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Pelvic Surgery

Guest Editors: Constantine P. Karakousis and Harold Wanebo

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Editorial Board

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Editorial

Pelvic Surgery

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The present issue of the International Journal of Surgical Oncology on Pelvic Surgery contains a series of articles on prostate cancer, gynecologic malignancies, and rectal cancer.

The article on "radical prostatectomy as a first-line treatment in patients with initial PSA >20 ng/mL" by Hinev et al. reports on patients diagnosed with prostate cancer (PCa) and PSA >20 ng/mL. The elevated PSA level is considered an adverse prognostic factor in PCa often regarded as contraindication to radical surgery. The authors purported to estimate the impact of radical prostatectomy (RP) on biochemical-recurrence-(BCR-) free and cancer specific survival (CSS) for these patients. Men in this group had significantly lower 10-year BCR-free and CSS rates than patients with initial PSA <20 ng/mL (20.7% versus 79.6%/$P < 0.001$/and 65% versus 87.9%/$P = 0.01$, resp.). Pathological stages were found to be independent predictors of PSA failure in men with PSA >20 ng/mL. Patients with favorable prognostic variables (pT2, NO) had significantly longer disease-free and overall survival similar to those with initial PSA <20 ng/mL. High PSA values do not indicate poor prognosis uniformly and therefore along with patients with organ-confined PCa and negative lymph nodes may benefit from RP. In one series more than 50% of patients with initial PSA values above 20 ng/mL had undetectable PSA values over the first 5-years after RP. Similar results have been reported in other series with RP used as monotherapy. Neoadjuvant hormonal therapy is no longer recommended for patients subjected to radical surgical treatment. The authors suggest further studies in patients with initial PSA values >20 ng/mL and use of RP in order to verify the results of their study.

The article "Total pelvic exenteration (PE) for gynecological malignancies" by Diver et al. describes PE as the en-bloc resection of pelvic organs including reproductive structures, bladder, and rectosigmoid. It is commonly indicated for advanced primary or locally recurrent cancer without evidence of metastatic disease or elements which preclude resection. Major complications occur in as many as 50% of the patients. In carefully selected patients with gynecologic cancer PE can be curative. Separate stomata for urine and fecal diversion and the use of omentum to protect and cover the denuded surfaces and more recently development of techniques to remove involved pelvic side wall have increased the chance of curative surgery. Laparoscopic and robotic-assisted technology has improved operative recovery while a 5-year survival rate of about 50% has been reported. Various techniques for functional neovaginas have been developed. Anterior and posterior exenteration techniques are described. PE is usually performed with curative intent but palliative PE has been used in cases mainly of severe radiation necrosis. The authors describe extensively complications and quality of life after PE and provide useful overall information in doing PE for gynecological malignancies.

The article by A. F. R. Cubal et al. on "Fertility-sparing surgery for early-stage cervical cancer" reviews data on procedures for fertility preservation, that is, vaginal and abdominal trachelectomy. The overall oncologic safety is good compared to radical hysterectomy offered traditionally and the obstetrical outcomes are promising. Good selection of patients and complete information with a detailed informed consent is required. The authors describe the eligibility criteria in terms of tumor dimensions, depth of invasion,

type and grade and lymphovascular space involvement. The procedures of vaginal and abdominal radical trachelectomy are described, as well as the follow-up and use of less radical procedures. Neoadjuvant chemotherapy has been employed in women with larger cervical lesions (>2 cm) in order to decrease the tumor size and provide a more conservative endocervical tissue resection. In conclusion, radical vaginal trachelectomy is a well-established safe procedure for early cervical cancer (<2 cm) with good oncological and obstetrical outcomes and low morbidity-mortality rates. Open abdominal or laparoscopic approaches are increasingly used which along with robotic surgery will provide more surgical options for these patients.

The article on "The Retrograde and Retroperitoneal Totally Laparoscopic Hysterectomy for Endometrial Cancer" by E. Volpe et al. describes their experience for total laparoscopic hysterectomy based on completely retrograde and retroperitoneal technique for surgical staging and treatment of endometrial cancer. The technique used was based on a combination of a retroperitoneal approach with a retrograde and lateral dissection of the bladder and retrograde culdotomy with variable resection of parametrium. The authors' laparoscopic technique and retroperitoneal approach allows control of the main uterine vessels, constant monitoring of the ureters and exposure and removal of the lymph nodes as needed. The procedure has been used in 95 patients (Jan 2002–Dec 2011). It has cost savings implications and does not require a uterine manipulator which is, when used, a concern for possible dissemination of tumor.

The article on "Intersphincteric resection and coloanal anastomosis in the treatment of distal rectal cancer" by Gokhan Cipe et al describes clearly the technique of intersphincteric resection providing sphincter saving surgery for patients with distal rectal cancer as an alternative to abdominoperineal resection (APR). The extent of the intersphincteric resection (ISR) is distinguished into partial, subtotal and total. When the tumor spread is to or beyond the dentate line, total ISR should be done. If the distal edge of the tumor is more than 2 cm from the dentate line, subtotal ISR is performed, the distal resection margin being between the dentate line and the intersphincteric groove. When there is sufficient distal surgical margin, the distal line of resection can be on or above the dentate line (partial ISR). The common complications of ISR are anastomotic leakage, stricture, fistula, pelvic sepsis, bleeding etc. ISR has rates of local recurrence between 2% and 3%. The 5-year survival with ISR has been reported to be about 80% and disease-free survival 69%. In some studies the survival after abdominoperitoneal resection (APR) was lower than after ISR. Complete continence after ISR is observed in 30% to 86%, while fecal soiling occurs in 15% to 63% of patients. The authors conclude that sphincter-saving surgery may be the treatment of choice for distal rectal cancer which is of early stage, well differentiated or underwent objective regression after neoadjuvant therapy.

The article on "The role of secondary surgery in recurrent ovarian cancer" by D. Lorusso et al. reports that although primary complete cytoreduction and adjuvant Platinum-Paclitaxel chemotherapy is a well established treatment for intraperitoneal spread of ovarian cancer, the 5-year survival being about 30% the role of secondary cytoreductive surgery for recurrent disease is controversial. The authors discuss on how to identify patients most likely to benefit from a secondary cytoreduction and the prognostic factors for survival of whom complete debulking is the strongest predictor. Absence of ascites and reintroduction of platinum are also associated with prolonged survival. In addition, the authors address the issue of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). HIPEC has attracted considerable interest due to promising results in peritoneal colon cancer carcinomatosis but in ovarian carcinomatosis the survival benefit is not evident requiring a well designed prospective randomized phase III Trial. The authors believe that there is a role for secondary cytoreductive surgery in well selected patients (absence of ascites, good performance status and complete debulking).

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Review Article

The Role of Secondary Surgery in Recurrent Ovarian Cancer

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Despite optimal treatment (complete cytoreduction and adjuvant chemotherapy), 5-year survival for advanced ovarian cancer is approximately 30% and most patients succumb to their disease. Cytoreductive surgery is accepted as a major treatment of primary ovarian cancer but its role in recurrent disease is controversial and remains a field of discussion mainly owing to missing data from prospective randomized trials. A critical review of literature evidence on secondary surgery in recurrent ovarian cancer will be described.

1. Introduction

Despite optimal treatment (complete cytoreduction and adjuvant platinum-paclitaxel chemotherapy), 5-year survival for advanced ovarian cancer is approximately 30% [1] and most patients succumb to their disease. Overall, 85% of ovarian cancer patients will experience recurrent disease, with virtually no long-term survival after recurrence. Cytoreductive surgery is accepted as a major treatment of primary ovarian cancer but its role in recurrent disease is controversial and remains a field of discussion mainly owing to missing data from prospective randomized trials and to the broad variety of definitions of surgical procedures. Moreover, different studies include different groups of patients ranging from patients with persistent disease at the end of first line treatment (which possibly includes patients with persisting and/or progressing disease at the completion of carboplatin-paclitaxel chemotherapy) to patients with recurrent disease after a disease-free period variable from some weeks to several years [2, 3].

In addition, all but one series are represented by retrospective studies and obviously suffer from selection bias. Generally, the rate of patients not offered secondary surgery at recurrence varied from 7 to 64% among different trials but unfortunately informations about selection criteria and outcomes of nonsurgery selected populations are lacking.

Moreover, given the long time span of most studies (>5–10 years), the pre- and postoperative chemotherapy treatments varied widely between patients thus increasing the difficulties in the interpretation of data.

