexposed sites (RR 2.7 versus 1.6; $P < 0.05$), which remained elevated for more than 35 years. In another study [46], infradiaphragmatic radiotherapy administered at doses 40–50 Gray (Gy) compared with 26–35 Gy increased the HR for SMN from 2.3 to 3.2, respectively, when using a surgery-only group as control. Two recent studies of 5-year TCS reported a 5.9-fold increased risk of stomach cancer (95% CI 1.7–20.7) [58] and a 2.9-fold increased risk of pancreatic cancer (95% CI 1.0–7.8) after radiotherapy [59]. The risks of stomach and pancreatic cancers increased with higher radiation doses to stomach [58] and pancreas [59], respectively (P trend < 0.001), and risks remained elevated for ≥20 years after exposure ($P < 0.01$) [58, 59]. Several other studies of TCS [46, 60, 61] similarly reported significant associations between radiotherapy and SMN risks.

Cisplatin and etoposide are integral chemotherapeutic agents used in standard chemotherapy regimens to treat TC [62]. Both cisplatin and etoposide are associated with significantly elevated risks of secondary leukemia [56, 63–65]. An international nested case-control study [56] among TCS estimated a 3.2-fold risk of leukemia after cumulative cisplatin dose of 650 mg, although the excess risk was small with only 16 excess cases among 10,000 TC patients after 15 years of follow-up. The same study also reported a significant dose-response relationship between cumulative dose of cisplatin and leukemia risk after adjustment for radiation dose

Table 2: Relative risks of second malignant neoplasms (SMN) in testicular cancer survivors.

	No. of patients	Calendar years of testicular cancer diagnosis	Duration of follow-up (years)	Treatment	Obs.	RR	(95% CI)
Study populations[a]							
All SMNs							
Norwegian radium hospital [66]	2006	1952–1990	Mean = 12.5	Any	153[b]	1.7	1.4–1.9
				RT	130	1.6	1.3–1.9
				CT	4	1.3	0.4–3.4
				RT + CT	15	3.5	2.0–5.8
Fourteen population-based tumor registries in Europe and North America [55]	40,576	1943–2001	Mean = 11.3	Any	1694	1.9	1.8–2.1
				RT	892	2.0	1.9–2.2
				CT	35	1.8	1.3–2.5
				RT + CT	25	2.9	1.9–4.2
Thirteen International Cancer Registries [164]	29,511	1943–2000	Median = 8.3	Any	1811[c]	1.7	1.6–1.7
Netherlands testicular cancer survivor cohort [46]	2707	1965–1995	Median = 17.6	Any	270[d]	1.7	1.5–1.9
				RT	199	1.7	1.5–2.0
				CT	23	1.4	0.9–2.1
				RT + CT	29	3.0	2.0–4.4
				SDRT	N/A	2.6[g]	1.7–4.0
				SDRT + MRT	N/A	3.6[g]	2.1–6.0
				PVB/BEP	N/A	2.1[g]	1.4–3.1
				SDRT (26–35 Gy)	N/A	2.3[g]	1.5–3.6
				SDRT (40–50 Gy)	N/A	3.2[g]	2.1–5.1
Swedish family cancer database [165]	5533	1980–2006	N/A	Any	274[e]	2.0	1.8–2.2
Second solid cancers	12,691	1980–2008	Median = 7.0	Initial surgery only	99	0.9	0.8–1.1
Sixteen population-based registries within the SEER program [67]				Initial CT (no RT)	111[f]	1.4	1.2–1.7
Therapy-associated leukemia							
Nested case-control study of leukemia in 8 population-based tumor registries in Europe and North America [56]	18,567	1970–1993	N/A	No RT/CT	4	1.0	—
				RT	22	3.1	0.7–2.2
				CT	8	5.0	1.1–40
				RT + CT	2	5.1	0.5–28

*Adapted with permission from *Fung* et al. *J Natl Compr Canc Netw 2012; 10:545-56* (Table 2). RR: relative risk; CI: confidence interval; Obs.: observed number of cases; RT: any radiation treatment; CT: chemotherapy; IDRT: infradiaphragmatic radiation; SDRT: supradiaphragmatic radiation; MRT: mediastinal radiation; PVB: cisplatin, vinblastine, bleomycin; BEP: bleomycin, etoposide, cisplatin; N/A: not available (data not provided). (a) There was overlap in the cancer registries included in the cohort studies by Richiardi et al. [164] and Travis et al. [55], with the following countries contributing patients to both studies: Denmark, Finland, Norway, and Sweden; (b) six cases of leukemia were observed with a RR of 1.9 (95% CI: 0.7–4.1); (c) thirty-eight cases of myeloid leukemia were observed with a RR of 3.6 (95% CI: 2.6–5.0); thirteen cases of lymphoid leukemia were observed with a RR of 1.0 (95% CI: 0.5–1.7); twenty-three cases of other types of leukemia were observed with a RR of 3.5 (95% CI: 2.2–5.2); (d) six cases of leukemia were observed with a RR of 1.6 (95% CI: 0.6–3.5); (e) hazard ratios are shown, with the referent group consisting of patients treated with surgery alone (HR = 1.0). Twelve cases of leukemia were observed with a RR of 3.8 (95% CI: 2.0–6.7); (f) significantly increased risks occurred for cancers of the kidney (SIR = 3.4; 95% CI 1.8–5.7; $n = 13$); thyroid (SIR = 4.4; 95% CI: 2.2–7.9; $n = 11$); and soft tissue (SIR = 7.5; 95% CI: 3.6–13.8; $n = 10$).

(P trend = 0.001) [56]. The 5-year cumulative incidence of leukemia is approximately 0.5% after a cumulative etoposide dose of <2000 mg/m^2 and 2.0% after a cumulative etoposide dose of ≥2000 mg/m^2 [65].

Most prior studies of second solid cancer focused on TCS treated before modern cisplatin-based chemotherapy became widely adopted prior to early 1980s (Table 2) [10, 13, 22, 23]. Whereas an international series of more than 40,000 TCS showed a 1.8-fold (95% CI 1.3–2.5) significantly increased risk of second solid cancers among a subgroup of 10-year TCS who received initial chemotherapy during 1943–2001, three smaller epidemiologic studies [10, 39, 57] (ranging from 346 to 710 patients) found no significantly elevated risk of SMN after chemotherapy [27, 46, 66], though they may have inadequate statistical power. To evaluate the risks of second solid cancer among TCS treated in the modern era of cisplatin-based chemotherapy during 1980 to 2008, a recent large population-based investigation by Fung et al. [67] of more than 12,000 TCS reported a 1.4-fold significantly increased risk of solid cancers after initial treatment with chemotherapy compared to those who underwent initial surgery alone. Significantly increased three- to seven-fold risks of cancers of the kidney (standardized incidence ratio (SIR) 3.4), thyroid (SIR 4.4), and soft tissue (SIR 7.5) were also observed. After chemotherapy, elevated risks of solid cancer were reported in most follow-up periods

with a median latency of 12.5 years, including at more than 20 years after treatment (SIR 1.54; 95% CI 0.96–2.3). However, detailed information on cytotoxic drug name and dose were not available [67].

TCS should follow national guidelines for cancer screening as applied to the general population, given their increased risks of SMN [53]. Earlier or additional cancer screening may be clinically indicated in TCS deemed at high risk due to prior treatment history and/or health habits [53]. In addition, health care providers should advise TCS of the modest 15-year cumulative risk (1.9%) of metachronous contralateral testicular cancer [68].

4. Neurotoxicity

Approximately 20 to 40% of long-term TCS experience symptoms of peripheral neuropathy after cisplatin-based chemotherapy [28, 29, 69]. Common clinical manifestations of peripheral neuropathy include numbness, tingling, and a decrease in vibratory sense in distal extremities [70]. The cumulative dose of cisplatin administered affects the incidence of peripheral neuropathy. At a median of 11 years after TC treatment, 46% of TCS in a population-based long-term Norwegian survey self-reported paresthesia after ≥5 cycles of cisplatin-based chemotherapy compared to 28% after 1 to 4 cycles of chemotherapy or 10% after orchiectomy alone [28]. Compared to TCS who did not receive chemotherapy, those who underwent 1 to 4 cycles and ≥5 cycles of cisplatin-based chemotherapy had higher risks of symptomatic paresthesia of the hands (OR 2.0, 95% CI 1.5–2.7; OR 3.9, 95% CI 2.1–7.3, resp.) and feet (OR 2.2, 95% CI 1.7–3.0; OR 3.1, 95% CI 1.7–5.7, resp.) [28]. In the same study [28], radiotherapy was significantly associated with symptomatic paresthesias of the feet (OR 1.5), but retroperitoneal lymph node dissection (RPLND) was not an independent risk factor. Increasing levels of residual serum platinum are also directly associated with severity of neurotoxicity after adjusting for initial cisplatin dose [71]. Sprauten et al. reported [71] that the total score for the Scale for Chemotherapy Induced Neuropathy (SCIN) had a significant four-to five-fold association with the highest residual serum platinum quartile in cisplatin-treated TC patients.

Oldenburg et al. [72] investigated the impact of germline single nucleotide polymorphisms (SNPs) of glutathione S-transferase (*GST*) *P*1, *M*1, and *T*1 on self-reported paresthesia among long-term TCS. The *GSTP1-GG* genotype conferred a significantly lower risk of developing paresthesia in the fingers (OR = 0.46, 95% CI 0.22–0.96) and toes (OR = 0.42, 95% CI 0.20–0.88) than the *GSTP1-AA* and *GSTP1-AG* genotypes. Recently, a genome-wide analysis of cisplatin-induced peripheral neuropathy in survivors of adult-onset cancer reported that genetically determined expression level of *RPRD1B* was associated with cisplatin-induced peripheral neuropathy [73]. Defects in *RPRD1B* expression or knockdown cause a deficiency in DNA repair mechanisms known to be critical in repairing cisplatin-induced lesions [74] and result in increased sensitivity to cisplatin in a breast cancer cell line, MDA-123 [75].

No therapeutic agents are currently recommended for the prevention of peripheral neuropathy due to the paucity of high-quality, consistent evidence. For management of drug-induced peripheral neuropathy, the ASCO Clinical Practice Guideline [76] recommends treatment with duloxetine as potentially the most effective drug. Health care providers may also offer tricyclic antidepressants (i.e., nortriptyline), gabapentin, and a compounded topical gel containing baclofen, amitriptyline HCL, and ketamine based on clinical benefits observed for other neuropathic pain conditions [76].

5. Ototoxicity

Cisplatin selectively damages the outer hair cells of the cochlea [77], causing tinnitus and hearing loss that predominantly affect high frequencies [77–79] similar to age-related presbycusis. After a median follow-up of 58 months, Bokemeyer et al. [78] found that 20% of TCS (median age: 31 years) reported symptomatic ototoxicity (59% tinnitus, 18% hearing loss, 23% both) after cisplatin-based chemotherapy. For TCS who received >400 mg/m^2 of cumulative cisplatin dose, 50% self-reported tinnitus and hearing loss compared to 20% of those treated with ≤400 mg/m^2 [78]. Older age, higher cumulative cisplatin dose, a history of noise exposure, hypertension, and impaired baseline renal function and hearing are each independently associated with more severe ototoxicity [78–80]. A recent comprehensive audiometric analysis of 488 North American TCS [79] reported that almost one in five (18%) had severe to profound hearing loss as defined by the American Speech-Language-Hearing Association criteria (median follow-up: 4.25 years after completion of cisplatin-based chemotherapy). Tinnitus (40% patients) was significantly correlated with reduced hearing at each frequency ($P < 0.001$). The same study [79] also found that increasing cumulative cisplatin dose was significantly related to hearing loss at 4, 6, 8, 10, and 12 kHz (P trend for each <0.05). For each 100 mg/m [2] increase in cumulative cisplatin dose, a 3.2 dB impairment in age-adjusted overall hearing threshold (4–12 kHz; $P < 0.001$) resulted. However, cisplatin dose did not affect noise-induced hearing damage (10% patients) ($P = 0.59$) [79].

A few reports have identified significant associations of germline genetic polymorphisms of various genes with platinum-related ototoxicity, including megalin [81], *GSTP1* [72, 82], *GSTM3* [72, 82], *COMT* [83], *TPMT* [83], and *WFS1* [84]. Both alleles of *105Val-GSTP1* protected against cisplatin-induced ototoxicity in cisplatin-treated TCS, whereas *GSTM1* positivity was detrimental for hearing ability [82]. Functional polymorphisms of the glutathione *S*-transferases (*GSTs*) genes likely cause differential expression of the cisplatin-detoxifying enzymes, consequently rendering TCS suspcetible to varying degrees of cisplatin-induced hearing impairment. A recent genome-wide association study [85] of 511 TC patients of European genetic ancestry reported that one SNP, rs62283056, in the first intron of *WFS1* (wolframin ER transmembrane glycoprotein) was significantly associated with cisplatin-associated ototoxicity ($P = 1.4 \times 10^{-8}$), with higher cisplatin doses exacerbating

hearing loss in TC patients with the risk allele. In the general population, *WSF1* mutations causes the Mendelian disorders DFNA6 (deafness, autosomal dominant 6) and the recessive Wolfram syndrome (with hearing loss) [86, 87].

There are no effective pharmacologic agents available to prevent or treat cisplatin-induced ototoxicity. TCS should use ear protection to minimize noise exposure and additional hearing loss. Since the peak concentration of cisplatin may be directly associated with the severity of ototoxicity [28, 88], where indicated, the 5-day BEP regimen seems preferable to a 3-day regimen [7].

6. Pulmonary Toxicity

The incidence of fatal bleomycin-induced pulmonary toxicity is approximately 1–3% [89, 90]. Corticosteroids remain the mainstay of treatment of bleomycin-induced pneumonitis, although there are no data from prospective randomized trials to support this approach [91]. Health care providers should withhold bleomycin at the earliest signs or symptoms of bleomycin-induced pulmonary toxicities during chemotherapy. Since age of more than 40 years [89] and increased tobacco use [92] are both significantly associated with pulmonary toxicity during bleomycin treatment, a careful assessment of patient history (i.e., age, smoking status, and preexisting lung disease) are important to consider prior to the administration of any bleomycin-containing regimen [93]. Avoiding perioperative overhydration is important to minimize the risk of perioperative lung complications, but perioperative oxygen restriction in patients a few months after administration of bleomycin is not necessary [94, 95].