None of the studies details how recurrence was detected, the type of followup adopted after primary treatment, and the selection criteria used for secondary cytoreduction which broadly differ between studies.

Although the recently published MRC OVO5/EORTC 55955 trial [4] concluded that early intervention with chemotherapy for recurrent ovarian cancer detected only on the basis of serum CA 125 rising does not alter overall survival with respect to waiting for the appearance of symptomatic disease, Tanner et al. [5] found that survival after ovarian cancer recurrence was greater in asymptomatic patients than in those with symptoms (45 versus 29.4 months, $P = 0.006$), and this was due to the rate of successful secondary cytoreductive surgery which was higher in the asymptomatic group (90% versus 57%, $P = 0.053$). Even if retrospective in nature, this study seems to suggest that early surgery in asymptomatic patients with recurrent ovarian cancer may be of benefit thus underling the opportunity of continuous clinical and radiological followup at the end of first line treatment.

Unfortunately, the only prospective randomized trial addressing the role of secondary surgery in recurrent ovarian

cancer, the LOROCSON trial, sponsored by European Organization for Research and Treatment of Cancer (EORTC), aborted prematurely due to low recruitment.

Since the publication by Berek et al. in 1983, which first introduced the term "secondary cytoreduction," the clinical scenarios and indications of repeated tumor cytoreductive operations for recurrent ovarian cancer have been more precisely defined [21]. According to most clinicians, secondary cytoreductive surgery for recurrent ovarian cancer is defined as an operative procedure performed at some time remote (generally disease free interval of more than 6 months) from the completion of primary therapy with the intended purpose of tumor reduction. Although usually not curative, this kind of surgery aims at prolongation of survival by reducing tumor burden and at improvement of quality of life and cancer-related symptoms.

The only 2 studies looking at secondary cytoreduction in patients with suboptimal response to primary treatment showed a marginal benefit of surgery at the cost of high morbidity (24%) and limited long-term benefit with a median survival of 9 months [6, 22] so, at present, there is no evidence that secondary surgery is of significant benefit in this population.

2. Rationale for Surgery

The rationale of surgical removal or recurrent tumor is high and it is supported by the mathematical model of Goldie and Coldman predicting drug resistance in cancer [23] and suggesting that the likelihood of chemotherapy being curable is related to the number of tumor cells present (10^5 tumor cells are likely to be curable with chemotherapy, but 1 cm tumor nodules contain 10^6–10^7 cells). Other theoretical benefits are the removal of a poorly vascularized tumor which may represent pharmacologic sanctuaries of drug resistance; a higher growth fraction in the better perfuse small residual tumor masses which favors the action of cytotoxic therapy; the potentially fewer number of chemotherapy cycles required by small tumor masses limiting the probability of inducing drug resistance; finally the enhancement of host immunocompetence generated by the removal of large tumor bulk.

3. Definition of Residual Disease

Almost all series reported a relationship between survival and surgical outcome in univariate analysis and complete debulking is one of the strongest predictors for survival in all multivariate analyses (Table 1). At present what is considered "optimal cytoreduction"? The definition of optimal residual disease widely varies across studies; while some authors argue that optimal cytoreduction can only be described as "absence of visible disease" at the end of the operation, others use less than 0.5 cm [10, 13], less than 1 cm [16, 17, 19, 20], less than 1.5 cm [21], or less than 2 cm cutoff [6–9, 12, 14]. All the studies report superior overall survival in optimally cytoreducted patients, regardless of the discrepancy in how "optimal cytoreduction" was defined. The studies stratifying the subgroup with "absence of visible disease" consistently demonstrate superior results in this group [6, 7, 10–13, 15, 17, 20] with respect to all the other residual disease cutoff groups.

The large multicenter prospective trial DESKTOP I (Descriptive Evaluation of Preoperative Selection Criteria for Operability) [24] has clearly demonstrated that only complete debulking has prognostic influence and that the "so-called" optimal debulking with residuals up to 1 cm plays no role in surgery for recurrent ovarian cancer. The DESKTOP I trial identified residual disease after surgery as the strongest independent prognostic factor for survival in combination with the absence of ascites and platinum-based reinduction chemotherapy.

Most studies document approximately 50% of patients being cytoreducted to absence of residual disease, but the complete debulking rate varied from 9% to 85% [13, 16] likely being these differences expression of variances in patients selection criteria, definitions of optimal cytoreduction, surgical techniques, and aggressiveness of surgeons.

4. How to Identify Patients Who Most Likely Benefit?

The DESKTOP I trial [24] identified an independently predictive score for complete resection (AGO score) comprehensive of good performance status (Eastern Cooperative Oncology Group 0), complete resection at primary surgery (or alternatively, International Federation of Gynecology and Obstetrics stage I/II), and the absence of ascites. If all the 3 factors were contemporarily present (positive AGO score), complete resection was feasible in 79% of patients. The subsequent international multicenter trial DESKTOP II prospectively validated this score [25]: 129 patients with positive AGO score submitted to secondary surgery for ovarian cancer recurrence were enrolled with a confirmed complete resection rate of 76%.

Several studies have been published addressing the role of radiological evaluation in predicting successful secondary surgery but all of the series were retrospective evaluations, never prospectively validated [26]. Laparoscopic evaluation of successful surgery was published by an Italian group with percentages of complete resections comparable to what obtained with AGO score but at higher price in terms of complications and feasibility of the procedure [27].

None of the published series reported age as a predictor of resectability but most of them excluded patients older than 70 years old from secondary surgery.

The presence of cancer-related symptoms, tumor burden, presurgical serum CA 125 values, localizations of disease, and treatment-free interval (TFI) were inconstantly reported as predictive factors of tumor resectability in univariate and multivariate analysis.

5. Prognostic Factors for Survival

Complete debulking was the strongest predictor for survival in all the multivariate analyses performed across the studies

Table 1: Published results on secondary cytoreduction for recurrent ovarian cancer.

Reference	*n*	Definition used	Cytoreduced (%)	Median survival after secondary surgery (months)
Berek [3]	21	RD<o>1.5 cm;	6/21 (29); 15/21 (71)	<1.5, (20); >1.5 (5) $P < 0.01$
Morris [6]	30	NVD; RD<o>2 cm	9/30 (30); 8/30 (27); 13/30 (43)	<2 (18.8); > 2(13.3) ns
Janicke [7]	28	NVD; RD<o> 2 cm	14/28 (50); 12/28 (43); 2/28 (7)	NVD, (29); RD, (9) $P = 0.0000$
Segna [8]	100	RD<o>2 cm	61/100 (61); 39/100 (39)	<2,(27.1); >2, (9) $P = 0.0001$
Pecorelli [9]	270	NVD; RD RD<o>2 cm	3/5 stage I (60); 2/5 stage I (40); 13/22 stage III (58); 9/22 stage III (41)	<2 (20); >2 (12) $P = 0.045$
Vaccarello [10]	57	RD<o>0.5 cm	38/57 (67); 23/38	<0.5, NYR; >0.5 (23)
Cormio [11]	21	NVD; no cytoreduction	15/21 (71); 6/21 (25)	NVD, (32); RD (9) $P = 0.029$)
Gadducci [12]	30	NVD RD<o>2 cm	17/30 (57); 8/30 (27); 5/30 (17)	NVD (37); RD (19) $P = 0.04$
Eisenkop [13]	106	NVD; RD<o>2 cm	87/106 (82); 3/106 (3); 16/106 (15)	NVD (44.4); RD (19.3) $P = 0.0007$
Munkarah [14]	25	NVD; RD<o>2 cm	12/25 (48); 6/25 (24); 7/25 (28)	NVD (56.9); RD (25.1) $P = 0.08$
Tay [15]	46	NVD; RD	19/46 (41); 27/46 (59)	NVD (38); RD (11) $P = 0.002$
Zang [16]	107	NVD; RD<o>1 cm	11/107 (10); 61/107 (57); 35/107 (33)	NVD nyr; RD < 1 (26); >1(14.5)
Onda [17]	44	NVD; RD<o>1 cm	26/44 (59); 11/44 (25); 7/44 (16)	NVD (52); RD<1 (23) $P = 0.0007$; >1 (20)
Güngör [18]	44	Surgery; chemo only; NVD	44/75 (59); 31/75 (41); 34/44 (77)	NVD (19); RD (9) $P = 0.007$
Pfisterer [19]	267	NVD; RD<o>1 cm	133/267 (50); 69/267 (26); 65/267 (24)	NVD (45.3); RD (19) $P < 0.0001$
Ayhan [20]	64	NVD; RD<o>1 cm	28/64 (44); 25/64 (39); 11/64 (17)	<1 (28); >1 (18) $P = 0.004$

RD: residual disease, NVD: no visible disease, NS: not significant, NYR: not yet reached.

(Table 2). All the other analyzed factors provided conflicting results. Treatment free interval before secondary surgery did not show any significant impact on outcome in univariate analysis in approximately half of the published series and even where reported did not retain independent prognostic significance in multivariate analysis. Of note, a very poor percentage of enrolled patients presented TFI less than 6 months (0–13.5%) suggesting that data addressing a possible impact of TFI on survival are mainly valid for different periods beyond 6 months.

The absence of ascites and the reintroduction of platinum as adjuvant treatment after surgery are generally associate with prolonged survival. On the contrary, unfavorable outcome was reported for patients receiving preoperative chemotherapy possibly for the emergence and selections of chemotherapy resistant foci. The impact of preoperative tumor load remains controversial: an exploratory analysis of DESKTOP 1 trial showed that peritoneal carcinomatosis is a significant negative predictor for complete resection, but if complete resection is still possible there is no difference in survival compared to completely debulked patients without peritoneal carcinomatosis [28].

6. Comparison with Chemotherapy

Platinum-based combinations appear as the most suitable and active treatments for recurrent platinum-sensitive (platinum-free interval >6 months) ovarian cancer patients. Combinations with taxanes [29], gemcitabine [30], and pegylated liposomal doxorubicin [31] reported a median survival of 29, 18, and 31.5 months in the respective superior arms which is generally poorer than the median overall survival reported by the majority of trials of optimally debulked recurrent ovarian cancer patients [32]. Moreover, a meta-analysis on the role of secondary surgery for recurrent ovarian cancer on 40 studies in 2019 patients reported that each 10% increase in optimally cytoreducted patients translates into a 3-month increase of overall survival [33].

Güngör et al. [18] reported in a retrospective review that patients who underwent successful secondary cytoreductive surgery had an improved survival over patients who had chemotherapy as exclusive treatment at recurrence. Unfortunately, in absence of a prospective randomized trial, such conclusions may represent the result of selection bias rather than the effect of surgery.

A recently published Cochrane Review [34] found no evidence from randomized clinical trials to inform decisions about secondary surgical cytoreduction and chemotherapy compared to chemotherapy alone for women with recurrent epithelial ovarian cancer. The author concluded that ideally, a large randomized controlled trial or, at the very least, well-designed nonrandomized studies that use multivariate analysis to adjust for baseline imbalances are needed to compare these two treatment modalities.

The AGO group started with the DESKTOP III trial in Q3 2011. This study is a randomized phase III trial comparing cytoreductive surgery followed by platinum-based chemotherapy versus chemotherapy alone in a population of 408 recurrent platinum sensitive ovarian cancer with positive AGO score at first event of disease recurrence.

A similar study, the GOG 213 study, is ongoing in the United States addressing two different questions: the role of

Table 2: Multivariate analysis for survival.

	Zang [16]	Eisenkop [13]	Tay [15]	Zang [16]	Onda [17]	Pfisterer [19]	Ayhan [20]
n	60	106	46	107	44	267	64
Age		Ns		Ns	Ns		Ns
PS		Ns			Ns		Ns
Initial FIGO	Ns		Ns	Ns	Ns		Ns
Grade	Ns	Ns	Ns				Ns
Histology	Ns			0.017	Ns		0.005
RD after primary surgery				Ns	Ns		0.003
DFI	0.0116	0.005	0.001			<0.001	0.003
RD after secondary surgery	0.0041	0.007	0.002			<0.001	0.04
Disease localization		Ns			0.013		
No disease sites					<0.001		
Largest tumor diameter	Ns	0.04			<0.001		
Ascites[1]	0.0191	Ns			Ns	0.012	
Ca 125[1]		Ns					
No cycles chemo[2]	Ns						
Chemo[2]	Ns	0.001					

Ns: not significant, RD: residual disease, DFI: disease-free interval.
[1]At secondary surgery.
[2]Prior to secondary surgery.

secondary surgery in recurrent platinum-sensitive ovarian cancer and the inclusion of bevacizumab in combination or not to standard carboplatin-paclitaxel treatment as adjuvant chemotherapy.

7. Morbidity and Quality of Life

Due to the retrospective nature of most studies, reliable information on QOL and postoperative morbidity are often not available. Most studies reported around 30–40% postoperative morbidity with severe morbidity (including sepsis, hemorrhage, adult respiratory distress syndrome, bowel obstruction, and disseminated intravascular coagulation) quoted around 10% and up to 2% postoperative mortality registered [12, 13, 15].

Very little is known about quality of life (QOL) after secondary cytoreduction. Wenzel et al. [35] reported no difference in QOL in a randomized multicenter trial comparing FIGO stage III-IV ovarian cancer patients who did and did not undergo interval debulking surgery after incomplete primary cytoreduction and 3 cycles of platinum-paclitaxel chemotherapy thus suggesting that additional surgical interventions in ovarian cancer may not have any significant impact (positive or negative) on QOL.

8. Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Cytoreductive surgery and HIPEC have yielded promising results in malignant disease for which no other systemic therapies have been shown to be beneficial [36–38]. As far as ovarian cancer is concerned, Chua et al. [39] systematically reviewed the oncologic outcome, morbidity and mortality of cytoreductive surgery, and HIPEC of 19 retrospective observational studies from 10 high volume specialized treatment centers and reported a severe morbidity rate ranging from 12% to 63%, a treatment-related mortality ranging from 0.9% to 10%, and a median overall survival ranging from 22 to 64 months. Such a broad variability in reported oncologic outcomes and toxicities represents the clear expression of the extreme heterogeneity in enrolled population, the different time point of HIPEC administration during the natural history of ovarian cancer (published data are a miscellanea of interval debulking surgery, second-look surgery, and secondary cytoreduction of mixed platinum-sensitive and resistant patients), the variability of chemotherapy employed, the center expertise, and also possibly may represent the expression of a wide different clinicians' interpretation and reporting of data which make it exceptionally difficult to draw definitive conclusions.

The absence of valuable alternative treatment option, as suggested by few authors, is not an acceptable criteria "per se" for further promoting this concept: the high level of perioperative morbidity and mortality might be considered acceptable when no other alternate therapy has been shown to be effective in curing or controlling the disease but this is not the case of ovarian cancer recurrence in which surgery and platinum-based chemotherapy represent accepted, evidence-based, valuable options.

Ovarian cancer moreover is quite a different disease with respect to colon cancer in which only one randomized trial comparing HIPEC versus palliative surgery plus chemotherapy has ratified HIPEC as the new standard treatment of peritoneal colon cancer carcinomatosis [40],

and conclusions derived from one type of malignancy should not be arbitrarily applied to another tumor.

Finally, all the published studies so far are phase I and II feasibility, nonrandomized trials, which makes it difficult to meaningfully compare neither the risk-benefit ratio associated with HIPEC+ cytoreductive surgery (CRS) versus CRS alone (no doubts remain on the usefulness of maximal cytoreduction "per se" among all the investigators who manage ovarian carcinoma), nor the exact role of hyperthermia in combination with intraperitoneal delivery of chemotherapy versus the more established benefit of intraperitoneal chemotherapy alone. The benefit of CRS plus HIPEC depends on all these procedures being carried out in selected patients but no data are available on the relative weight of each of them.

For all of these reasons, we emphasize that the real survival benefit of HIPEC in ovarian cancer could only be assessed by a well-designed prospective randomized phase III trials. At present, no evidence yet shows that HIPEC benefit in ovarian cancer outweigh the contraindications or risks related to morbidity, mortalitys or costs. At this regard our controlled randomized experience on HIPEC in recurrent ovarian cancer (submitted paper) and Pomel et al. prospective experience [41] registered unacceptable high level of morbidity and mortality causing the premature conclusion of the two trials.

9. Conclusions

Although the role of secondary surgery in recurrent ovarian cancer remains controversial, most retrospective studies showed better survival in patients for whom maximal cytoreduction was achieved. Due to the retrospective nature of these studies, multiple confounding factors play a role in selection and operability of these patients; moreover, at present, the indications for surgery when a recurrence is diagnosed appear more often dependent on the physician's preference and surgical skill than on patients' attitudes or tumor characteristics.