Bleomycin hydrolase is an enzyme encoded by the *BLMH* gene, which inactivates bleomycin [96]. A Dutch investigation of 340 TC patients treated with bleomycin-containing chemotherapy between 1977 and 2003 reported that the genetic polymorphism of 1450A > G was not associated with bleomycin-induced pneumonitis or changes in pulmonary function tests [97].

A large Norwegian study [92] of 1049 long-term TCS treated during 1980 to 1994 (median follow-up: 11.2 years) reported that 8% of survivors had restrictive lung disease as defined by predicted FVC <80% and a value of ≥70% for forced expiratory volume (FEV) 1/forced vital capacity (FVC). In multivariate analyses adjusting for bleomycin, etoposide, and vinblastine doses, higher cumulative cisplatin dose ($P = 0.007$) and older age ($P = 0.008$) were both significantly related to restrictive lung disease [92]. Compared with men treated with surgery only, patients who received large cumulative doses of cisplatin (>850 mg) as well as combined chemotherapy and pulmonary surgery were at significantly increased risk of demonstrating decreased spirometry variables, including age-adjusted FVC, FEV1, FVC% predicted, and FEV1% predicted [92]. A population-based study of TCS reported to North American and European cancer registries found that patients treated with chemotherapy (with or without radiotherapy) in 1975 or later had a 1.6-fold higher risk of mortality (95% CI 1.25–2.01) (median follow-up: 10 years) due to respiratory diseases compared to the general population. The extent to which bleomycin-induced lung toxicity may have contributed to these excesses is not known.

7. Nephrotoxicity

Cisplatin damages the proximal and distal renal tubular epithelium and the renal collecting duct system, as well as the glomeruli at higher doses [98, 99]. Two long-term studies [100, 101] reported persistently decreased renal function in TCS for years after completion of treatment compared with baseline assessments. A Norwegian study [100] of 85 TC patients more than 10 years after treatment showed that renal function among TCS who received radiotherapy alone decreased by 8%, whereas survivors who had cisplatin-based chemotherapy had reductions of 14%. Cumulative cisplatin dose and age at treatment were both directly associated with long-term impairment of renal function ($P < 0.05$). A Danish investigation [101] of 34 TCS who received systemic chemotherapy with PVB (median dose of cisplatin: 583 mg/m^2) reported that the glomerular filtration rate (GFR) decreased by a median of 18% during treatment. At a median follow-up of 65 months (range, 43 to 97 months), 38% of survivors had persistent renal dysfunction. Research in the general population has demonstrated a relationship between decreased GFR and the presence of microalbuminuria, leading to increased risks of CVD and all-cause mortality [102, 103]. Among long-term TCS, treatment-related nephrotoxicity may contribute to the reported increases in incident CVD events, including hypertension and MI [34, 35, 47]. To limit the severity of acute- and long-term renal damage, health care providers should administer hydration [104] and avoid nephrotoxic drugs [7] during cisplatin-based chemotherapy.

8. Hypogonadism

Orchiectomy, testicular dysgenesis syndrome, postorchiectomy chemotherapy or radiotherapy, and aging are the predominant causes of hypogonadism and premature hormonal aging in long-term TCS [105]. A Norwegian investigation [105] reported that 307 TCS treated between 1980 and 1994 had significantly increased risks of low testosterone as well as high-luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels after radiotherapy or chemotherapy at long-term follow-up. The degree of hypogonadism was directly related to the intensity of TC treatment [105–110]. A recent meta-analysis reported that both standard cisplatin-based chemotherapy (OR: 1.8) and infradiaphragmatic radiotherapy (OR: 1.6) significantly increased the risk of hypogonadism among TCS, as defined by total testosterone levels less than reference levels or use of testosterone replacement therapy, when compared to orchiectomy alone [110]. Hypogonadism may lead to reduced sexual functioning and well-being, fertility problems, muscle weakness, osteoporosis, loss of energy, and depression [111–117]. Further, hypogonadism is directly associated with the metabolic syndrome and CVD [29, 30, 32]. A recent multi-institutional cross-sectional study [118] reported that

over one-third of North American TCS had hypogonadism at a median age of 38 years; in addition, hypogonadism was associated with increased CVD risk factors (i.e., dyslipidemia, hypertension, and diabetes), erectile dysfunction, and medication use for anxiety/depression ($P < 0.05$). Health care providers should regularly assess TCS for symptoms of hypogonadism and check hormonal status as clinically indicated. Clinical symptoms of hypogonadism should guide treatment decisions with testosterone replacement therapy [7]. Referral to endocrinologists for evaluation and management of difficult cases should also be considered.

9. Infertility

The association of infertility and TC is well established. Approximately 50% of patients with newly diagnosed TC have decreased sperm counts (<20 million/mL), low sperm motility indices (<40), and a high percentage of abnormal sperm cells (>80%) prior to initiation of any radiation or chemotherapy [119]. In a multicenter prospective study of 2318 TC patients in Germany and Austria [120], TC patients had significantly reduced spermatogenesis in their contralateral testicles confirmed histologically when compared to healthy subjects. The overall conception and paternity rates among long-term TCS with known intention to conceive a child after treatment completion range from 49% to 88% in several investigations (range of median follow-up: 7 to 12 years) [109, 121–123].

Radiotherapy can adversely affect reproductive function of TCS in the short-term [124, 125], since spermatogonia are the most sensitive germ cells to radiation treatment [126]. In the SWOG-8711 clinical trial of 207 patients with seminoma [124], sperm concentration reached a nadir 4 to 6 months after completion of radiotherapy, but returned to pretreatment level by 10 to 24 months after end of treatment. Similarly, Gandini et al. [127] reported that the sperm counts of TC patients reached a nadir at 6 months after radiation treatment, but 94% of patients recovered sperm counts by 2 years after end of radiotherapy. Higher dose of radiation is directly associated with longer recovery time for sperm concentration, and the use of testicular shielding devices significantly improves recovery of spermatogenesis [124]. A recent investigation of 1191 Norwegian TCS (median follow-up: 11 years) confirmed that radiotherapy had no significant long-term effects on sperm counts when compared to the surgery-only cohort [125].

In a retrospective study [128] of 178 TC patients treated with cisplatin-based chemotherapy in England, 64%, 24%, and 15% of patients who were normospermic, oligospermic and azoospermic, respectively, in the prechemotherapy period recovered normal spermatogenesis at least one year after chemotherapy completion. Prechemotherapy normospermia (HR 6.0), use of carboplatin versus cisplatin (HR 4.4), and noninclusion of a vinca alkaloid (HR 5.3) in chemotherapy regimen were significantly associated with normal recovery of sperm counts [128]. Cumulative dose of cisplatin-based chemotherapy is directly associated with infertility risk [112, 123, 125, 128]. In a multicenter investigation [123] of 316 Norwegian TCS (median follow-up: 12 years), 100%, 83%, and 76% of survivors self-reported achieving posttreatment paternity after 2, 3, and 4 cycles of standard cisplatin-based chemotherapy, respectively ($P = 0.022$). However, sperm counts were not significantly related to number of cycles of chemotherapy in a limited cohort of patients for whom the results of semen analysis were available ($N = 71$) [123]. After a median follow-up of 10.6 years, another study [112] showed that TCS treated with high-dose chemotherapy (>850 mg cumulative cisplatin dose) had the lowest 15-year actuarial posttreatment paternity rate (48%) compared to 92% in the surveillance group and 60% in those treated with low-dose chemotherapy (≤850 mg cumulative cisplatin) ($P < 0.001$). Similarly, a recent investigation [125] reported that sperm counts and serum level of inhibin B were significantly lower in TCS treated with >850 mg cumulative cisplatin dose compared to those who had either surgery only or ≤850 mg cumulative cisplatin, whereas the serum FSH was significantly higher.

Among patients with stage II or III nonseminomatous germ cell tumor who have had a serologic complete response but have persistent enlarged retroperitoneal lymph nodes after cisplatin-based chemotherapy, RPLND is a standard treatment. To potentially avoid toxicities associated with cisplatin-based chemotherapy, RPLND is another treatment option for low-volume stage II nonseminomatous germ cell tumor with normal β-hCG and AFP levels after orchiectomy [62]. Injury to the retroperitoneal postganglionic sympathetic nerves during RPLND may result in retrograde ejaculation [126], leading to inability to conceive without use of cryopreserved sperm. The rate of retrograde ejaculation ranges from 1 to 9% after primary RPLND [129–131], 11% to 29% after nerve-sparing postchemotherapy RPLND [130, 132–134], and 75% after full bilateral postchemotherapy RPLND [135].

Health care providers should address the possibility of infertility and discuss fertility preservation options with TC patients as detailed by the American Society of Clinical Oncology Clinical Practice Guideline for fertility preservation for patients with cancer [136]. If clinically indicated, referral to appropriate reproductive specialists should be considered [136]. Sperm cryopreservation is a standard fertility preservation practice [136] that may be offered to interested TC patients undergoing treatment.

10. Avascular Necrosis

Avascular necrosis commonly affects the femoral head, often bilaterally [137], with an incidence of approximately 1-2% in long-term TCS treated with cisplatin-based chemotherapy [137, 138]. The etiology for avascular necrosis is multifactorial [7] but likely to be partially attributable to corticosteroids used as antiemetics during TC treatment [137–140]. Bleomycin and vinblastine have also been hypothesized as causative agents in a case of avascular necrosis in one TCS who did not receive corticosteroids during chemotherapy [141]. Health care providers should review with TC patients who receive high-dose corticosteroids the potential risk of avascular necrosis. For any long-term TCS who develops early symptoms suggestive of avascular necrosis, including

decreased hip motion and/or limp, prompt evaluation with plain radiograph or MRI is critical [7].

11. Cognitive Impairment

The underlying mechanisms of chemotherapy-related cognitive impairment have not been elucidated. Several neuroimaging studies of breast cancer survivors have reported that white matter activation patterns involved in cognitive functioning are altered after chemotherapy [142–144], likely due to neurotoxic effects [145]. A study [146] of 66 TC patients suggested that cortisol levels prior to chemotherapy may be a predictor of later cognitive complaints. The prevalence of cognitive impairment in men with newly diagnosed TC before receipt of any chemotherapy ranges from 46% to 58% and is significantly higher than expected in the healthy normal population ($P < 0.01$) [146, 147]. A prospective clinical trial [88] of 666 patients with metastatic TC in Europe showed that cognitive function decreased at 3 months after chemotherapy, though not at the level of clinical relevance but recovered to baseline values at 2 years for most patients, with 19% still having worsened cognitive function at that time. However, the association of cisplatin-based chemotherapy with cognitive impairment in TCS remains unclear. Whereas three studies [148–150] of TCS ($N = 70$–112; median follow-up: 1–3 years) reported no significant differences in performance on cognitive tests between TC treatment groups (i.e., surgery only versus chemotherapy), two investigations [151, 152] reported increased risks of cognitive impairment after chemotherapy. Among 1173 TCS with a median follow-up of 9 years, Skoogh et al. [151] reported a 2-fold increased risk (95% CI 1.3–3.1) of long-term compromised speech in survivors who completed five or more cycles of cisplatin-based chemotherapy compared to those who received no chemotherapy. Similarly, a single institutional prospective study [152] of TC patients after orchiectomy who either received adjuvant chemotherapy ($N = 55$) or no additional treatment ($N = 14$) reported that chemotherapy was significantly associated with cognitive decline with a dose-response relationship observed at 12 months (surveillance group: 0%; 2-3 cycles of chemotherapy: 52%; and 4–7 cycles of chemotherapy: 67%). Although the extent to which cisplatin-based chemotherapy may have negative effects on long-term cognitive function in TCS is unclear, cognitive complaints among long-term survivors are common and independent of treatment modality [88, 148–151]. These subjective complaints may reflect the effects of anxiety and depression, which are prevalent in TCS [148]. The first step in managing cognitive complaints may include managing specific stressors by implementing effective coping strategies.

12. Anxiety/Depression

A Norwegian study [153] reported a significantly higher prevalence of a Hospital Anxiety and Depression Scale-(HADS-) defined anxiety disorder among TCS (mean follow-up time: 11.3 years) compared to age-adjusted men from the general population (19.2% versus 13.5%, $P < 0.001$). Young age, peripheral neuropathy, economic difficulties, excess alcohol use, sexual concerns, and prior treatment for mental illness were significantly associated with HADS-defined anxiety disorder [153]. A recent investigation [154] showed that the prevalence of clinically significant anxiety among TCS (mean: 11.6 years after diagnosis) in Germany was 6.1%. Anxiety was significantly associated with younger age at diagnosis and shorter time since diagnosis in multivariate analyses. Prior studies [153–156] reported that the prevalence of depression among TCS ranges from 7.9% to 20%, but the extent to which TCS may experience significantly more depressive orders compared to the general population is uncertain. Feeling helpless/hopeless [156], lower social support [156], a higher number of physical symptoms [154], and having children [154] were reported to be significantly associated with higher levels of depression.

13. Fatigue

Chronic fatigue, defined as symptoms with a duration of ≥6 months, is a common and distressing cancer-related adverse effect [157]. The prevalence of chronic cancer-related fatigue among Norwegian TCS was significantly higher compared to age-matched men in the general population (17.1% versus 9.7%) [158]. A recent longitudinal investigation [159] of 812 TCS treated between 1980 and 1994 in Norway reported that the prevalence of chronic fatigue increased from 15% at survey I (1998–2002) to 27% at survey II (2007-2008) ($P < 0.001$). Several factors were significantly associated with chronic fatigue in this study: [159] high level of neuropathy, Raynaud-like phenomena, testosterone level in the lowest quartile, low level of physical activity, as well as higher levels of anxiety and depression. Health care professionals should consider exercise and psychological interventions for early prevention and treatment of chronic fatigue among TCS. A recent meta-analysis of cancer survivors [160] reported that exercise and psychological interventions are effective for reducing cancer-related fatigue during and after cancer treatment and significantly more effective than available pharmaceutical options.

14. Adverse Health Outcomes

To develop risk-stratified, evidence-based follow-up recommendations for TCS, characterization of long-term adverse health outcomes (AHOs) is critical. A recent multi-institutional investigation [40] of 952 North American TCS examined the type and prevalence of AHOs after chemotherapy with four cycles of EP (EPX4) or three or four cycles of BEP (BEPX3/BEPX4) (Table 3). At a median age of 37 years, more than one-third of survivors reported three or more AHOs with similar prevalence and type after EPX4 and BEPX3, except for Raynaud phenomenon (11.6% versus 21.4%; $P < 0.01$), peripheral neuropathy (29.2% versus 21.4%; $P = 0.02$), and obesity (25.5% versus 33.0%; $P = 0.04$). The type and prevalence of AHOs after BEPX4 were largely similar to EPX4 and BEPX3. Increasing age at clinical evaluation, current tobacco use, and nonmarried status were associated with increased numbers of AHOs, whereas weekly vigorous

Table 3: Numbers and types of self-reported adverse health outcomes among 952 cisplatin-treated germ cell tumor survivors in North America*.