We strongly believe that there is a role for secondary cytoreductive surgery in a well-selected population. At present, the main recognized factors improving the likelihood of optimal secondary cytoreduction and possibly contributing to prolong patients survival are the absence of ascites, a good performance status, and the complete debulking during primary surgery (AGO score). A better understanding of the benefits and patients selection criteria for this procedure will be achieved after the completion of the ongoing randomized phase III trials evaluating the role of surgery for recurrent disease. A positive outcome of these trials will lead to the addiction of this strategy to the standard armamentarium therapies of ovarian cancer recurrence.

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Clinical Study

Radical Prostatectomy as a First-Line Treatment in Patients with Initial PSA >20 ng/mL

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Initial PSA >20 ng/mL is generally considered an adverse prognostic feature in prostate cancer (PCa). Our goals were to estimate the impact of radical prostatectomy (RP) on biochemical recurrence- (BCR-) free and cancer-specific survival (CSS) rates of PCa patients with PSA >20 ng/mL, and to identify patients with favorable oncological outcome. Using 20 ng/mL as a cut-point value, 205 PCa patients, who underwent RP, were stratified into two groups. Multivariate analysis was used to determine the significant outcome predictors among patients with PSA >20 ng/mL. Men in this group had significantly lower 10-yr BCR-free and CSS rates than patients with PSA ≤20 ng/mL (20.7% versus 79.6% ($P < 0.001$) and 65.0% versus 87.9% ($P = 0.010$), resp.). Pathological stage and lymph node status were found to be the only independent predictors of PSA failure. Patients with favorable combination of these variables (pT2, N0) had significantly longer 10-yr BCR-free and CSS rates (44.3% versus 0% ($P = 0.001$) and 100.0% versus 33.6% ($P = 0.011$), resp.). High PSA values do not uniformly indicate poor prognosis after surgery. Patients, who might benefit the most from RP, are those with organ confined PCa and negative lymph nodes.

1. Introduction

The stage migration of prostate cancer (PCa), due to its prostate-specific antigen (PSA-) based early detection, dramatically changed the pattern of presentation in many patients with potentially lethal disease. Nowadays, an increasing number of patients are initially diagnosed with cancer confined to the prostate. However, approximately one third of these men are found to have aggressive pathological features by the final histological report: extraprostatic extension (EPE), seminal vesicle invasion (SVI), and/or lymph node involvement (LNI) [1, 2]. These numbers could be even higher, if a more aggressive treatment policy of performing radical prostatectomy (RP) is implemented [3, 4].

PSA is one of the most established tumor markers that is widely used in screening, diagnosis, staging, and monitoring of prostate cancer patients [5, 6]. PSA has an established prognostic impact and is one of the three basic parameters (together with the biopsy Gleason score and the clinical stage) that is included in all preoperative prognostic tools [5, 7–9].

Serum PSA above 20 ng/mL is generally considered as an adverse prognostic feature in PCa, associated with a higher prevalence of a locally advanced disease and/or distant metastases [10, 11] and with a higher probability of developing recurrent disease after radical local treatment [7, 9, 12]. Therefore, many urologists are reluctant to perform RP on patients with PSA values >20 ng/mL [13–15].

Some contemporary studies in which patients are diagnosed earlier suggest, however, that the risk may not be so dire [14, 16–21], as some patients, subjected to RP, showed favorable outcomes despite high PSA values [13, 18–23].

In addition, adjuvant treatment has been used in such patients with contradictory results, with some studies suggesting that there is no benefit from adjuvant treatment, while many others claim the opposite [24–28].

Therefore, two issues need more clarification: what is the exact detriment to having initial PSA values above 20 ng/mL,

Table 1: Patient characteristics and pathological parameters.

Parameter	Group A ($n = 131$)	Group B ($n = 74$)	P value
Patient age (years) ± SD	65.7 ± 6.1	65.4 ± 7.7	0.760
Mean PSA (ng/mL) ± SD	9.4 ± 5.4	64.9 ± 123.9	<0.001
Clinical stage (n/%/)*			
cT1	32 (24.4%)	3 (4.1%)	<0.001
cT2	91 (69.5%)	43 (58.1%)	0.101
cT3-T4	8 (6.1%)	28 (37.8%)	<0.001
Gleason score (n/%/)			
<7	52 (39.7%)	13 (17.6%)	0.001
=7	55 (42.0%)	28 (37.8%)	0.557
>7	24 (18.3%)	33 (44.6%)	<0.001
Pathological stage (n/%/)*			
pT2	89 (67.9%)	24 (32.4%)	<0.001
pT3	37 (28.2%)	42 (56.8%)	<0.001
pT4	5 (3.8%)	8 (10.8%)	0.049
Extracapsular extension (n/%/)	42 (32.1%)	50 (67.6%)	<0.001
Seminal vesicles invasion (n/%/)	35 (26.7%)	45 (60.8%)	<0.001
Lymph node involvement (n/%/)	19 (14.5%)	35 (47.3%)	<0.001
Positive surgical margins (n/%/)	20 (15.3%)	31 (41.9%)	<0.001

* Based on TNM classification, v. 2009.

and whether adjuvant treatment may benefit this particular subset of patients.

The main goals of the present study were: (1) to estimate the impact of radical prostatectomy on biochemical recurrence- (BCR-) free and cancer-specific survival (CSS) rates of patients with PCa and PSA >20 ng/mL and (2) to identify a subset of patients who might have a favorable oncological outcome.

2. Materials and Methods

Since April 1996, a total of 205 male patients, aged between 46 and 79 years (mean age 65.6 ± 6.7 years), underwent extended pelvic lymph node dissection (ePLND), followed by RP for localized or locally advanced PCa (Table 1). Digital rectal examination (DRE) and transrectal ultrasound (TRUS) of the prostate were used as the compulsory initial staging procedures. They were supplemented by an abdominal and pelvic computer tomography (CT) or magnetic resonance imaging (MRI) and bone scintigraphy in case of a palpable bulky tumor of the prostate, initial PSA >20 ng/mL, or biopsy Gleason score ≥8. Patients with preoperatively proven metastatic disease were considered not eligible for radical surgery.

Seventy-one patients, included in the present study, had already received some form of neoadjuvant hormonal therapy (Table 2). Twelve of these patients had bilateral orchiectomy performed prior to surgery. The decision to start this type of therapy had been taken at the primary urological institution, where the disease had been detected. Interestingly, only 33 (46.5%) of these 71 patients had initial PSA >20 ng/mL, while 38 (53.5%) patients had initial PSA below this crucial cut-point value.

The patients were informed in detail about the study objectives and the study protocol and about all potential side effects and complications that might be associated with it. All patients gave their written consent prior to surgery.

2.1. Radical Prostatectomy. All surgical procedures were performed by a single expert surgeon (AIH), according to the recently described surgical technique [29]. RP was performed via the same suprapubic approach, after the completion of ePLND. Whenever it was technically feasible and oncologically justified, unilateral or bilateral preservation of the neurovascular bundles (NVBs) was implemented. In case of clinically organ-confined PCa, associated with preserved potency prior to the operation, all efforts were done to spare bilaterally the NVBs, as well as the bladder neck. This was rarely possible in case of clinically locally advanced PCa, where wide excision of the NVBs on one or both sides of the prostate was intentionally performed. In any such case, the excision extended to the anterior wall of the rectum, including in the specimen both layers of the Denonvilliers' fascia. The bladder neck was intentionally sacrificed, as well, and a "tennis racket" type bladder neck reconstruction was done after specimen's removal.

All surgical specimens were fixed in neutral formalin and then processed separately for routine histological haematoxylin-eosin (H&E) and immunohistochemical prostate-specific antigen (PSA) and cytokeratin (CK) examination. Frozen section analysis was rarely performed—only in case of suspicious lymph nodes (LNs) found at surgery, with or without the assistance of a gamma probe and a radioactive counter [4]. A positive histological result from the frozen section analysis did not affect the initial decision to remove the prostate and the seminal vesicles.

Table 2: Neoadjuvant and adjuvant treatment modalities.

Parameter	Group A ($n = 131$)	Group B ($n = 74$)	P value
Neoadjuvant hormonal therapy (n/%/)	38 (29.0%)	33 (44.6%)	0.025
Adjuvant radiotherapy (ART) (n/%/)	21 (16.0%)	27 (36.5%)	0.001
Adjuvant hormonal therapy (ADT) (n/%/)	29 (22.1%)	29 (39.2%)	0.010
Adjuvant combined (ART & ADT) therapy (n/%/)	13 (9.9%)	17 (23.0%)	0.012

Table 3: Oncological outcome at the 10th year after surgery.

Patient group	BCR-free survival		Overall survival		Cancer-specific survival	
	% Censored cases	KM estimates (10th year)	% Censored cases	KM estimates (10th year)	% Censored cases	KM estimates (10th year)
A (PSA ≤20 ng/mL)	84.7%	79.6%	87.8%	71.7%	95.4%	87.9%
B (PSA >20 ng/mL)	51.4%	20.7%	83.8%	55.7%	86.5%	65.0%
P value	**<0.001**		**0.172**		**0.010**	

2.2. Adjuvant Treatment. As an adjunct to surgery, adjuvant hormonal therapy and/or radiotherapy was administered according to the current guidelines and the decision of the institutional multidisciplinary Oncological Committee (Table 2).

In case of pT3-T4 disease, or positive surgical margins, patients received adjuvant radiotherapy (ART) within the first 3 months after surgery. The external beam radiotherapy was realized in two sessions, by the so-called box technique: (1) large volume irradiation, applied to the prostatic bed and the regional pelvic LNs (1.8–2 Gy daily dose, 46–50 Gy total dose); (2) small volume irradiation, additionally applied to the prostatic bed only, thus achieving a total dose of 60–64 Gy.

In case of persistent or rising PSA after surgery, or in case of lymph node metastases (LNM) found by the morphologists, patients received permanent adjuvant hormonal therapy (combination of a luteinising hormone-releasing hormone analogue and antiandrogen, to achieve a complete androgen blockage), with an option to switch to intermittent androgen deprivation therapy (ADT) after the first disease-free year with permanent undetectable PSA values.

2.3. Group Stratification. Patients were stratified into two groups, according to the initial PSA values prior to RP: *group A*, comprising 131 men with initial PSA ≤20 ng/mL and *group B*, comprising 74 men with initial PSA >20 ng/mL. The two groups were compared with regard to the functional and oncological outcome after surgery.

2.4. Statistical Analysis. Clinicopathological variables and outcome data were compared across the groups using chi-square and log-rank tests. Univariate analysis, based on the Kaplan-Meier method, and multivariate analysis, based on the Cox's proportional hazards regression model, were performed to determine the significant predictors of outcome among men with PSA >20 ng/mL. Commercially available statistical software packages (SPSS for Windows, v. 16.0, and GraphPad Prism, v. 5.04) were used for the purpose. The endpoints of the study were: the BCR-free survival, the overall survival (OS), and the cancer-specific survival (CSS). The BCR-free patient survival was defined as the percentage of PCa patients with no residual or recurrent disease after RP: serum PSA less than 0.2 ng/mL and no clinical evidence of local recurrence and/or distant metastases. OS was defined as the percentage of PCa patients who had been alive after a particular duration of time. CSS was defined as the percentage of PCa patients who had not died due to PCa at a particular point of time.

3. Results

All cases were followed till July 1st, 2011. The mean followup in the entire series was 50.9 months (±46.5 SD).

Patients in group B with initial PSA >20 ng/mL had significantly higher clinical stage and biopsy Gleason score, and were more likely to have concomitant EPE, LNI, and positive surgical margins (PSMs) on final pathology, as compared to those in group A (Table 1). Neoadjuvant hormonotherapy and adjuvant treatment modalities (ADT and ART) were more commonly used in group B, as compared to group A (all P values <0.05) (Table 2).

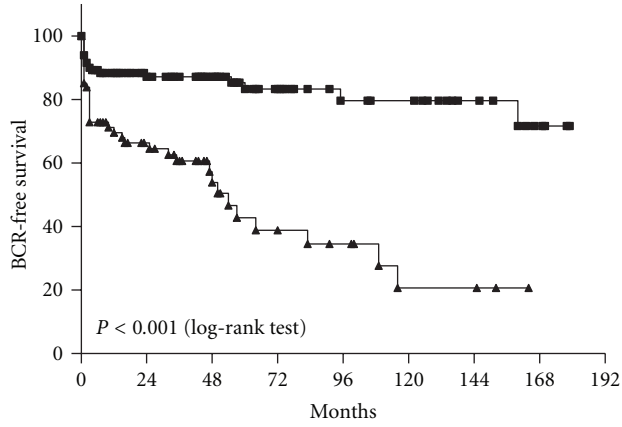
The Kaplan-Meier survival curves distribution between patients with PSA ≤20 ng/mL and patients with PSA >20 ng/mL is presented in Figure 1. There was a statistically significant difference between curves with regard to the BCR-free survival (Figure 1(a)) ($P < 0.001$) and the CSS rates (Figure 1(c)) ($P = 0.010$). Although lower than in group A, the OS rate of the patients in group B was not significantly altered (Figure 1(b)) ($P = 0.172$).

The Kaplan-Meier estimates of the BCR-free survival, the OS, and the CSS at the 10th year after surgery were 79.6%, 71.7% and 87.9% for patients in group A and 20.7%, 55.7% and 65.0% for patients in group B, respectively (Table 3).

Using multivariate analysis, the pathological T stage ($P = 0.009$) and the lymph node status ($P = 0.034$) were found to be independent predictors of PSA failure among men with PSA >20 ng/mL (Table 4).

Patient group	Means for BCR-free survival time (95% confidence interval)
A (PSA ≤ 20 ng/mL)	147.2 (134.1–160.4)
B (PSA > 20 ng/mL)	67.9 (49.1–86.7)

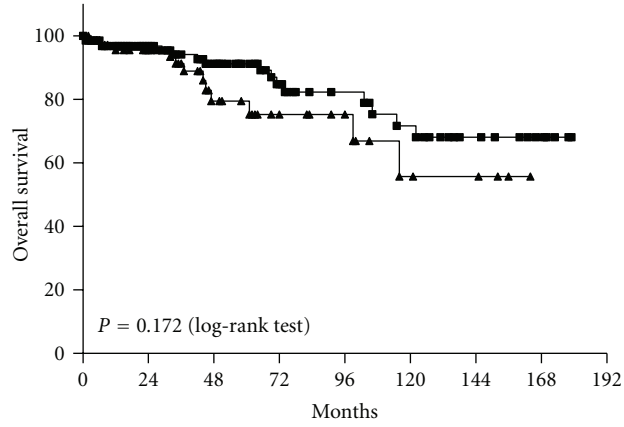
	Time	0	24	48	72	96	120	144	168
Group A	PR	131	71	55	35	22	20	11	5
	CE	0	16	16	18	19	19	19	20
Group B	PR	74	36	16	9	7	3	2	0
	CE	0	24	29	33	34	36	36	36



(a)

Patient group	Means for OS time (95% confidence interval)
A (PSA ≤ 20 ng/mL)	146.2 (132–160.3)
B (PSA > 20 ng/mL)	122 (101.8–142.3)

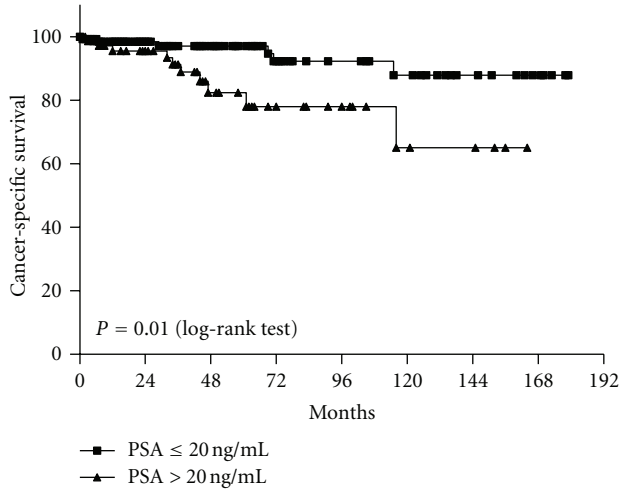
	Time	0	24	48	72	96	120	144	168
Group A	PR	131	78	60	37	24	20	12	6
	CE	0	4	8	11	12	15	16	16
Group B	PR	74	48	22	13	9	5	4	0
	CE	0	3	9	10	10	12	12	12



(b)

Patient group	Means for CSS time (95% confidence interval)
A (PSA ≤ 20 ng/mL)	166.2 (156–176.3)
B (PSA > 20 ng/mL)	129.9 (110.6–149.3)

	Time	0	24	48	72	96	120	144	168
Group A	PR	131	78	60	37	24	20	12	6
	CE	0	2	3	5	5	6	6	6
Group B	PR	74	48	22	13	9	5	4	0
	CE	0	3	8	9	9	10	10	10



(c)

Figure 1: (a) Kaplan-Meyer curves distribution: comparison between patients with PSA ≤20 ng/mL versus patients with PSA >20 ng/mL with regard to BCR-free survival rates. PR: patients at risk; CE: cumulative number of events. (b) Kaplan-Meyer curves distribution: Comparison between patients with PSA ≤20 ng/mL versus patients with PSA >20 ng/mL with regard to OS survival rates. PR: patients at risk; CE: cumulative number of events. (c) Kaplan-Meyer curves distribution: comparison between patients with PSA ≤20 ng/mL versus patients with PSA >20 ng/mL with regard to CSS survival rates. PR: patients at risk; CE: cumulative number of events.