Adverse health outcomes (AHOs)	Total patients ($N = 952$) N (%)	Treatment regimen		
		EP (4 cycles) ($N = 294$) N (%)	BEP (3 cycles) ($N = 364$) N (%)	BEP (4 cycles) ($N = 170$) N (%)
Total number of AHOs				
Median (range)	2 (0–11)	2 (0–9)	2 (0–11)	2 (0–10)
0	194 (20.4)	64 (21.8)	83 (22.8)	25 (14.7)
1	209 (21.9)	68 (23.1)	71 (19.5)	42 (24.7)
2	191 (20.1)	61 (20.8)	82 (22.5)	27 (15.9)
3	143 (15.0)	48 (16.3)	48 (13.2)	25 (14.7)
4	96 (10.1)	28 (9.5)	38 (10.4)	18 (10.6)
5 or more	119 (12.5)	25 (8.5)	42 (11.5)	33 (19.4)
Type of AHOs[†]				
Yes	353 (37.1)	104 (35.4)	130 (35.7)	65 (38.2)
No[‡]	599 (62.9)	190 (64.6)	234 (64.3)	105 (61.8)
Hearing impairment[§]				
Yes	300 (31.5)	95 (32.3)	109 (30.0)	56 (33.0)
No	652 (68.5)	199 (67.7)	255 (70.0)	114 (67.0)
Peripheral neuropathy[‖]				
Yes	257 (27.0)	86 (29.2)	78 (21.4)	54 (31.8)
No	695 (73.0)	208 (70.8)	286 (78.6)	116 (68.2)
Peripheral neuropathy plus tinnitus and/or hearing issue				
Yes	156 (16.4)	49 (16.7)	48 (13.2)	31 (18.2)
No	796 (83.6)	245 (83.3)	316 (86.8)	139 (81.8)
Hypertension and on prescription medication				
Yes	110 (11.6)	35 (11.9)	45 (12.4)	15 (8.8)
No[¶]	842 (88.4)	259 (88.1)	319 (87.6)	155 (91.2)
Hypercholesterolemia and on prescription medication				
Yes	100 (10.5)	32 (10.9)	31 (8.5)	20 (11.8)
No[**]	852 (89.5)	262 (89.1)	333 (91.5)	150 (88.2)
Cardiovascular disease[††]				
Yes	14 (1.5)	4 (1.4)	4 (1.1)	2 (1.2)
No[‡‡]	938 (98.5)	290 (98.6)	360 (98.9)	168 (98.8)
Raynaud phenomenon				
Yes	178 (18.7)	34 (11.6)	78 (21.4)	49 (28.8)
No[§§]	774 (81.3)	260 (88.4)	286 (78.6)	121 (71.2)
Peripheral vascular disease				
Yes	29 (3.0)	5 (1.7)	8 (2.2)	10 (5.9)
No[‖‖]	923 (97.0)	289 (98.3)	356 (97.8)	160 (94.1)
Thromboembolic disease[¶¶]				
Yes	5 (0.5)	0	0	4 (2.4)
No	947 (99.5)	294 (100)	364 (100)	166 (97.6)
Renal disease				
Yes	25 (2.6)	7 (2.4)	6 (1.6)	7 (4.1)
No[***]	927 (97.4)	287 (97.6)	358 (98.4)	163 (95.9)
Diabetes and on prescription medication[†††]				
Yes	30 (3.1)	9 (3.1)	10 (2.7)	3 (1.8)
No	922 (96.9)	285 (96.9)	354 (97.3)	167 (98.2)
Benign thyroid disease				
Yes	23 (2.4)	6 (2.0)	9 (2.5)	5 (2.9)

Table 3: Continued.

Adverse health outcomes (AHOs)	Total patients ($N = 952$) N (%)	Treatment regimen		
		EP (4 cycles) ($N = 294$) N (%)	BEP (3 cycles) ($N = 364$) N (%)	BEP (4 cycles) ($N = 170$) N (%)
No[‡‡‡]	929 (97.6)	288 (98.0)	355 (97.5)	165 (97.1)
Problems with balance/vertigo/dizziness[§§§]				
Yes	89 (9.3)	26 (8.8)	37 (10.2)	16 (9.4)
No	863 (90.7)	268 (91.2)	327 (89.8)	154 (90.6)
Hypogonadism with testosterone therapy[‖‖‖]				
Yes	93 (9.9)	25 (8.6)	37 (10.3)	16 (9.5)
No	851 (90.1)	267 (91.4)	323 (89.7)	152 (90.5)
Erectile dysfunction				
Yes	115 (12.1)	28 (9.5)	39 (10.7)	34 (20.0)
No[¶¶¶]	837 (87.9)	266 (90.5)	325 (89.3)	136 (80.0)
Psychotropic prescription medication for anxiety and/or depression[****]				
Yes	99 (10.4)	34 (11.6)	27 (7.4)	20 (11.8)
No	853 (89.6)	260 (88.4)	337 (92.6)	150 (88.2)

*Adapted with permission from Fung et al. [40] (Table 3). BEP: bleomycin, etoposide, cisplatin; CAD: coronary artery disease; EP: etoposide, cisplatin; MI: myocardial infarction. †P values are derived from the chi-square test comparing the proportions of AHOs reported by TCS in the EPX4 and BEPX3 treatment groups. Except for Raynaud phenomenon ($P < 0.01$) and peripheral neuropathy ($P = 0.02$), the P values for all other AHOs were >0.05; category includes 3 participants for whom this outcome was not stated; among all 952 participants, 270 (28.4%) reported problems hearing words, sounds, or language in crowds, 13 (1.4%) required hearing aid, and 2 (0.2%) had complete deafness (questions derived from the hearing handicap inventory by Ventry and Weinstein) [166]; 109 (11.4%) had "quite a bit" or "very much" difficulty hearing and 75 (7.9%) had "quite a bit" or "very much" reduced hearing (EORTC-CIPN20 and SCIN) ([167, 168]). Category includes 48 participants for whom this outcome was not stated; among all 952 participants, the number of patients reporting "quite a bit" or "very much" to the following questions are as follows: 123 (12.9%) tingling fingers or hands, 167 (17.5%) tingling toes or feet, 121 (12.7%) numbness in fingers or hands, 161 (16.9%) numbness in toes or feet, 34 (3.6%) shooting/burning pain in fingers or hands, 70 (7.4%) shooting/burning pain in toes or feet (EORTC-CIPN20) [167]; 134 (14.1%) pain and tingling in toes or feet, and 86 (9.0%) pain and tingling in hands or fingers (SCIN) [168]. Category includes 16 participants for whom this outcome was not stated; category includes 11 participants for whom this outcome was not stated; ** category includes 3 participants for whom this outcome was not stated; ††includes coronary artery disease, heart failure, and cerebrovascular disease (categories not mutually exclusive, and each category was counted as one AHO). Among all participants, 7 (0.7%) reported coronary artery disease (3 occurrences for coronary artery disease, 5 occurrences of angioplasty or stent, and 5 occurrences of heart attack or myocardial infarction); 1 patient reported heart failure; and 10 (1.0%) reported cerebrovascular disease (6 occurrences of transient ischemic attacks, 4 occurrences of stroke, and 1 occurrence of carotid artery surgery); ‡‡category includes 21 participants for whom this outcome was not stated; §§category includes 12 participants for whom this outcome was not stated; ‖‖category includes 19 participants for whom this outcome was not stated; ¶¶deep vein thrombosis (DVT) and pulmonary embolism (PE) developed simultaneously in 3 participants and was counted as one thromboembolic event for each. The remaining 2 participants reported DVT only. Category includes 19 participants for whom this outcome was not stated; ***category includes 26 participants for whom this outcome was not stated; †††among all participants, 13 (1.4%) and 22 (2.3%) reported use of insulin and oral antiglycemic agents, respectively (categories not mutually exclusive). Category includes 15 participants for whom this outcome was not stated; ‡‡‡category includes 19 participants for whom this outcome was not stated; §§§of the 89 patients, 47 reported persistent dizziness or vertigo and 63 reported symptoms of dizziness when standing up (categories not mutually exclusive). Category includes 40 participants for whom this outcome was not stated; ‖‖‖eight participants who underwent bilateral orchiectomy were excluded from this category; ¶¶¶category include 7 participants for whom this outcome was not stated; ****participants could report more than one psychotropic medication. Psychotropic medications used by the 99 participants include aripirazole ($n = 2$), alprazolam ($n = 5$), amphetamine-dextroamphetamine ($n = 9$), bupropion ($n = 10$), buspirone ($n = 1$), citalopram ($n = 6$), clonazepam ($n = 8$), desvenlafaxine ($n = 1$), diazepam ($n = 1$), duloxetine ($n = 7$), escitalopram ($n = 16$), fluvoxamine ($n = 1$), fluoxetine ($n = 4$), hydroxyzine ($n = 1$), lisdexamfetamine ($n = 4$), lorazepam ($n = 6$), methylphenidate ($n = 5$), nortriptyline ($n = 2$), olanzapine ($n = 2$), paroxetine ($n = 7$), trazodone ($n = 5$), sertraline ($n = 11$), and venlafaxine ($n = 7$).

physical activity was protective ($P < 0.05$). Self-reported health was excellent/very good in approximately 60% of TCS, but this proportion decreased as number of AHOs increased ($P < 0.001$) (Figure 2).

15. Conclusions

Due to their young age at diagnosis, long-term survival, and current use of largely homogeneous therapies, TCS comprise an ideal cohort for adult-onset cancer survivorship research [161]. Moreover, these patients now comprise approximately 4% of all male cancer survivors [162]. Table 4 summarizes major research priorities for TC survivors set forth at an international consensus conference [161]. An overarching recommendation was the development of longitudinal cohort studies to evaluate the life-long burden and latency trends of medical and psychosocial morbidities by category of treatment. TC is relatively unique among cancer types in that it provides for the ready availability of a "comparison group" cured with surgery only without the confounding effects of cytotoxic treatment, with which to compare the late effects of radiotherapy and chemotherapy. Moreover, study of the surgery-only group itself is informative and presents a unique opportunity to study the long-term history of a cancer cured without cytotoxic therapy, including any inherently preprogrammed development of adverse metabolic and other outcomes. This type of proposed cohort investigation, which gathers comprehensive exposure and outcome

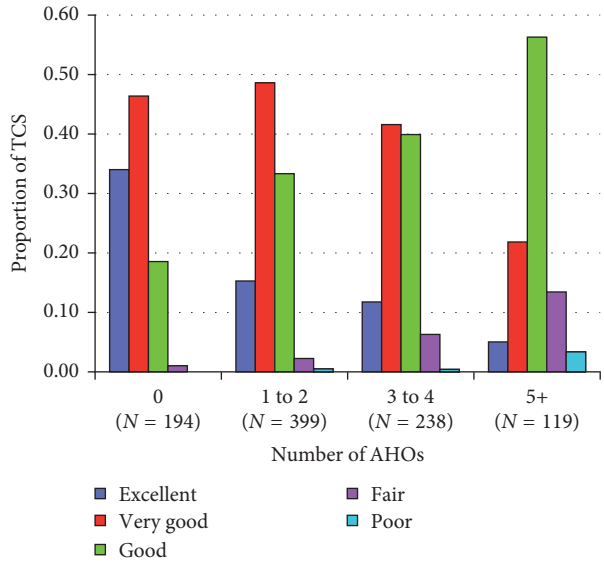

Figure 2: Proportion of testicular cancer survivors (TCS) with excellent, very good, good, fair, and poor self-reported health by number of adverse health outcomes (AHOs). P value for association of number of AHOs with self-reported health was <0.01 (Mantel 1 df chi-square test of trend). Self-reported health was not indicated by one participant with 1-2 AHOs and one participant with 3-4 AHOs. *Adapted with permission from Fung et al. [40] (Figure 1).

Table 4: Summary of major research recommendations: late effects of testicular cancer and its treatment.

(1) *Overarching recommendation: lifelong follow-up of all testicular cancer survivors (TCS)*
(i) Integrate observational and analytic epidemiologic studies with molecular and genetic approaches to ascertain the risk of emerging toxicities and to understand the evolution of known late effects, especially with the aging of TCS.
(ii) Evaluate the influence of race and socioeconomic status (SES) on the late effects of TC and its treatment.
(iii) Characterize long-term tissue deposition of platinum (sites and reactivity), serum levels, and correlation with late effects.
(iv) Evaluate the life-long burden of medical and psychosocial morbidity by treatment.
(v) Utilize research findings to establish evidence-based, risk-adapted, long-term follow-up care.
(2) *Specific recommendations*
(i) Second malignant neoplasms (SMN) and late relapses
(a) Determine the effect of reductions in field size and dose of radiotherapy, along with the use of carboplatin as adjuvant therapy in seminoma patients, on the risk of SMN.
(b) Examine relation between platinum-based chemotherapy and site-specific risk of solid tumors, the associated temporal patterns, and the influence of age at exposure and attained age.
(c) Compare risk of SMN in TCS managed with surgery alone to cancer incidence in the general male population.
(d) Examine delaying influence of platinum-based chemotherapy (and duration and magnitude of effect) on development of contralateral testicular cancer.
(e) Characterize the evolution of cured testicular cancer, in particular, the molecular underpinnings of late recurrences.
(ii) Cardiovascular disease (CVD)
(a) Evaluate the contributions and interactions of subclinical hypogonadism, platinum-based chemotherapy, radiotherapy, lifestyle factors (diet, tobacco use, and physical activity), body mass index, family history of CVD, race, socioeconomic status, abnormal laboratory values, and genetic modifiers.
(b) Develop comprehensive risk prediction models, considering the above variables, to stratify TCS into risk groups in order to customize follow-up strategies and develop evidence-based interventions.
(iii) Neurotoxicity
(a) Evaluate evolution of neurotoxicity across TCS lifespan, role of genetic modifiers, and extent to which symptoms impact on work ability and quality of life.
(iv) Nephrotoxicity
(a) Determine whether the natural decline in renal function associated with aging is accelerated in TCS, any influence of low-level platinum exposure, and the impact of decreased GFR on CVD and all-cause mortality.
(b) Determine the incidence of hypomagnesemia, together with the role of modifying factors and resultant medical consequences, in long-term TCS.