Table 4: Univariate and multivariate analysis of pathologic variables.

Parameter	Univariate analysis	Multivariate analysis	
	P value	*P* value	HR* (95% CI**)
Age (years)	0.164	0.506	—
Initial PSA (ng/mL)	0.042	0.116	—
cT (cT1 versus cT2 versus cT3)	0.003	0.806	—
Gleason score (<7 versus 7 versus >7)	0.002	0.065	—
pT (pT2 versus pT3 versus pT4)	**<0.001**	**0.009**	**3.515 (1.882–6.565)**
Seminal vesicle invasion (yes versus no)	0.006	0.932	—
Surgical margins (neg. versus pos.)	0.003	0.084	—
Lymph node status (N0 versus N1)	**<0.001**	**0.034**	**1.002 (1.000–1.003)**
Adjuvant radiotherapy (yes versus no)	0.968	0.506	—
Adjuvant hormonal therapy (yes versus no)	0.023	0.105	—

*HR: hazard ratio; **CI: confidence interval.

Table 5: Oncological outcome at the 10th year after surgery in patients with favorable combination of prognostic variables (pT2, N0) versus patients with unfavorable prognostic variables (pT3-4 and/or N1).

Patient group	BCR-free survival		Overall survival		Cancer-specific survival	
	% Censored cases	KM estimates (10th year)	% Censored cases	KM estimates (10th year)	% Censored cases	KM estimates (10th year)
Favorable (pT2, N0)	71.4%	44.3%	90.5%	72.0%	100.0%	100.0%
Unfavorable (pT3-4 and/or N1)	43.4%	0%	81.1%	33.6%	81.1%	33.6%
P value	**0.001**		**0.097**		**0.011**	

Table 6: Kaplan-Meier survival analysis, log-rank test: comparison between patients with initial PSA ≤20 ng/mL versus patients with PSA ≤20 ng/mL in four patient groups (patients treated by RP only versus RP plus ART versus RP plus ADT versus RP plus ART plus ADT) with regard to BCR-free, OS, and CSS rates.

Patient group	*P* value		
	BCR-free survival	Overall survival	Cancer-specific survival
RP	0.002	0.501	0.155
RP + ART	0.034	0.315	0.101
RP + ADT	0.008	0.312	0.206
RP + ART + ADT	0.221	0.238	0.238

Patients with favorable combination of these prognostic variables (pT2, N0) had significantly longer BCR-free ($P = 0.001$) (Figure 2(a) and CSS ($P = 0.011$) rates (Figure 2(c)), similar to those of men with initial PSA ≤20 ng/mL. The OS rates were not significantly altered (Figure 2(b)).

The Kaplan-Meier estimates of the BCR-free survival, the OS, and the CSS at the 10th year after surgery in patients with initial PSA >20 ng/mL are shown on Table 5.

There was no statistically significant difference between the patients who received some form of hormonal manipulation prior to surgery, compared to those who did not, with regard to the BCR-free survival ($P = 0.347$), the CSS ($P = 0.317$), and the OS ($P = 0.091$) rates.

The univariate analysis, based on the Kaplan-Meier method, showed a statistically significant difference between the four treatment groups (patients treated by RP only versus RP plus ART versus RP plus ADT versus RP plus ART plus ADT) with regard to the BCR-free survival rate ($P < 0.001$, log-rank test) (Figure 3). The Kaplan-Meier estimates of the 10-year BCR-free survival were 83.6%, 62.5%, 26.8% and 38.1% for patients, who were treated by RP only, by RP plus ART, by RP plus ADT, and by combination of all treatment modalities (RP, ART and ADT), respectively.

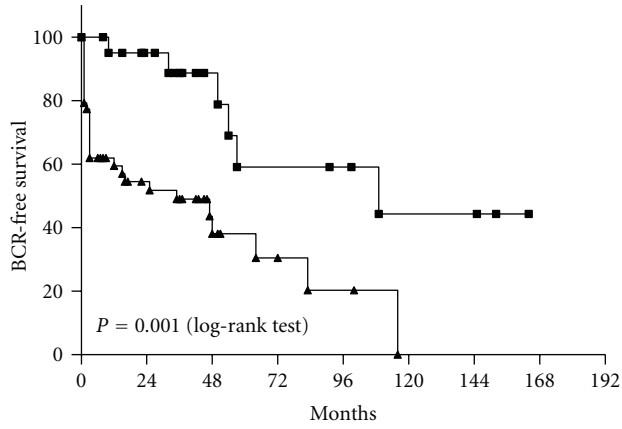
The results of the Kaplan-Meier survival analysis in the different treatment groups are shown on Table 6. In all groups of patients there was no statistically significant difference between men with initial PSA ≤20 ng/mL versus those with PSA >20 ng/mL with regard to OS and CSS rates (all *P* values >0.05, log-rank test).

4. Discussion

Although PSA is an established prognostic variable, its high values to some extent limit its predictive accuracy. These high levels are often due to a large prostate weight, or to a large volume of a tumor, being otherwise localized within

Patient group	Means for BCR-free survival time (95% confidence interval)
Favorable	107.2 (74.2–140.2)
Unfavorable	45.5 (30–60.9)

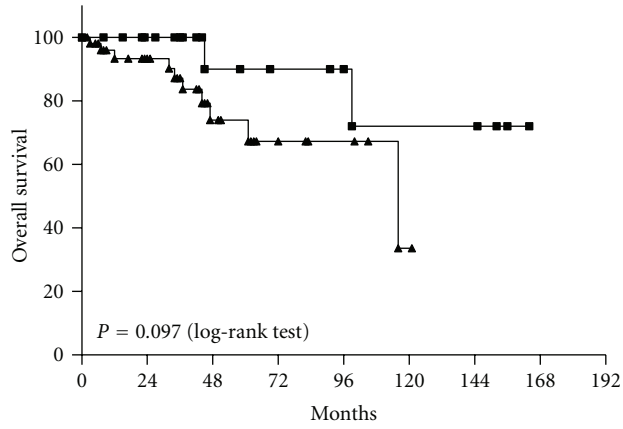
	Time	0	24	48	72	96	120	144	168
pT2 N0	PR	21	16	9	6	5	3	3	0
	CE	0	1	2	5	5	6	6	6
pT3-4 N1	PR	53	20	7	3	2	0	0	0
	CE	0	23	27	28	29	30	30	30



(a)

Patient group	Means for OS time (95% confidence interval)
Favorable	140.4 (112–168.8)
Unfavorable	92 (76.8–107.2)

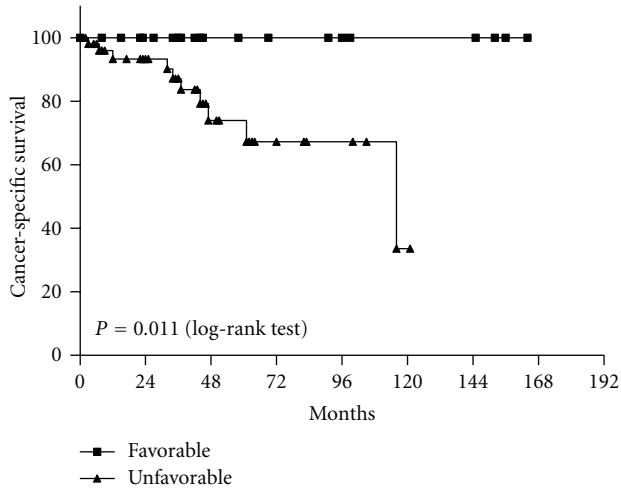
	Time	0	24	48	72	96	120	144	168
pT2 N0	PR	21	10	9	7	5	4	4	0
	CE	0	0	1	1	1	2	2	2
pT3-4 N1	PR	53	31	13	6	4	1	0	0
	CE	0	3	8	9	9	10	10	10



(b)

Patient group	Means for CSS time (95% confidence interval)
Favorable	-
Unfavorable	-

	Time	0	24	48	72	96	120	144	168
pT2 N0	PR	21	21	21	21	21	21	21	21
	CE	0	0	0	0	0	0	0	0
pT3-4 N1	PR	53	31	13	6	4	1	0	0
	CE	0	3	8	9	9	10	10	10



(c)

Figure 2: (a) Kaplan-Meyer curves distribution in group B: comparison between patients with favorable versus unfavorable prognostic features with regard to BCR-free survival rates. PR: patients at risk; CE: cumulative number of events. (b) Kaplan-Meyer curves distribution in group B: Comparison between patients with favorable versus unfavorable prognostic features with regard to OS survival rates. PR: patients at risk; CE: cumulative number of events. (C) Kaplan-Meyer curves distribution in group B: comparison between patients with favorable versus unfavorable prognostic features with regard to CSS survival rates. PR: patients at risk; CE: cumulative number of events.

Patient group	Means for BCR-free survival time (95% confidence interval)
A (RP)	143.8 (132.3–155.3)
B (RP + ART)	56.9 (42.7–71.2)
C (RP + ADT)	66.4 (39.2–93.6)
D (RP + ART + ADT)	86.3 (58.5–114.2)

	Time	0	24	48	72	96	120	144	168
RP	PR	129	64	48	26	14	12	7	1
	CE	0	15	16	17	17	17	17	17
RP + ART	PR	18	12	4	1	0	0	0	0
	CE	0	3	3	4	4	4	4	4
RP + ADT	PR	28	14	13	9	8	7	5	4
	CE	0	13	14	18	19	20	20	21
RP + ART + ADT	PR	30	16	11	8	7	4	3	0
	CE	0	9	12	12	13	14	14	14

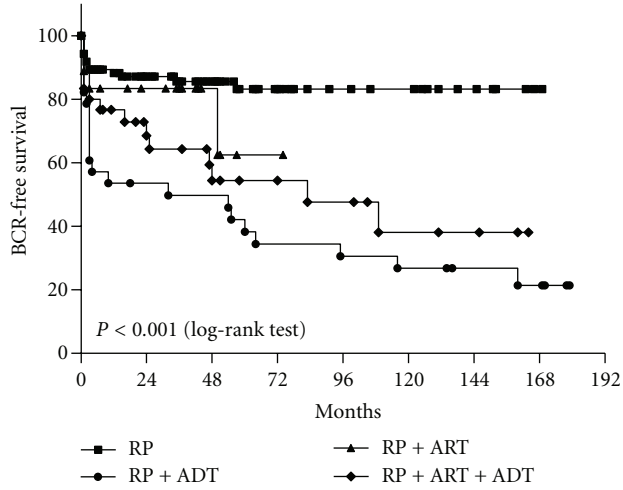


Figure 3: Kaplan-Meyer curves distribution: comparison between patients treated by RP only versus RP plus ART versus RP plus ADT versus RP plus ART plus ADT with regard to BCR-free survival rates. PR: patients at risk; CE: cumulative number of events.

the prostate. For that reason some authors suggest that a high PSA value is an insufficient indicator of a proper treatment [16, 22].

Anyway, PCa patients with initial serum PSA values above 20 ng/mL are generally considered as a "high-risk group", suggesting a poor oncological outcome [7, 9, 21]. Therefore, they are often rejected as potential candidates for definitive local treatment.

Some of these cases, however, respond favorably to radical surgery. Nguyen et al. [30] recently reported that more than 50% of their PCa patients with initial PSA values above 20 ng/mL remained with undetectable PSA values during the first 5 years after RP. This result is in agreement with other patient series, where the 5-year biochemical recurrence-free (BCR-free) survival is within the range between 48% and 65% [5, 12, 14, 18]. In the majority of these cases favorable results had been achieved by RP, used as monotherapy, without the application of adjuvant treatment strategies [14, 18, 30].

These results support the fact that RP might be considered as a viable treatment option in selected high-risk patients [12, 16, 20, 21, 31].

In many cases, however, locally advanced disease or recurrence after RP had been found, necessitating second-line therapy (ADT and/or ART). Therefore, all patients with PSA values above 20 ng/mL should initially be warned that surgery might not be sufficient to control PCa, and adjuvant treatment modalities might be used at a later time [32].

In the absence of large scale, multicenter, randomised prospective trials, comparing early versus deferred adjuvant treatments, it is difficult to decide when to start adjuvant therapy in this particular patient subset. In our study ADT was applied in 39.2%; ART in 36.5%, and combined adjuvant therapy (ADT plus ART)—in 23.0% of the cases. Our current treatment strategy is to use these two methods only in case of clear, distinct indications: locally advanced disease (EPE, SVI, PSM, and/or LNI), or biochemical recurrence after RP (raise in PSA above the cut-point value of 0.2 ng/mL).

There is obviously a need for better identification of the subgroup of patients with initial serum PSA >20 ng/mL, who are more likely to benefit from RP.

Briganti et al. [20] reported that roughly 40% of patients with high-risk PCa had specimen-confined disease at final pathology—namely, pT2-pT3a, node negative PCa with negative surgical margins. These patients showed excellent outcomes in the long term, thus representing the ideal candidates for RP as a primary treatment. The authors suggested a nomogram based on routinely available clinical parameters (age and PSA level at surgery, Gleason score at biopsy, and clinical stage) to better identify the subset of high-risk PCa patients who might have favorable pathologic outcomes when surgically treated.

Our results corroborate these findings. The pathological tumor stage and the LN status were found to be the only independent prognostic variables to predict the BCR-free patient survival among men with PSA >20 ng/mL at the time of RP. Patients with favorable combination of these prognostic variables, that is, patients with specimen-confined disease (pT2, N0), had significantly longer BCR-free ($P = 0.001$) and CSS ($P = 0.011$) rates, similar to those of men with initial PSA ≤20 ng/mL.

Recently, it has been shown that multiparameter MRI of the prostate can detect initial EPE, and even distinguish benign from neoplastic tissue with a promising specificity [33, 34]. The current improvements of MRI and other imaging modalities used for diagnosis and staging will lead to a more accurate definition of the tumor stage, which is particularly important in patients with PSA values above 20 ng/mL.

Our study, however, has a few limitations that have to be taken into consideration.

Firstly, the total number of patients, comprising the study, was quite low ($n = 205$). Patient number was even lower within each subgroup analyzed. For that reason, the KM curves and all other results achieved should be interpreted with caution.

Secondly, too many patients (roughly one third of the entire series) had some kind of hormonal manipulation prior to surgery (neoadjuvant hormonotherapy and/or bilateral orchiectomy). The decision to do that had been taken by the urologists at the primary urological institution, probably because of the adverse clinical and pathological characteristics of the patients and their tumors. The majority of these cases belong to our early series, when neoadjuvant hormonal treatment was a common practice. This strategy continues to be used, even nowadays, in some European centers [19]. Nevertheless, when later reassessed in our institution, which functions as a tertiary referral center for the North-Eastern part of the country, all these 71 patients were found eligible for surgical treatment and subjected to radical prostatectomy.

One might think that this manipulation would have an impact on patient outcome. In a profound review and meta-analysis, Shelley et al. [35] studied the role of neoadjuvant hormonal therapy and RP. The authors reported that this type of treatment does substantially improve local pathological variables, such as organ-confined rates, pathological downstaging, PSM, and rate of LNI, but does not provide significant BCR-free, CSS and OS advantages over RP alone. Therefore, neoadjuvant hormonal therapy is no longer recommended to patients who will be subjected to radical surgical treatment. Our study also confirmed that this type of treatment had no impact on patient survival.

Another limitation of our study is that the majority of our patients received some form of adjuvant treatment (ART and/or ADT) after radical surgery. Accumulated evidence in the literature shows that patient outcomes are largely altered by the use of adjuvant treatment options. In order to assess this issue we divided our patients into four groups with respect to the mode of treatment applied: RP only, RP plus ART, RP plus ADT, and RP plus combination from ART and ADT. We found that there was statistically significant difference ($P < 0.001$) between KM curves when the BCR-free patient survival was used as a study end-point. Interestingly, the highest BCR-free survival was found among patients left without any adjuvant treatment after surgery. This ostensible paradox could be explained by the fact that this patient group usually comprises patients with favorable pathological characteristics which do not require the application of adjuvant treatment modalities, like ART and/or ADT. It was also interesting to note that there were no statistically significant differences between group A and group B when the CSS and OS were used as study end-points. Although the patient numbers in each of the previously mentioned four treatment groups are low and for that reason cannot lead to definite conclusions, this result means that RP, either alone or as part of a multimodal treatment, is a viable treatment option even in patients with PSA values above 20 ng/mL at the time of radical surgery.