Table 4: Continued.

(v) Hypogonadism and decreased fertility
(a) Address the incidence, course, and clinical effects of subclinical hypogonadism.
(b) Evaluate effect of all levels of gonadal dysfunction in TCS on CVD, premature aging, fatigue, osteoporosis, mental health, quality of life, and sexuality.
(vi) Pulmonary function
(a) Examine role of platinum compounds on long-term pulmonary damage in TCS, and interactions with other influences, including bleomycin, tobacco use, and occupational risk factors.
(vii) Psychosocial effects
(a) Identify prevalence and predictors of depression, cancer-related anxiety, fatigue, infertility-related distress, problems with sexuality and paired relationships, and posttraumatic growth.
(b) Examine the impact of different cultural backgrounds on posttreatment quality of life.
(c) Evaluate TCS work ability throughout life.
(d) Determine whether normal age-related declines in cognitive function are accelerated in TCS.
(3) *Interventions*
(i) Conduct targeted intervention trials aimed at promoting smoking cessation, healthy dietary habits, and an increase in physical activity.
(ii) Evaluate the role of information and communication technologies in promoting a healthy lifestyle among TCS.
(iii) Consider randomized, pharmacologic intervention trials among TCS with biochemical parameters approaching threshold values to avoid accelerated development into treatment-requiring CVD.
(iv) Determine optimal schedule of testosterone replacement therapy among TCS with clinical hypogonadism.
(v) Consider screening strategies for selected SMN.
(4) *Genetic and molecular considerations*
(i) Evaluate genetic risk factors (identified in the general male population) as modifiers for all late effects in TCS, in particular, CVD, SMN, neurotoxicity, nephrotoxicity, hypogonadism, and psychosocial effects.
(ii) Investigate the role of genome-wide association studies, epigenetics, mitochrondrial DNA, microRNA, proteomics and related approaches in identifying genetic variants that contribute to the late effects of treatment.
(iii) Develop standardized procedures for biospecimen collection to support genetic and molecular studies, as reviewed previously.
(5) *Risk prediction models*
(i) Develop comprehensive risk prediction models that incorporate genetic modifiers of late sequelae.

*Adapted with permission from Travis et al. [161] (Table 2).

data, can provide the basis for identifying predictors of AHOs, either singly or jointly, for the eventual development of preventive and interventional measures. An important goal not only for TCS, but for cancer survivors in general, is the identification of genetic variants that predispose to the development of acute and long-term treatment toxicities. This elucidation of etiopathogenetic pathways provides another step towards developing targeted prevention and intervention strategies to optimize risk-based care, minimize chronic morbidities, and improve patients' quality of life.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Pediatric Germ Cell Tumors: A Developmental Perspective

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Germ cell tumors (GCTs) arising in infants, children, and adolescents present a set of special challenges. GCTs make up about 3% of malignancies in children aged 0–18 and nearly 15% of cancers in adolescents. Epidemiologic and molecular evidence suggests that GCTs in young children likely represent a distinct biologic group as compared to GCTs of older adolescents and adults. Despite this difference, pediatric GCTs are typically treated with cisplatin-based multiagent regimens similar to those used in adults. There is evidence that children are particularly vulnerable to late effects of conventional therapy, including ototoxicity, pulmonary abnormalities, and secondary malignancies, motivating the search for molecular targets for novel therapies. Evidence is accumulating that the genes and mechanisms controlling normal germ cell development are particularly relevant to the understanding of germ cell tumorigenesis. Perturbations in the epigenetic program of germ cell differentiation, with resulting effects on the regulation of pluripotency, may contribute to the marked histologic variability of GCTs. Perturbations in the KIT receptor signaling pathway have been identified via next-generation sequencing studies and in genome-wide association studies of testicular cancer susceptibility. Here, we review these and other biological insights that may fuel further translational and clinical research in childhood GCTs.

1. Introduction

"Pediatric germ cell tumor" is the term used to describe malignant cancers of germline cells in patients aged 0–18 years. These cancers may arise in the testis, the ovary, or the extragonadal sites including the sacrococcygeal area and the mediastinum. Germ cell tumors (GCTs) also occur in the brain in children and young adults. Though intracranial GCTs (iGCTs) are histologically similar to extracranial GCTs, it is unclear if tumors in the different sites arise by similar or different mechanisms, and the treatment approaches used are somewhat different; for these reasons, iGCTs are not further considered here.

Though the biology and clinical presentation of pediatric GCTs share significant overlap with that of adult testicular (T) GCTs, there are important differences that should be kept in mind. First, epidemiologic data reveal two distinct peaks in GCT incidence, one in young children (aged approximately 0–4 years) and a second peak beginning in puberty [1]. While the histologic presentation and molecular biology of GCTs arising in adolescents appear similar to those in adult TGCTs, germ cell tumors in very young children have important differences (reviewed below), suggesting that they may represent a distinct disease. Altogether GCTs make up about 3% of malignancies in children aged 0–18 and incidence rises with onset of puberty, GCTs account for 15% of the malignancies diagnosed during adolescence. As with adult TGCTs, the mainstay of treatment for pediatric GCTs is cisplatin-based multiagent regimens that have proved to be highly effective even in the setting of advanced disease. However, increasing evidence has emerged of adverse late effects in adult male survivors of TGCT, including a doubling of the risk of early-onset cardiovascular disease [2] and second malignancies [3, 4]. It is worth noting that GCTs were not included in the malignancies studied in the landmark Children's Cancer Survival Study, and thus, the potential long-term toxicities of

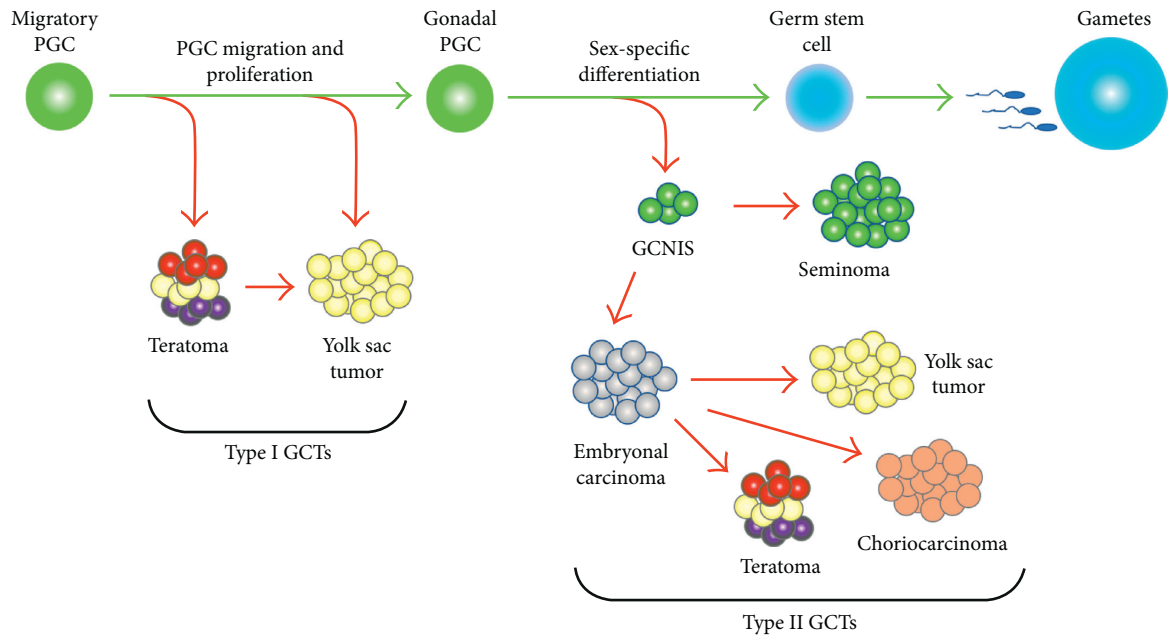

Figure 1: Germline development and histologic subtypes of GCTs. Primordial germ cells (PGCs) are specified early in embryogenesis and migrate through the embryo to the developing gonad. Type I GCTs exhibit a limited histologic spectrum, a partial erasure of genomic imprinting, and a propensity for development at extragonadal sites, all suggesting a derivation from early stages of germ cell development. Type II GCTs frequently contain foci of germ cell neoplasia in situ (GCNIS) and exhibit the full range of seminoma and nonseminoma histologies. Together with a more complete erasure of imprinting, these features suggest that the Type II tumors arise at a later stage of germline development.

conventional chemotherapy in pediatric GCT patients are still largely unknown. There is evidence that children are particularly vulnerable to late effects of therapy, especially ototoxicity and pulmonary abnormalities [5]. In a large cohort study, the cumulative risk of secondary malignancy also increased with decreasing age at diagnosis [4].

Finally, treatment regimens for pediatric GCT have largely been based on clinical trial results from adult men with TGCT, who represent the largest patient population. Whether these results apply equally to children with gonadal or extragonadal GCT remains to be established. In recent years, investigators in the Children's Oncology Group (USA) and the Children's Cancer and Leukaemia Group (UK) have joined forces to form the Malignant Germ Cell Tumor International Collaborative (MaGIC) Consortium to improve outcomes for patients with germ cell tumors (GCTs) by generating new insights into etiology, prognosis, toxicity reduction, and optimal treatment. MaGIC investigators have produced a revised evidence-based risk stratification for pediatric and adolescent GCTs based on amalgamation of 25 years of clinical trial data from the US and the UK [6] that separated patients into low-, standard-, and poor-risk groups. This risk stratification has in turn informed the development of the clinical trial AGCT1531 recently opened by the Children's Oncology Group (https://clinicaltrials.gov/show/NCT03067181), which aims to eliminate unnecessary chemotherapy in patients with Stage I disease at all sites (testicular, ovarian, and extragonadal) likely cured with surgery alone who will undergo active surveillance. AGCT1531 will also test whether the less-toxic carboplatin can be substituted for cisplatin in standard-risk patients. The COG will also be opening in the near future a trial for poor-risk patients, testing the efficacy of standard BEP chemotherapy versus accelerated BEP given every 2 weeks instead of every 3 weeks. This trial is conducted by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP). The clinical management of pediatric GCTs was recently comprehensively reviewed [7].

2. Histologic Presentation of Germ Cell Tumors

Several lines of evidence suggest that GCTs do not arise from a mature gonadal cell (e.g., a spermatogonial stem cell) but rather from a germ cell in early stages of development. This was discovered through an interesting set of observations that linked etiological phenomena to characteristics of the developing germline [8]. GCTs can be classified into two major types based on histology, known as seminomatous GCTs and nonseminomatous GCTs (Figure 1). Seminomatous GCTs are tumors which are made of undifferentiated germ cells which can histologically resemble early spermatogonia, oogonia, or even germ cells from developmental lineages. These tumors are called seminoma when present in the testis, dysgerminoma when present in the ovary, and germinoma when found in an extragonadal site. Nonseminomatous GCTs can be further subdivided into the distinct histologies of embryonal carcinoma (EC), yolk sac tumor (YST), teratoma (TER), and choriocarcinoma (CC). EC comprised undifferentiated cells that histologically resemble embryonic cells from the blastocyst. YST is the most common malignant GCT of young children. These tumors have a very complex endodermal morphology with components of both

embryonic and extraembryonic endoderm. TER histologically presents as a disordered mixture of differentiated cell types from all three somatic germ layers. In some cases, a component of a TER may acquire a unique neural differentiation state, known as an immature teratoma. CC is a rare histology and represents trophoblastic differentiation. In general, NSGCTs are more likely to be resistant to standard therapies. GCTs may present as a pure form with only one histology or as an amalgam of multiple types, known as mixed malignant germ cell tumor (MMGCT).

GCTs arising in children and adolescents can be further classified into two types depending on the age at presentation and histologic features [9]. Type I tumors generally present in children less than 4 years of age and may present as TER, YST, or mixtures of the two. Type II tumors arise around the time of puberty up through young adulthood and exhibit the full range of seminomatous and nonseminomatous histologies. Type II GCTs are often associated with a presumptive precursor lesion known as germ cell neoplasia in situ (GCNIS). GCNIS is a histologically diagnosed cell pattern usually seen in the normal tissue adjacent to the tumor [10] and is composed of undifferentiated germ cells that have proliferated within a seminiferous tubule [11]. GCNIS is not observed adjacent to Type I tumors, which are thus designated as non GCNIS-associated GCTs. These differences, along with molecular features discussed below, suggest that Type I and Type II GCTs may develop from germ cells at different stages of development.

3. Molecular Genetics of Pediatric GCTs

The most frequent chromosomal aberrations in Type II GCTs are amplification of chromosome 12p, usually through creation of isochromosome 12p, and amplification of the X chromosome. However, X amplification is an uncommon event in pediatric germ cell tumors, and 12p gain, while present, is infrequent [12]. Instead, pure YST, the most common malignant Type I GCT, has been shown to most commonly possess gain of 1q, 11q, 20q, and 22 and loss of 1p, 6q, and 16q [13]. Germ cell tumors also exhibit loss of genomic imprinting, which is partial in Type I GCTs and more complete in Type II GCTs. Since primordial germ cells undergo erasure of imprinting during germline development, this difference further suggests that Type I GCTs may arise from an earlier stage of development compared to Type II GCTs [14].

While the spectrum of somatic mutations in TGCTs is beginning to be defined (reviewed in this issue by Woldu et al.), little is known about the mutational status of pediatric GCTs. Addeo et al. found that *BAX* mutations in pediatric GCTs correlated with outcome [15]. At the transcriptional level, Palmer and coworkers found that Type I and Type II GCTs exhibit distinct gene expression profiles, even when controlling for histologic subtype [16]. Another important finding within GCTs is that the landscape of microRNAs (miRNAs) is changed relative to the normal gonad [17]. Palmer and coworkers demonstrated that the eight main miRNAs from the miR-371–373 and miR-302/367 clusters were overexpressed in all malignant GCT tissues [18]. Murray et al. further showed that levels of miRNAs from these two clusters were elevated in the serum at the time of diagnosis of an extragonadal malignant GCT, with levels falling and remaining low during uneventful clinical follow-up [19]. These serum findings were confirmed in extracranial malignant GCTs across a range of representative ages (pediatric/adult), anatomical sites, and histological subtypes, the majority of which were tumor marker negative [17]. These and subsequent studies suggest a possible role for miRNA profiling in GCT diagnosis and risk stratification.

4. Pediatric Germ Cell Tumors as a Developmental Disease: Vulnerabilities in Primordial Germ Cells

The primordial germ cell (PGC), responsible for specification of the germline, is unique among cells of the body in its requirement to maintain the pluripotent potential necessary for gamete generation. This requirement creates a unique developmental cycle which involves stages of vulnerability to improper differentiation. The PGC must be specified from the rest of the developing embryo through genetic and epigenetic events; it subsequently migrates throughout the body to the site of the gonad, and it must then undergo sex specific differentiation. Each of these stages reflects both a developmental feature and a clue related to the phenotypes and characteristics of germ cell tumors.

5. PGC Specification and Pluripotency

The first event in the development of the germline is the specification of PGCs in the early embryo. This specification event endows the PGCs with pluripotency as marked by a unique histological and genetic signature. PGC specification in humans occurs at ~2 weeks after fertilization when BMP signals target to the mesendoderm of the preprimitive streak embryo, which leads to the induction of SOX17 which, with BLIMP1, suppresses endodermal differentiation and activates PGC differentiation [20]. These cells express the pluripotency-associated markers OCT3/4, LIN28A, and NANOG histologically and begin a process of global DNA demethylation necessary for the later establishment of sex-specific gametic imprinting [21–23]. This genetic and epigenetic state creates the platform for development of the gamete, which leads to formation of the totipotent zygote after fertilization.

This unique developmental licensing of pluripotency is likely partially responsible for the extremely heterogeneous histological variation amongst germ cell tumors. Unlike most other tumor types, germ cell tumors may present with cells from each of the three germ layers as well as undifferentiated germline and extraembryonic cells [24]. In addition to GCTs exhibiting histological heterogeneity, it has been shown that both seminomas and nonseminomas retain pluripotency-associated protein expression (SALL4, OCT3/4, and LIN28A), which indicates the pluripotent growth potential even amongst the different differentiation states [24]. Furthermore, it has been shown that LIN28A expression in malignant GCTs is responsible for maintaining an undifferentiated

state through repression of the tumor suppressive let-7 miRNA family [25]. Additionally, the protein EPCAM, which is expressed in undifferentiated embryonic stem cells (ESCs), is associated with malignant nonseminomatous GCTs and has been suggested as a serum diagnostic marker in the treatment of GCTs [26, 27].

The second step of PGC specification, global demethylation, is another hallmark of GCTs and may be related to GCT susceptibility [20]. GWAS studies have revealed a GCT-associated SNP near the gene *PRDM14*, a key PGC pluripotency marker in mice [28, 29]. Though the function of PRDM14 is still being elucidated in humans, it is possible that it is involved in maintenance of the pluripotent state through the initiation of global demethylation, as it is in mice [30]. DNA demethylation at this stage allows for biallelic expression of genes [31]. Research on methylation states of the gene *SNRPN* revealed that most GCTs possess hypomethylation which lends credence to the idea that GCTs were derived from PGCs [32]. In addition to connecting GCTs to PGCs, this loss of transcriptional control likely provides a vulnerability in GCT development as loss of imprinting is a common event in many cancers [33]. This open epigenetic environment is thought to be protected by activation of the repressive chromatin modifications H3K27me3 and H3K9me3 concurrent with global demethylation. However, another testis cancer GWAS SNP near *ATF7IP*, a gene related to chromatin dynamics, may play a role in disrupting this repressive mark [34, 35]. Disregulation of ATF7IP with its cofactor SETDB1 may interfere with proper repressive chromatin marks, as it is known to be involved in creation of H3K9me3 marks, though further work is needed to establish this connection [36, 37]. It is likely that the pluripotent specification of PGCs as well as the physiological loss of imprinting naturally provides two pro-oncogenic conditions that may be coopted by improper differentiation cues.

This creation and maintenance of the pluripotent state prior to and during migration may explain the histologies specific to Type I GCTs, namely teratoma (TER) and yolk sac tumor (YST) [24]. As mentioned previously, TER frequently presents in a mature form with fully differentiated cell types. It is likely that these tumors are the result of improper regulation of pluripotency in which reacquisition of epiblast-like pluripotency during improper PGC specification results in cells that attempt to recapitulate embryonic development, including creation of the three germ layers. Cells in teratomas may not, however, receive the very specific spatial and temporal differentiation cues needed for proper embryogenesis, resulting in disorganized development. Type I teratomas are likely benign because the improper differentiation is the result of a failure of development rather than the acquisition of an oncogenic mutation.

In contrast to teratomas, YSTs are highly malignant. Old and new insights into PGC development may reveal why this tumor, which is composed of one germ layer, that is, endoderm (or two if one considers embryonic and extraembryonic endoderms separately), takes on a much more traditional tumorigenic phenotype. These tumors histologically resemble many differentiated endodermal structures, possess regions of primitive endoderm histology, and grow rapidly requiring treatment through surgical resection and adjuvant chemotherapy [24, 38]. As mentioned previously, PGC specification is controlled by a concerted effort between SOX17 and BLIMP1, the second of which is responsible for preventing endodermal differentiation [39]. This is required because SOX17 in the absence of BLIMP1 or even in excess of BLIMP1 is responsible for specification of the definitive endoderm, an endodermal structure responsible, through complex differentiation programs, for the development of most adult endodermal structures [40]. Kobayashi et al. recently showed in porcine, monkey, and human systems that even after PGC priming of mesendoderm cells, overexpression of SOX17 or loss of BLIMP1 resulted in differentiation to definitive endoderm [41]. Interestingly, almost 3 decades ago, it was shown in rats that externalization of fetal yolk sac primitive endoderm after fetectomy was capable of formation of malignant YSTs which could be transplanted to syngeneic rats [42]. This provides evidence that primitive endoderm cells have the capacity to grow rapidly and acquire oncogenic lesions which enhance growth when removed from their normal developmental location. Rather than terminally differentiating like their teratoma counterparts, they grow rapidly and act as the source of their own growth regulatory signals, as do many endodermal compartments [43]. This proliferative licensing of primitive endoderm may serve as the explanation for the GWAS SNP associated with HNF1β, which is an important transcription factor related to endoderm differentiation and maintenance [44]. Aberrations in HNF1β signaling in the context of a PGC may favor primitive endoderm misdifferentiation and subsequent YST formation.

6. PGC Migration and Proliferation

After the PGCs have been specified as the independent germ lineage, they must make their way to the gonadal ridge, proliferating en route, where they will receive subsequent differentiation cues for sex-specific development. However, this journey serves as a source of developmental vulnerabilities that may explain the frequent extragonadal localization of pediatric GCTs. After specification of the PGCs in the early mesendoderm ~2 weeks after conception, they make their way to the wall of the yolk sac endoderm [45]. Subsequently, PGCs migrate along the hindgut and midgut endoderm until near the gonadal ridge (GR) [46]. At this point, they migrate through the dorsal mesentery to the dorsal body wall where they migrate laterally to the GR. This migration generally results in the specific localization of viable PGCs to the GR; however, multiple sections of this tightly controlled migratory pathway present developmental vulnerabilities.

Pediatric germ cell tumors frequently present in extragonadal locations in pediatric patients. These locations are limited to midline structures such as the sacrococcygeal, retroperitoneal, mediastinal, cervical, and intracranial regions. The migratory route coupled with the molecular mechanisms governing PGC migration is likely the causal factor in GCT localization. Though the exact mechanism by

which PGC migration is controlled is not fully understood, multiple cytokine mechanisms have been implicated. Interruptions of these pathways have revealed ectopic germ cell localization. The GWAS SNP most strongly correlated to GCT risk resides in the *KITLG* locus. KITLG is the ligand of the KIT tyrosine kinase receptor, which is thought to regulate migration from the midgut to the GR, among other roles [47, 48]. Knockdown of CXCR4 and its ligand CXCL12 results in PGC mismigration and failure to reach the gonadal ridge after PGCs reach the dorsal wall [49]. β-integrin and E-cadherin cell surface proteins as well as surface lipids have been implicated in migration along the midgut endoderm [50]. Finally, a study by Runyan et al. revealed that PGCs that fail to exit the midline to enter the gonadal ridge are cleared through a BAX-dependent apoptotic program [51]. Intriguingly, GWAS studies found that an SNP near the *BAK1* locus, which is an important member of the BCL2-BAX-BAK1 antiapoptotic axis, was associated with GCT risk [52]. These observations together reveal the developmental vulnerabilities of PGC migration.

If perturbations of these migratory mechanisms result in failure to appropriately reach the GR, we might expect to find extragonadal GCTs (EGGCTs) in body regions that develop from the tissues along which PGCs migrate. The germ cells must migrate past the dorsal aorta from the dorsal mesentery on the way to the GR. Migration failure at this point would result in PGCs residing along and near the aorta which eventually reside in the mediastinum and the retroperitoneum, two frequent sites of EGGCTs [46]. Anterior-posterior, rather than lateral, mismigration along the body wall may be the mechanism for EGGCTs occurring in the sacrococcygeal and cervical regions. Aberrant migration from the hindgut could explain sacrococcygeal GCT prevalence as this structure is caudal and adjacent to the region which will form the tailbone. Intriguingly, another mechanism based on nerve fibers may explain the distal localization of some EGGCTs. Mollgard et al. found that PGCs migrate along nerve fibers from the midgut along the dorsal mesentery and into the GR. These PGCs associated intimately with the peripheral Schwann cells [53]. These data suggest that cells of the autonomic nervous system (ANS) may be responsible for secreting cytokines which PGCs recognize as migration and proliferative cues. This idea is further corroborated by studies involving the secreted neural signaling molecules PACAP and GDNF, both of which have migratory and proliferative effects on germ cells in vitro [53–55]. These proteins are both secreted by the ANS and could explain the cranial, cervical, and sacrococcygeal localization of ectopic PGCs and EGGCTs as these regions are thoroughly enervated by the ANS. Based on this evidence, further investigation of the link between PGC migration and ANS signaling is warranted.

During the migratory phase of PGC development, their numbers expand rapidly in order to properly colonize the GR. This proliferative step may be a key in the initiation of pediatric GCTs. The primary determinant of this proliferative step is KIT signaling. As PGCs migrate from the midgut to the GR, somatic KIT ligand (KITLG) secretion induces rapid PGC proliferation and suppresses apoptotic pathways used to clear ectopic cells [56]. The signaling axis relating to KIT-controlled proliferation has proven especially interesting due to the fact that two primary interactors have been discovered to have associated SNPs linked to GCT risk. SNP variants near the KITLG have revealed a GCT-associated odds ratio of approximately 2.5 which represents the strongest GCT SNP association to date and one of the highest general cancer associations described [47, 48, 57]. Mahakali et al. showed through a series of mutations to the KITL (murine KITLG homolog) that interruption of KITLG signaling resulted in diminished PGC proliferation [56]. In vitro assays have shown that excess KITLG can induce rapid proliferation of PGCs [58]. The KITLG association with GCTs may thus be due to a variation that causes some increase in KIT signaling, resulting in more robust PGC proliferation. This expansion of the pool would create two independent vulnerabilities to GCT development. Firstly, the rapidly dividing pool of cells is vulnerable to acquisition of mutations that may drive oncogenesis and becomes doubly so when proliferation is increased through excess KITLG secretion. Secondly, KIT signaling activates prosurvival pathways that would allow for expansion of cells that have acquired genetic lesions as well as survival of ectopic PGCs if the range of KITLG secretion was increased by the SNP variants. Further evidence strengthening the relationship of the KIT axis to GCTs is the discovery that an SNP near the gene SPRY4 is associated with GCT risk [47]. SPRY4 is an inhibitor of RTK signaling and has been shown to abrogate KIT signaling [59, 60]. An SNP at this locus resulting in reduced SPRY4 expression could serve a function similar to KITLG increase by failing to reduce KIT signaling. It has also been found that KIT is frequently mutated in intracranial germinomas; however, this finding may be an independent mechanism that helps to drive RAS signaling in Type II GCTs rather than an aberration of normal developmental pathways as would be the case in KITLG-mediated PGC proliferation [61]. This might explain why KITLG is associated with GCT risk for all histologies, while KIT mutations are limited to germinomas. These results suggest that pediatric GCTs are the result of specific aberrations in normal developmental pathways.

7. Germline Differentiation

Upon arrival to the nascent gonad, the PGCs must begin the transition from migratory pluripotent cells to either sperm or egg progenitors. This process is controlled through induction of sex-specific gene expression mediated by ligand secretion from the somatic cells of the gonad as well as circulating hormones. The set of developmental processes responsible for sex determination is tightly controlled, and interruption of these differentiation mechanisms represents the final set of vulnerabilities to pediatric GCT development. Work from Looijenga and colleagues has carefully laid out the case that failure of sexual development in the context of disorders of sex development (DSDs) is the proximate cause of the additional GCT risk observed in these patients [62].

As described above, Type II GCTs frequently exhibit a precursor lesion known as germ cell neoplasia in situ

(GCNIS) in otherwise normal gonadal tissue adjacent to tumor tissue [9]. These lesions exhibit histological markers, methylation status, and gene expression profiles that are remarkably similar to PGCs, which should normally be absent at the developmental stages at which GCNIS is observed [63]. The molecular mechanisms leading to the development of GCNIS and the transition of GCNIS to invasive cancer, including the possible role of oncogenic mutations, are active areas of investigation. In vitro, PGCs can dedifferentiate to a state resembling a pluripotent embryonic germ cell (EGC), under the control of Akt/PI3 kinase signaling [64]. EGCs exhibit epiblast pluripotency marks such as OCT3/4 and SOX2 and are capable of teratoma formation [65]. Additionally, newly discovered SNP variants of the embryonic pluripotency-related genes ZFP42 and TFCP2L1 have been associated with GCT risk [66, 67]. Taken together, these experimental results emphasize the importance of the OCT3/4-SOX2-SOX17-BLIMP1 network in controlling the fate of developing germ cells. If primitive germ precursors indeed exist in a metastable state between pluripotency and differentiation, perturbations in this network could explain how GCTs can present with such varied histologies.

The unique susceptibility of PGCs to aberrant differentiation may explain the variety of genes implicated in GCT GWAS studies. Rather than traditional SNPs involved in pro-oncogenic or tumor suppressive activities, such as MYC or CDKN1A in colorectal cancer [68, 69], GCT SNPs may cause slight perturbations in PGC development that lead to differentiation failure, mismigration, or aberrant proliferation. This hypothesis is evidenced by multiple mouse models in which the loss of genes responsible for PGC maintenance and eventual sexual differentiation occurs, and testicular teratomas resembling Type I pediatric GCTs result [70, 71]. Two sentinel GWAS loci near the genes DAZL and DMRT1, which are responsible for specification of the germline during sexual development, have also been implicated in teratoma susceptibility [28, 47]. Loss of any of these three genes releases suppression of proliferation and pluripotency in PGCs [72, 73].

8. Conclusions

As the only nonsomatic tumor lineage in the body, GCTs exhibit a unique combination of varied histology, wide range of sites of presentation, and apparent lack of traditional oncogenic drivers, suggesting a prominent role for aberrant developmental pathways in the etiology of these cancers. A perspective that focuses on these mechanisms could be key to the development of differentiation-based therapies using either exogenous signaling ligands or small molecule activators or inhibitors of the relevant pathways, which might one day supplement or substitute for conventional cytotoxic therapies. The challenges of long-term adverse effects that arise in the treatment of malignant tumors in young children and adolescents create a powerful incentive for pursuing such approaches.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Review Article

Retroperitoneal Lymph Node Dissection as Primary Treatment for Metastatic Seminoma

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Reducing the long-term morbidity in testicular cancer survivors represents a major area of interest. External beam radiation therapy and systemic chemotherapy are established treatments for seminoma; however, they are associated with late toxicities such as cardiovascular disease, insulin resistance, and secondary malignancy. Retroperitoneal lymph node dissection (RPLND) is a standard treatment for nonseminomatous germ cell tumors (NSGCT) that has minimal long-term morbidity. Given the efficacy of RPLND in management of NSGCT, interest has developed in this surgery as a front-line treatment for seminoma with isolated lymph node metastasis to the retroperitoneum. Four retrospective studies have shown promising results when surgery is performed for seminomas with low-volume retroperitoneal metastases. To better determine if RPLND can be recommended as a primary treatment option, two prospective clinical trials (SEMS and PRIMETEST) are underway. This review will examine the literature, discuss the benefits/limitations of RPLND, and compare the methodologies of the two ongoing clinical trials.

1. Introduction

Seminoma with isolated retroperitoneal lymphadenopathy is typically treated with external beam radiation therapy (XRT) or systemic chemotherapy. There has been little change in these recommendations over the last few decades. However, evidence continues to mount with regard to the long-term morbidities associated with these treatments. The risk of secondary malignancies is approximately twofold higher in patients who have had either chemotherapy or XRT for management of germ cell cancers [1]. The risk of cardiovascular disease is also high with testicular cancer survivors having up to a 2.6-fold increased risk over 20 years. Importantly, these long-term toxicities have been linked to decreases in overall survival [2, 3]. Other side effects can include lung injury, metabolic syndrome, renal toxicity, and decreases in fertility. As most testicular cancer survivors will live many decades, the impact and incidence of these toxicities can be profound.

There has been a concerted emphasis to reduce treatment-related morbidity in testicular cancer. A greater utilization of active surveillance in stage I disease, decrease in radiation dosage, limitations in the fields of radiation, and single-agent chemotherapy are examples of efforts to mitigate long-term toxicities. In line with this philosophy, investigators have looked to surgery for treatment of low stage metastatic seminoma given its effectiveness in treating germ cell tumors.

2. Rationale for Retroperitoneal Lymph Node Dissection

Retroperitoneal lymph node dissection (RPLND) represents an attractive treatment option for metastatic seminoma mainly because of the surgery's well-established efficacy. In seminoma, RPLND is generally recommended for residual retroperitoneal masses >3 cm following risk-adapted chemotherapy. In nonseminomatous germ cell tumors (NSGCT), RPLND is a treatment option for patients with high-risk stage I

Table 1: Series of RPLND as primary treatment for seminoma.

Study	n	Stage	Type of RPLND	Discordant staging	Recurrence rate	Follow-up
Warszawski et al. [8]	63	I ($n = 45$) IIA ($n = 7$) IIB ($n = 6$) IIC ($n = 5$)	Open	24% 17.5% upstaged 6.3% downstaged	14% Stage I: 7% Stage IIA: 0% Stage IIB: 67% Stage IIC: 40%	79 mo
Mezvrishvili et al. [10]	14	I ($n = 10$) IIA ($n = 4$)	Open, nerve sparing	21% (all upstaged)	0%	56 mo
Hu et al. [11]	4	IIA ($n = 3$) IIC ($n = 1$)	Open, midline extraperitoneal, nerve sparing	50% 25% upstaged 25% downstaged	0%	25 mo
Lusch et al. [13]*	11	IIA and IIB	Open and robotic, nerve sparing	Not described	36%	18 mo

*Abstract.

disease and for residual retroperitoneal masses ≥1 cm following systemic chemotherapy for metastatic disease [4]. Importantly, it can be also the primary treatment for stage IIA NSGCT with negative serum tumor markers. Not only is the surgery therapeutic, but it offers accurate pathologic staging with up to 30% of patients with stage I NSGCT having occult metastases and up to 35% of patients with clinical stage IIA disease being downstaged to stage I disease [5].

There are several other reasons that make RPLND a logical treatment for seminoma. A major reason why the surgery has proven to be effective is because of the predictable pattern of lymphatic spread of germ cell cancers. Given that pure seminoma lacks choriocarcinoma, the histology known to spread hematogenously, this could theoretically make RPLND for seminoma even more efficacious. Additionally, physicians treating testicular cancer are already familiar with the procedure and the surgical morbidity continues to decrease. Template dissections and nerve-sparing approaches are established methods for preventing retrograde ejaculation. Newer techniques with laparoscopy or a midline, extraperitoneal approach can also minimize morbidity including decreases in blood loss and length of hospitalization [6, 7].

Lastly, XRT and chemotherapy have limitations. For example, patients with a horseshoe kidney, inflammatory bowel disease, or a history of radiotherapy are not good candidates for XRT. Those with renal insufficiency or pulmonary disease could be precluded from effective chemotherapy. In these cases, another treatment option could prove invaluable.

3. Retrospective Data

There have been four published studies that evaluate RPLND as a primary treatment for testicular seminoma (Table 1). The first study was reported by Warszawski and Schmucking in 1997 from Germany [8]. This study retrospectively reviewed the results of 63 patients with stage I and II seminoma after RPLND ($n = 63$) from 1975 to 1985 and compared the results with patients who received XRT. Most patients had stage I seminoma ($n = 45$), though some had stage IIA ($n = 7$), IIB ($n = 6$), and IIC ($n = 5$) disease. Table 2 provides a review of stage II seminoma TNM staging [9].

Table 2: Stage II seminoma.

IIA	Any pT/Tx	N1	M0	S0 or S1
IIB	Any pT/Tx	N2	M0	S0 or S1
IIC	Any pT/Tx	N3	M0	S0 or S1

cN1 = metastases to single or multiple retroperitoneal lymph nodes ≤2 cm in size; cN2 = metastases to single or multiple retroperitoneal lymph nodes 2–5 cm in size; cN3 = metastases to single or multiple retroperitoneal lymph nodes >5 cm in size; pN1 = metastases to single or multiple retroperitoneal lymph nodes ≤2 cm in size, no more than 5 positive lymph nodes; pN2 = metastases to single or multiple retroperitoneal lymph nodes 2–5 cm in size, metastases to >5 lymph nodes with none >5 cm in size, extranodal extension; pN3 = metastases to single or multiple retroperitoneal lymph nodes >5 cm in size. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, seventh edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

In those with clinical stage I seminoma, there was a 17.5% incidence of occult retroperitoneal disease, in line with current relapse rates seen in surveillance series. In patients with stage II seminoma, 6.3% were downstaged. In patients with stage I or IIA seminoma, with a median follow-up of 79 months, there was a 5.7% recurrence rate. The surgery provided excellent regional control with all the recurrences being identified as out of the retroperitoneal field. The efficacy of RPLND with larger nodal disease (>2 cm) decreased, with 6/11 (55%) patients recurring in the retroperitoneum.

Though there was no statistical difference in recurrence rates or actuarial survival when comparing XRT to RPLND, the authors concluded that results of XRT "seem to be superior." One reason the authors cited was that the in-field recurrence rate was lower after XRT. When closely examining this, the recurrence rates varied drastically when stratified by clinical stage. Importantly, there were no in-field recurrences after RPLND for stage I and IIA seminoma, which was the same for XRT.

The first of the three more modern studies was by Mezvrishvili and Managadze [10]. They evaluated the outcomes of ten patients with high-risk stage I seminoma and four patients with stage IIA disease. Of the patients with stage I seminoma, there were three (30%) with retroperitoneal metastases at the time of surgery. All patients with clinical lymph node metastases had confirmation of disease after

Table 3: Prospective clinical trials of RPLND in seminoma.

	SEMS (Surgery in Early Metastatic Seminoma)	PRIMETEST (Trial to Evaluate Progression Free Survival with Primary Retroperitoneal Lymph-Node Dissection (pRPLND) Only in Patients with Seminomatous Testicular Germ Cell Tumors with Clinical Stage IIA/B)
Phase	II	II
Inclusion criteria	Testicular seminoma Retroperitoneal *lymph node 1–3 cm in size* No more than two enlarged lymph nodes	Testicular seminoma Inguinal, paraaortic, or retroperitoneal lymph nodes classified as local or regional unilateral metastasis Maximum dimensions of *lymph node metastasis 5 cm* Allow patients who have received single dose carboplatin for stage I seminoma
Exclusion criteria	Second primary malignancy History of radiation/chemotherapy	Prior scrotal or retroperitoneal surgery History of radiation/chemotherapy (other than carboplatin)
Serum tumor markers	Beta-HCG normal Allow LDH and AFP up to 1.5 times upper limit of normal	Exclude AFP elevation suspicious for NSGCT
Primary endpoint	2-year recurrence-free survival	3-year progression-free survival
Secondary endpoints	5-year recurrence-free survival Treatment-free survival (time free from radiotherapy or chemotherapy) Complication rate (long and short term)	Overall survival Quality of life Complication rate Long-term sequelae
Accrual goal	46	30
Start date	August 2015	June 2016
Target completion date	August 2020	June 2021
Number of institutions	9	1
Primary location	University of Southern California	Department of Urology, Heinrich-Heine University, Duesseldorf
Principal investigator	Siamak Daneshmand	Peter Albers

RPLND, and none underwent adjuvant treatment. With a mean follow-up of 56 months, they did not have any cases with local or distant recurrence.

Our group has reported on the outcomes of four patients with pure testicular seminoma after RPLND [11]. Three patients had clinical stage IIA seminoma, and one patient had clinical stage IIC disease, with a lymph node 5.5 cm in size. This patient had a presumed burned out primary tumor with scar with dystrophic calcification on the orchiectomy specimen. Patients underwent an open, modified-template RPLND through a midline, extraperitoneal approach [12]. All patients were discharged home on postoperative day 3. Three patients had pathologic stage IIA disease, and one had stage IIB due to a 2 cm lymph node with extranodal extension. No patients underwent adjuvant therapy. With a median follow-up of 25 months, there were no recurrences or deaths.

Lastly, Lusch et al. from Germany have recently presented a series on open or robotic RPLND in patients with stage IIA/B seminoma [13]. They identified 11 patients who underwent RPLND. Three of these patients (22%) received one cycle of carboplatin prior to RPLND. With a mean follow-up of 18 months, they had a 36% recurrence rate. One of the patients with recurrence had more advanced disease with clinical stage IIC disease, an initial lymph node metastasis >6 cm, and a clinically positive inguinal lymph node. All patients who recurred were salvaged with radiotherapy and chemotherapy, and 3 out of 4 have no evidence of disease.

Taken together, these studies include a total of 92 patients with stage I-IIC seminoma and 14 who experienced recurrence. The overall recurrence rate for all patients was 14% with patients having higher stage disease being at greater risk of recurrence.

4. Clinical Trials

This retrospective data has established promising oncologic benefit of RPLND in early stage seminoma. There are currently two active prospective clinical trials formally evaluating the efficacy of the surgery (Table 3).

4.1. SEMS. Our group has started the SEMS (Surgery in Early Metastatic Seminoma) trial, which is a multiinstitutional phase II trial of primary RPLND to treat testicular seminoma with isolated retroperitoneal metastases [14]. The main inclusion criteria are testicular seminomas with the presence of at least one retroperitoneal lymph node between 1 and 3 cm in size. No more than two lymph nodes can be clinically positive. Serum tumor markers may be mildly elevated. The lymphadenopathy can be identified at diagnosis or can represent recurrence in a patient originally diagnosed with stage I

seminoma. The recurrence must be within 3 years of the cancer diagnosis in order to avoid enrolling those with late relapse that may represent a different biology.

The trial is currently open and accruing at 9 sites in the United States (University of Southern California, Loma Linda University, University of California San Francisco, Emory University, University of Chicago, Indiana University, Johns Hopkins, Mayo Clinic, and University of Oklahoma). The study has a primary endpoint of recurrence-free survival at 2 years. Secondary endpoints are recurrence-free survival at 5 years, percent of patients who can avoid XRT or systemic chemotherapy, and the complication rate of RPLND (short and long term). The estimated enrollment is 46 with a planned study completion date in the year 2020.

A clinical correlation in this study is utilization of PET scanning preoperatively. Though the established role of PET scanning in germ cell cancer is in postchemotherapy seminoma, it is often utilized in earlier stage disease. Patients undergoing RPLND will have a PET/CT scan done prior to surgery. These results will be compared with intraoperative lymph node pathology and may determine if this imaging modality has any utility in seminoma prior to chemotherapy.

4.2. PRIMETEST. The second study is PRIMETEST (Trial to Evaluate the Progression Free Survival with Primary Retroperitoneal Lymph-Node Dissection pRPLND Only in Patients with Seminomatous Testicular Germ Cell Tumors with Clinical Stage IIA/B) [15]. This study is based out of Heinrich-Heine University in Duesseldorf, Germany, and includes patients with testicular seminoma and retroperitoneal or inguinal lymphadenopathy with a maximum size of 5 cm. Only patients with unilateral disease are included in the study. The study includes those with multiple metastases as long as none is >5 cm. This trial also includes patients who experienced recurrence after a single dose of carboplatin chemotherapy.

Patients will undergo a modified-template RPLND, which can be done in the open fashion or laparoscopically with robotic assistance. The primary endpoint is progression-free survival at 3 years, and the study was designed to exclude a recurrence rate of >30% compared with standard treatment. Secondary endpoints include overall survival, complication rates, quality of life, long-term sequelae, and the rate of retrograde ejaculation. The study plans to accrue 30 patients with an estimated study completion of June 2021.

5. Limitations and Safety of RPLND

Given that RPLND for germ cell tumors have been performed since the early 1900's, the short- and long-term risks have been well documented [16, 17]. The long-term effects of the surgery include retrograde ejaculation, incisional hernia, and bowel obstruction. Most of the risk of surgery is associated with short-term complications including injury to retroperitoneal or peritoneal structures, ileus, bowel obstruction, chylous ascites, thromboembolism, and infection. We recently reported outcomes of our midline extraperitoneal approach to RPLND with no cases of ileus noted in 68 consecutive cases [6].

Some have expressed concern regarding the surgical planes with seminoma. The desmoplastic reaction after chemotherapy in seminoma can be intense and greatly increase the morbidity and technical difficulty of the surgery. This is secondary to the significant fibrosis that is seen with treatment of metastatic seminoma. However, from personal experience and reports from other surgeons who have performed these surgeries, the surgical planes in a primary RPLND for untreated seminoma are the same as would be encountered in NSGCT.

6. Managing Pathology after RPLND

A major benefit from surgery is that pathology can help inform management decisions. Ideally, RPLND will cure a large majority of patients while identifying those at high risk of recurrence. The high-risk patients can then be directed towards adjuvant treatments to further reduce recurrences. Factors such as lymph node positive count, lymph node size, and extranodal extension could become important in risk stratification.

In general, patients will fall into one of three categories after RPLND: those with more favorable pathology, those with the same pathology, and patients who have worse disease than anticipated. Those who are downstaged (e.g., stage I seminoma) could be placed on a less rigorous surveillance schedule. For the other two scenarios, it is important that the reasoning behind surgery be delineated early. In the SEMS trial, the rationale for RPLND is to give patients the opportunity to completely avoid XRT and chemotherapy, which is one of the secondary endpoints. This is the major reason why a ≤3 cm lymph node size was chosen. In patients with nonbulky lymphadenopathy, the data demonstrates that RPLND has a good chance of cure without adjuvant treatment. Therefore, if the pathology matches with the clinical stage, we feel that surveillance should be encouraged. However, in cases of upstaging, adjuvant treatment with chemotherapy can be considered. Chemotherapy is favored over XRT because chemotherapy can treat systemic disease and is preferred for higher stage disease.

The rationale behind the RPLND in the PRIMETEST trial is slightly different. This study hypothesizes that the 3-4 courses of chemotherapy for stage IIA or IIB seminoma is overtreatment. The investigators have selected a larger lymph node size of up to 5 cm, which will likely result in a higher recurrence rate. However, the investigators also hypothesize that a single, adjuvant dose of chemotherapy will reduce the recurrence risk with minimal long-term morbidity. If the recurrence rate from surgery is less than 30%, the investigators feel justified that RPLND with a short course of adjuvant chemotherapy will reduce morbidity. Additionally, they plan future studies to determine which patients can undergo surveillance and who should preferentially receive chemotherapy.

7. Conclusions

There are many reasons why RPLND represents a logical treatment for seminoma metastatic to the retroperitoneum. To date, there have been four retrospective studies that have

shown promising results when RPLND is utilized as a primary treatment for early metastatic seminoma. As would be expected, recurrence rates seem to increase with larger retroperitoneal metastases. There are two active phase II clinical trials evaluating the recurrence-free survival of patients after a primary RPLND. The SEMS trial is multi-institutional effort in the United States that includes patients with lymph nodes 1–3 cm in size. The PRIMETEST trial from Germany includes patients with lymph nodes <5 cm in size. The results of these studies will help determine if patients with metastatic seminoma will have a treatment option with minimal long-term morbidity.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Review Article

Adolescent and Young Adult Testicular Germ Cell Tumors: Special Considerations

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While testicular germ cell tumors (T-GCTs) make up only 0.5% of pediatric malignancies and less than 2% of adult malignancies, they comprise 14% of adolescent malignancies, making it the most common solid tumor in this age group. The transition in incidence at this age is also accompanied by a transition in tumor histology with adolescents having mostly pure embryonal carcinoma and mixed nonseminomatous germ cell tumors. Similar to T-GCTs of all ages, surgical excision with orchiectomy is the standard initial step in treatment. Chemotherapy, retroperitoneal lymph node dissection, and targeted treatment of distant metastases make even widely disseminated disease treatable and curable. For this reason, in many ways, the future focus has expanded beyond survival alone to emphasize quality of life issues such as fertility and hypogonadism. However, adolescents remain the age group least studied or understood as they fall in between the ages included in most study designs. Also, they require the most psychosocial support because of the challenges unique to the adolescent period. In this review, we aim to highlight the known outcome data for T-GCTs in this population and also to discuss the unique aspects of treatment and support for this age group.

1. Introduction

In pediatric oncology, significant advances have been made in survival of a variety of malignancies. The OS of children with cancer as a group approaches 80%, largely due to the collaborative efforts of cooperative groups [1]. However, numerous reports have shown that this triumph has not been evenly distributed across patients of all ages—the adolescent age group has not enjoyed the same success as younger children, and this has been specifically demonstrated for T-GCTs [2]. In fact, cancer in those aged 15–29 years kills more patients than any disease except suicide [3]. This is due to a host of reasons: delayed presentation and diagnosis [4], transition between adult and pediatric providers which may limit access to care [5], the disproportionate presence of high-risk pathologic components [6], poor treatment compliance [7], and a paucity of clinical trials and research focused on adolescents specifically. Perhaps the most relevant, however, is the lack of awareness of this age group as being unique [3].

Often, we assess adolescents along with those just slightly older and consider this group as adolescents and young adults (AYAs). The AYA population with cancer is a vulnerable group [4]. Compared with older adults with testicular cancer specifically, survival patterns differ [8], there are insurance coverage issues [5], and these patients are less likely to participate in clinical trials, are more likely to experience delays in diagnosis or treatment [9], and are more likely to suffer psychosocial problems and decreased quality of life related to their diagnosis [10, 11]. Because of these disparities, in 2006, the American Cancer Society and National Cancer Institute with help from the LIVESTRONG Young Adult Alliance called for future research to focus on cancer outcomes in AYA patients and established the AYA Oncology Progress Review Group [12]. Similarly, COG and SWOG have established dedicated AYA committees, and recently, the Society for Adolescent and Young Adult Oncology was funded. It is very important to understand that this term is used differently between studies and between large study groups: SEER 15–29 yr, NCI's AYA Oncology

Progress Review Group 15–39 yr, and NCCN guideline 15–39 yr [13].

To properly develop a focus on AYA testicular cancer, there needs to be focus beyond just diagnosis and treatment—and must include a focus on fertility preservation, emotional support for patients and families, socioeconomic support, educational encouragement, palliative care, and survivorship specialists to meet the needs of this unique population [5]. There also must be collaboration and cooperation of providers who care for children and adults and fluid transition between the two.

2. Disease-Specific Aspects Unique to the AYA Population

2.1. Ethnicity. Testicular cancer is the most common urologic cancer in the AYA males [4, 13, 14]. Worldwide, it disproportionately affects men living in developed nations (USA, Canada, Denmark, Switzerland, Norway, Australia, New Zealand, etc.), where its incidence is attenuating over recent generations. In contrast, the incidence is rapidly increasing in countries undergoing developmental transition (Croatia, Slovenia, Singapore, the Philippines, China, Costa Rica, etc.) [15]. Testis cancer in general, disproportionately affects white men. While the incidence of testis cancer in AYAs is increasing overall, there has been a very large (58%) increase in the Hispanic population over the non-Hispanic white population (7%) [16]. Also, within the AYA group, in the adolescent population specifically, there appears to be a disproportionate population of Hispanic males affected [17]. While survival after testicular cancer is high, several large population-based studies of men with testicular cancer of all ages have shown that non-Hispanic whites have an increased OS when compared to Hispanic whites [18], African Americans [17, 19], and nonwhites [20]. This has been confirmed in the AYA population, with African Americans and Hispanics having worse OS and CSS than whites, even after adjustment for neighborhood socioeconomic status [21]. When looking at patients with pure seminoma, however, the racial disparities are less impactful for unclear reasons [21].

2.2. Neighborhood/Socioeconomic Status. A recent study using the California Cancer Registry examined the association between the patients' sociodemographic factors (race/ethnicity and neighborhood socioeconomic status) and survival of AYAs with testicular cancer from 1998 to 2000 [21]. They identified just over 14,000 patients and found that AYAs from middle and low socioeconomic neighborhoods had a much lower OS and cancer-specific survival than AYAs from high socioeconomic neighborhoods, even when controlling for race/ethnicity. This difference was seen in both patients with seminoma and those with nonseminoma [21]. This trend, worse outcomes in lower socioeconomic neighborhoods, has been well described in the oncologic literature, across various cancers and in both children and adults [17, 22, 23]. It has been suggested that neighborhood socioeconomic status is an independent risk factor for survival, not just a surrogate for individual socioeconomic status, and it mediates poorer outcomes through neighborhood level factors, such as social environment, reduced quality and availability of healthcare and support services, and chronic stress [21].

2.3. Age. Patients aged 15–24 years with T-GCTs had an improved OS, but not cancer-specific survival, than those aged 25–39 years [21]. However, when comparing patients aged 15–19 years to those <15 years, there are significant decreases in OS [1]. When examining event free survival (EFS), patients aged 13–19 years have been shown to have a 3-year EFS of 60%, significantly worse than patients aged < 13 years (87%) and patients aged >19 years (80%) [2]. The seeming contradictions of these studies are apparent; however, it is very important to identify the endpoint specified, because a disease like T-GCTs is very salvageable, even after metastasis and recurrence. Thus, differences in OS may not be appreciated despite difference in EFS and other measures. There can also be differences in histology (high incidence of embryonal component and rare seminomas) as well as more advanced disease at presentation for adolescents. Specifically, it appears that the incidence of clinical stage I disease decreases with age: 70–80% of prepubertal children with T-GCT, 50–60% of adolescents with T-GCT, and 40–50% of adults with NSGCT [24–27]. Another factor associated with age is marital status. Married AYAs with testicular cancer had improved OS and cancer-specific survival than their unmarried counterparts [17, 21].

2.4. Histology. Interestingly, T-GCTs in prepubertal males are usually pure yolk sac tumors, which rarely metastasize [28], and pure teratoma, which is benign in this age group [29]. Pure seminoma is rare in the pediatric and adolescent population. When compared to pure seminoma, nonseminoma is most common in the AYA population and generally is of mixed histology, more frequently involves metastatic disease at presentation, and has a higher rate of relapse [30]. These mixed tumors, especially with embryonal components, are the most common seen in AYAs [31].

Stokes et al. [32] recently performed an analysis of the NCDB looking at patterns of care and survival outcomes for AYAs (age ≥ 15 years) with seminoma treated with primary surgery, known histology, and known outcomes. They identified 12,880 AYAs and compared this group to both adults aged 40–55 years (8,022) and >55 years (1,459). Compared to their adult counterparts, AYAs in this cohort were more likely to be nonwhite/nonblack, be uninsured, have fewer comorbidities, have clinical stage 1 disease at presentation, receive care at a high-volume institution, forego RPLND, and undergo surveillance over adjuvant therapy. Unadjusted 5- and 10-year OS was significantly better for AYAs than their older counterparts (98% and 96.1%, resp.). Factors associated with improved OS included AYA age, private insurance, high facility volume, stage 1 disease, and receipt of radiation therapy. Even controlling for other factors, AYA status remains significantly associated with improved OS. Interestingly, race was not significantly

associated with OS, unlike previous studies, while socioeconomic factors (insurance status) were associated with OS. The authors suggest that the less frequent use of adjuvant therapy by AYAs than older adults highlights progress for these patients; judicious use of these therapies, all of which carry significant side effects over the long term, has still allowed an extremely high OS [32]. This study mirrors findings from a SEER database analysis and European registry data [33].

A complementary paper on NSGCT in the AYA population investigated the SEER database to evaluate the association between age and outcomes [17]. The authors identified 1,496 adolescents (13–19 years) and 12,467 adults (>19 years) with a median follow up of 71 months. 5-year OS for adolescents was 94% and adults was 92% ($p = 0.007$) with 5-year CSS of 95% and 94%, respectively ($p = 0.139$). Age was a significant predictor of both OS and CSS when controlling for other factors. They also found that, despite presenting more often with metastatic disease, adolescents had improved OS and CSS than adults.

2.5. Risk Factors for Metastatic Disease. Active surveillance is the current recommendation for both adults and children [34] with clinical stage 1 T-GCTs. However, we know that a significant proportion (20–30%) will harbor occult disease. In the adult population, the identification of high-risk features for harboring of occult metastases—lymphovascular invasion and an increasing component of embryonal carcinoma for NSGCT [35] and size > 4 cm and rete testis invasion for seminoma [36]—has allowed a risk-stratified treatment approach to be employed [34]. Cost et al. [37] reviewed 23 patients aged 7–21 years and found that about half of all patients had high-risk features (≥40% embryonal carcinoma or lymphovascular invasion), and almost 60% with high-risk features harbored occult metastatic disease. No patients without high-risk features had metastatic disease. This confirmed that these same high-risk features for NSGCT in the adult population confer a similar risk for harboring occult metastatic disease in the pediatric and AYA population. While all relapses were successfully managed with 100% survival, the validation of these same high-risk features in the AYA population may lend themselves to counseling points for families and perhaps future incorporation into treatment strategies; however, they are currently not part of any treatment guidelines.

2.6. Surgery. Traditional teaching calls for radical orchiectomy for all testicular masses concerning for malignancy. Recent data suggest that partial orchiectomy/excisional biopsy via an inguinal incision may be safe in certain highly selected patients, and this has become common practice for the management of prepubertal pediatric testis tumors, regardless of the preoperative suspicion of teratoma [38]. For postpubertal boys, the authors' current practice involves performing a partial orchiectomy if patients have a mass < 2 cm *and* normal tumor markers, regardless of suspected pathology (manuscript in submission). Intraoperative frozen section is then utilized; if there is any concern for T-GCT, a radial orchiectomy is completed at the same setting. However, if the pathology returns benign or not concerning for T-GCT, the partial orchiectomy is completed and that testis has retained fertility and hormonal function [39]. Partial orchiectomy is not being advocated for or used to treat T-GCTs, but rather it is proposed as an initial step to preserve gonadal function in patients with small testicular masses and normal tumor markers due to the associated high rate of benign pathology. Although unilateral radical orchiectomy preserves contralateral testicular function, Leydig cell dysfunction and hypogonadism may develop prematurely, making T-GCT survivors at risk for androgen deficiency into adulthood [40].

2.7. Treatment. Because of similar tumor biology, postpubertal T-GCTs are best managed using adult algorithms. Individual pubertal status needs to be determined before discussing any treatment. Traditional pediatric regimens have been thought to undertreat adolescents with T-GCTs and may contribute to worse outcomes in adolescents over adults [6]. Indeed, the staging is different for patients with T-GCTs that are prepubertal (COG staging system) compared to postpubertal (AJCC TNMS system and IGCCCG system for metastatic disease), and the emphasis on postchemotherapy surgery differs. These differences are highlighted in Table 1. Additionally, COG remains concerned about long-term effects of cisplatin exposure (ototoxicity, nephrotoxicity, peripheral neuropathy, etc.) and is investigating the role of carboplatin versus cisplatin for children with T-GCTs. While adult studies have demonstrated a superior effect of cisplatin, pediatric studies have shown that higher dose carboplatin is associated with similarly good outcomes for children with T-GCTs [41]. Many adult urologic oncologists may be hesitant to place patients onto this COG study given their belief that randomization to the carboplatin arm is substandard of care therapy. COG protocols generally target patients aged 15 years and younger, with most postpubertal patients, which would include AYAs, being treated per adult algorithms [5].

The vast majority of adolescents and AYAs with clinical stage I disease should undergo active surveillance, per NCCN guidelines. The relapse rate is 20–30%, with excellent survival after salvage therapy. Even in the presence of high-risk features and high risk of relapse, the potential for morbidity with overtreatment of 70–80% of patients without a clear survival advantage makes an aggressive upfront treatment approach less desirable [42]. This approach prevents overtreatment and associated side effects while reserving highly effective salvage therapy for those who truly need it.

2.8. Long-Term Outcomes. There have been huge advances with long-term survival of AYAs with testicular cancer, so there has been a focus shift towards quality of life and late effects of treatment. A recent review of quality of life outcomes has shown that long-term testicular cancer survivors were comparable to age-matched controls, including mental health and sexual function, and that any decreases in quality of life were not related to treatment modality [43, 44]. For

Table 1: AJCC versus COG staging for testicular tumors [5].

Stage	AJCC	COG
I	$pT_{1\text{-}4}N_0M_0S_0$ IA: $pT_1N_0M_0S_0$ IB: $pT_{2\text{-}4}N_0M_0S_0$ IS: $pT_{1\text{-}4}N_0M_0S_{1\text{-}3}$	Tumor limited to testis, completely resected by high inguinal orchiectomy; no clinical, radiographic, or histologic evidence of disease beyond the testis Normal or unknown tumor markers at diagnosis must have negative ipsilateral RPLND to confirm stage I disease if imaging shows LNs > 2 cm Scrotal orchiectomy with high ligation of the cord is also considered stage I
II	$pT_{1\text{-}4}N_{1\text{-}3}M_0S_{0\text{-}1}$ IIA: $pT_{1\text{-}4}N_1M_0S_{0\text{-}1}$ IIB: $pT_{1\text{-}4}N_2M_0S_{0\text{-}1}$ IIC: $pT_{1\text{-}4}N_3M_0S_{0\text{-}1}$	Transscrotal biopsy; microscopic disease in scrotum or high in spermatic cord (< 5 mm from proximal cord margin) Failure of tumor markers to normalize or decrease with an appropriate half-life
III	$pT_{1\text{-}4}N_{1\text{-}3}M_1S_{0\text{-}1}$ IIIA: $pT_{1\text{-}4}N_{1\text{-}3}M_{1a}S_{0\text{-}1}$ IIIB: $pT_{1\text{-}4}N_{1\text{-}3}M_{0\text{-}1b}S_2$ IIIC: $pT_{1\text{-}4}N_{1\text{-}3}M_{0\text{-}1b}S_3$	Retroperitoneal LN involvement without visceral or extraabdominal involvement LNs > 4 cm by CT or 2–4 cm if biopsy proven metastatic
IV		Distant metastasis, including liver

those treated during adolescence, however, lower rates of fertility, body image, and sexual function have been described [45].

3. Late Effects

Important to consider is that this group of patients has a longer life expectancy than older adults. Thus, the long-term sequelae of systemic treatments (radiation, chemotherapy, and surgery) should be seriously considered, and monitoring for these complications is necessary. The NCCN has published a clinical guideline for AYA oncology patients, which all providers caring for this group of patients should review and have readily available. This nicely summarizes risks specific to this patient population as well as screening guidelines for survivors [13].

3.1. Fertility. All adjunctive treatment strategies beyond radical orchiectomy (chemotherapy, RPLND, and radiation) are associated with potential fertility issues, either transient or permanent. A recent survey of cancer survivors ranked fertility questions as the second most common concern behind mortality [46]. Every effort should be made to perform nerve sparing RPLND when necessary, and some advocate for referral to high-volume centers. Sperm cryopreservation is the most effective method to maintain fertility potential, but this must be initiated prior to treatment for testicular cancer. There are a host of issues surrounding cryopreservation, including young age and collection methods, anxiety associated with cancer diagnosis, and high cost of preservation. AYA patients and their families may not immediately think of fertility to be important given a diagnosis of malignancy and the patient's current life stage, so it is the responsibility of the provider to address this issue head on, prior to treatment initiation. Early involvement of an oncofertility specialist can help patients and families work through banking [5].

3.2. Secondary Malignancy. For at least 35 years after treatment, patients who have received chemotherapy or radiation are at higher risk of developing a secondary malignancy over the general population who has not been exposed to these agents [47]. The relative risk of development of a secondary malignancy is 1.8 for radiation, 2 for chemotherapy, and 2.9 for a combination of chemotherapy and radiation [48]. Etoposide specifically carries a risk of developing a secondary leukemia that is highly resistant to available therapies. This risk is correlated with total dose received and is increased in combination with radiation exposure [49]. Smoking and excessive alcohol consumption, common behaviors in AYA cancer survivors, has been shown to increase the risk of malignancy in bladder/prostate rhabdomyosarcoma patients, who are also at increased risk of secondary malignancy due to the chemotherapeutic agents and radiation used to treat their disease [50]. Patients with T-GCTs may receive similar therapies to the rhabdomyosarcoma population, albeit with differing doses, fields, and agents. However, they too are at higher risk for secondary malignancies and probably also engage in cigarette use and excessive alcohol consumption. It is not unreasonable to infer that these patients may be further increasing their risk of malignancy with these behaviors and should be counseled to avoid these activities.

3.3. Chemotherapy. Cisplatin-related nephrotoxicity via proximal tubular dysfunction is well described. Decreases in glomerular filtration rate, hypomagnesemia, and proteinuria have all been reported with this drug that is highly effective for T-GCTs. A recent study calculated a 10% risk of stage 3 chronic kidney disease for those exposed to a median of 4 cycles of cisplatin during treatment, and rate of progression increased with more cycles of chemotherapy [51]. Another review of 63 children treated with cis- or carboplatin showed no significant change in renal function over time, measured 10 years after completion of therapy. However, 11% of patients had an eGFR < 60 mL/min/1.73 m^2, which is not insignificant. Older age at the initiation of therapy was associated with a lower GFR [52].

About 1 in 6 patients will report peripheral neuropathy, and this is due to cisplatin exposure [53]. Similarly, high-frequency hearing loss is seen in 20–40% of patients exposed to cisplatin (dose-dependent), and this is usually permanent

[54]. Other long-term effects of cisplatin exposure include cardiovascular disease, paresthesia, hypogonadism, hypercholesterolemia, and hypertension. Interestingly, studies have confirmed that platinum and platinum-based residuals remain in circulation up to 20 years, and it is thought that perhaps these contribute to long-term complications [55]. In this same study, renal function 1 year after treatment was associated with the level of platinum remaining, meaning that the relationship between renal function and drug goes both ways—the drug damages the kidneys, and because of this, there is more drug left in the system, perpetuating its effects [55]. It is postulated that there may be therapy-related vascular changes that could contribute to the increased cardiovascular disease and increased incidence (6%) of myocardial infarction in these patients, illustrating that the implication of a single agent/therapy as the cause for a specific complication has been difficult to determine thus far [56].

Bleomycin has been linked to lung disease in a dose-related fashion, with about 5% of patients developing pulmonary fibrosis. Risk factors for bleomycin toxicity include increased age, concomitant chest radiation, decreased renal function, and elevated concentrations of inspired oxygen. Unfortunately, radiographic evidence of bleomycin toxicity may be seen as pleural-based nodules, which may be mistaken for relapsed or refractory disease (these resolve over time) [54].

Metabolic syndrome has been reported to occur in about 25% of T-GCT survivors. The exact mechanism for this is unknown, but testosterone and Leydig cell function have been implicated, although not uniformly across studies [57].

Hypogonadism is estimated to occur in 10–15% of patients after unilateral orchiectomy [58, 59], resulting in the need for androgen replacement. Preserving gonadal function may also reduce the clinically underrecognized but real rates of osteopenia and osteoporosis in these patients [60].

3.4. Psychosocial Effects. Adolescence is a tumultuous time in life, where all changes and experiences are amplified. Most teenagers feel that even ordinary challenges are difficult to overcome and that they are facing these challenges alone. On top of this baseline feeling, a cancer diagnosis clearly radically changes the patient's life and their needs when confronted with cancer are greater than older patients. The AYA population has a significant need for psychosocial support; cancer and subsequent therapy will create significant change in their social lives and interactions, which are central to being a teenager. There are obvious changes that will occur; self-image will be affected by hair loss, weight changes, mood alterations, nausea, febrile illness and hospitalizations, isolation due to infectious risk, etc. Impaired sexual function due to infertility, impotence, and an inability to feel that the patient was having any type of intimate relationship are major issues during this life stage. While these issues are common for an adult urologist to discuss with their patients, regardless of whether the patient has cancer, pediatric patients and providers are often uncomfortable discussing these personal details. Conversely, adult providers rarely acknowledge the impact of adolescence and puberty on a patient's everyday health, attitudes, and compliance [32].

Patients in the AYA age group are often at a cross roads with respect to education and career decisions. Cancer obviously detracts from the attention that is usually paid to these decisions, which seriously impact a person's identity. Pursuing treatment may affect a patient's ability to work and earn an income, which may lead to financial challenges that are then augmented by the cost of cancer treatment and insurance issues that are already prevalent in this age group. In addition to the obvious financial implications, this may be associated with guilt about not being able to meet basic expectations. After therapy, in the survivorship stage, resuming normal work or school life activities can be difficult. More than half of cancer survivors have problems continuing work or education after therapy cessation [61]. Expectation for both the patient and employer/school is one of the biggest factors in the success of transitioning back to normal life. Additionally, maintaining some type of involvement in work/school life during therapy, even if minimal, is associated with increased success with reentry long term [61].

Relationships, both with friends and partners, are central to AYA lives and can be severely impacted by cancer diagnosis and treatment. Partners may be lost or have feelings of fear of relapse, guilt, or sympathy. A father or brother with testicular cancer increases a male's risk of testicular cancer four times over the general population (2 or more relatives, 10x increased risk), and the development of testicular cancer tends to be at a similar age, but not necessarily the same histology [62]. Thus, there are unknown genetics and predisposition for existing children and when considering expanding families, which may result in tension between partners and thus a strained relationship [5]. Additionally, care of young children during cancer treatment can be unpredictable and yet another source of strain on a relationship [13].

These challenges are more than those experienced in either the adult or pediatric population and thus providers are usually unprepared to handle them. Providers generally provide a narrow, focused, technical view of diagnosis and treatment, which may further isolate the patient and his family, marginalizing their concerns. To fix this, early involvement of a multidisciplinary team, including mental health providers, is necessary. Not only will this improve mental health, stress levels, and quality of life, but it will increase compliance and hopefully survival, a central issue with the AYA population. Being aware of the issues, creating a team, and being prepared is the first step to face these issues head on [5].

4. Conclusions and Future Directions

For all the above reasons, the AYA population truly is unique with its own particular set of challenges. While the end goal is to improve outcomes, namely survivorship, there are a host of other issues that need to be addressed. These issues will not be able to be tackled without a multilayered approach to both clinical and translational research. AYA oncology education and awareness need to be increased, areas of research that will most directly lead to improved survivorship or quality of life for need to be prioritized, and

there needs to be increased funding for researchers committed to studying this population. Increased awareness on the national level with various new societies and groups is occurring, but urologists need to be advocates at the institutional level to raise awareness and education about this unique population [5].

Recently, novel biomarkers such as microRNA clusters have been identified that are uniformly overexpressed in all malignant GCTs, regardless of patient age, subtype, or site. While these remain a research tool and are not yet prevalent in everyday practice, they remain an exciting possibility for diagnosis (new staging criteria?) and surveillance (instead of CT scans?) of patients with T-GCTs [63].

Patient care collaboration through the development of and referral to highly experienced treatment teams have been shown to improve outcome for patients with T-GCTs. With increasing technology available to share information between centers, expertise can reach farther than a single institution into smaller community practices for advice and allows for improved coordinated referrals to these large volume centers [64]. A huge area in need of improvement for this group is clinical trial participation. More than 90% of children participate in clinical trials, while about 10% of teenagers and even fewer young adults do participate [28]. Providers need to educate patients and families about study trial opportunities that exist and need to create trials that specifically target this population [5].

Abbreviations

OS: Overall survival
AYA: Adolescent and young adult
NCCN: National Comprehensive Cancer Network
NCI: National Cancer Institute
CSS: Cancer-specific survival
T-GCT: Testicular germ cell tumor
NSGCT: Nonseminomatous germ cell tumor
EFS: Event free survival
NCDB: National Cancer Database
RPLND: Retroperitoneal lymph node dissection
SEER: Surveillance, Epidemiology and End Results Program
COG: Children's Oncology Group
SWOG: Southwest Oncology Group
AJCC: American Joint Committee on Cancer
TNMS: Tumor, node, metastasis, serum
IGCCCG: International Germ Cell Cancer Collaborative Group
eGFR: Estimated glomerular filtration rate.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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