In spite of all these limitations, our study provides some evidence that patients with PSA values above 20 ng/mL should not be uniformly considered as a high-risk group. Among them, there are many patients with favorable pathologic characteristics, who might also benefit from radical surgical treatment, applied either alone, or as part of a multimodal treatment approach.

As there is paucity in the current literature regarding this specific matter [13, 14, 18], other studies are sorely needed to confirm our results.

5. Conclusions

High initial PSA values do not uniformly indicate poor prognosis after radical prostatectomy. This operation can still be considered as a viable therapeutic option, even in PCa patients with initial serum PSA values above 20 ng/mL. Patients, who might benefit the most from complete surgical excision, are those with organ confined prostate cancer and negative lymph nodes.

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Clinical Study

The Retrograde and Retroperitoneal Totally Laparoscopic Hysterectomy for Endometrial Cancer

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Introduction. We retrospectively report our experience with the utilization of an original procedure for total laparoscopic hysterectomy based on completely retrograde and retroperitoneal technique for surgical staging and treatment of the endometrial cancer. The surgical, financial, and oncological advantages are here discussed. *Methods*. The technique used here has been based on a combination of a retroperitoneal approach with a retrograde and lateral dissection of the bladder and retrograde culdotomy with variable resection of parametrium. No disposable instruments and no uterine manipulator were utilized. *Results*. Intraoperative and postoperative complications were observed in 10% of the cases overall. Operative time length and mean haemoglobin drop value results were 129 min and 125 mL, respectively. Most patients were dismissed on days 3–5 from the hospital. Seventy-eight percent of the patients were alive with no evidence of disease at mean followup of 49 months. *Conclusions*. Our original laparoscopic technique is based on a retroperitoneal approach in order to rapidly control main uterine vessels coagulation, constantly check the ureter, and eventually decide type and site of lymph nodes removal. This procedure has important cost saving implications and the avoidance of uterine manipulator is of matter in case such as these of uterine malignancy.

1. Introduction

In the last decade, laparoscopy as well as robotics have been increasingly applied with success to patients with gynaecological malignancies, including endometrial cancer [1]. Laparoscopic surgical staging often used in conjunction with a vaginal hysterectomy provides an alternative therapeutic approach to the standard abdominal laparotomic staging of endometrial cancer [2]. When compared to laparotomy, the laparoscopic approach is indeed associated with a faster return to normal activity and reduced intra- and postoperative morbidity [3, 4]. More recently, as shown by an increasing number of prospective and randomized studies, total laparoscopic hysterectomy has become a standardized way for proper surgical treatment and staging of early endometrial cancer [5–12]. The totally laparoscopic approach has some advantages over the laparoscopy-assisted procedure, including the avoidance of losing time to shift from one operative field to another, a direct visualization of the vaginal cuff resection margins and enhanced removal of the uterus and lymph nodes in case of enlarged uteri or narrow vagina. This is not only our own opinion but also the opinion of others [4]. In addition, the average cost for laparoscopic hysterectomy and staging favourably compares with both laparotomy and robotics [13]. On the other side, the utilization of the uterine manipulator which is essential for all laparoscopic hysterectomies is of concern in case of uterine malignancies [14, 15]. In fact, in these cases, the fear for a peritoneal and systemic spread of tumor cells is a reasonable preoccupation.

In this paper we describe our experience using a retrograde and retroperitoneal hysterectomy for minimally invasive comprehensive surgical staging of the endometrial cancer. In our opinion the retrograde and retroperitoneal approach allows to get optimal and constant protection of the ureter, faster control of unexpected intraoperative hemorrhages and better modulation of radicality.To this end we have adopted a combination of the retroperitoneal

laparoscopic approach as originally described by Köhler et al. [16] and Roman et al. [17] with that of retrograde culdotomy reported long time ago by Delle Piane (1967) [18], Hudson and Chir (1968) [19], Robert [20], and more recently by Bristow et al. [21]. At our department, this surgical approach is routinely chosen for most of all the laparoscopies regardless of the malignancy. Always not disposable instruments nor uterine manipulator are employed.

2. Materials and Methods

2.1. Patients. From January 2002 to December 2011, all patients with diagnosis of endometrial cancer were treated by the same team of gynecologic oncologists operators at two departmental hospitals: Turin and La Spezia. The analysis was based on the data of 95 patients. Data regarding patient characteristics and intraoperative details were elicited from an oncologic database developed for retrospective review. The patient characteristics retrieved were age, body mass index, concomitant diseases, previous surgeries, stage of disease according to the 2009 International Federation of Gynecology and Obstetrics [22], histopathologic subtype, and tumor grade. Intraoperative parameters included blood loss, perioperative blood transfusions, operative time, and number of pelvic lymph nodes removed. Postoperative parameters evaluated short-and long-term complications, postoperative adjuvant therapy (radio and chemotherapy), length of hospitalization, median followup duration, recurrence, and disease-free interval. Patients were not considered candidates for the laparoscopic approach in case of metastases beyond the uterus. Neither high body weight nor previous abdominal surgery was considered a contraindication for the laparoscopic approach. Pelvic and lumbar-aortic lymphadenectomies have been performed in most cases based upon the surgical staging (after hysterectomy) or as first surgical step (before hysterectomy) when preoperative information about grading and histologic subtype (G2 or serous papillary or clear cell or undifferentiated) would has warranted it. Informed consent was obtained for all patients about risks of anesthesia, hysterectomy, laparoscopy, and risk of conversion to laparotomy. All patients underwent general anaesthesia and endotracheal intubation. The day of surgery, Cefazolin 2 gr was i.v. administered. Always, prophylactic anticoagulation therapy was given for ten days.

2.2. Surgical Technique. Patients were positioned in a dorsal lithotomy with legs apart and semiflexed, and the arms tucked at the sides. The surgical table was kept in a low position and the monitor between the patient's legs, facing the two surgeons to facilitate an ergonomic working position. A simplified equipment of no disposable instruments was used including a scissor, two grasping forceps, a washing-aspiration cannulae, and a 3 mm bipolar coagulation forceps. Ligasure (ValleyLab, Boulder, CO, USA) was used only for radical hysterectomies. Never the uterine manipulator was utilized.

A gasless access to the peritoneum was obtained by grasping the skin at the umbilicus with 2 Backhaus forceps and strongly elevating it while a 2 cm depth and 1 cm long incision was blindly made inside the umbilicus at its deepest part. A 10 mm trocar was then gently inserted throughout the incision to hold the laparoscope with the camera. When indicated by the surgical history of the patient, a Veress needle was first inserted into the peritoneal cavity at the left upper abdominal quadrant (Palmer site) to obtain intraperitoneal gas distension. At this point, patient was put in Trendelenburg position and three 5 mm trocars placed in the lower abdomen under direct vision. Two of these trocars were placed laterally to the epigastric vessels at the level of the superior iliac spine while the third one was centrally sovrapubic.

An incision was made where the broad ligament overlies the psoas muscle thus allowing to enter into the pararectal space. The peritoneum was opened parallel to the infundibulopelvic ligament above the crossing with the external iliac artery and along the umbilical artery (which can be tracked upwards along the abdominal wall). An avascularized space of areolar tissue was developed by dissection between a medial leaflet of the broad ligament and the external and internal iliac vessel, taking care to dislocate the ureter on the medial leaflet and avoiding dissection laterally to the internal iliac artery. Following the course of the ureter by one side and the internal iliac artery by the other, the crossing of the uterine artery was encountered (generally 1-2 cm further back the origin of the superior bladder artery). The uterine artery was bipolarly coagulated over 1-2 cm distance. Often the uterine veins were grasped and coagulated altogether.

When necessary a pelvic lymphadenectomy was performed either as first surgical step or following surgical staging. In any case it was performed bilaterally from the level of the aortic bifurcation along the external iliac vessels to the circumflex iliac vein. Internal iliac lymph nodes are then removed. The obturator lymph nodes were removed taking care to identify the obturator nerve. Para-aortic lymphadenectomy was not routinely performed unless suspicious pelvic lymph nodes or deep endometrial invasion or serous papillary or other abnormal histological types were present. Lymph nodes were removed altogether in one single endobag from the vagina at the end of the operation. The round ligament was only partially divided and the anterior leaf of the broad ligament utilized to prepare the paravesical space. A blunt dissection toward the pelvic floor between the superior bladder artery and the cervix was created on both sides. The vesicouterine peritoneal fold was left aside and retrograde dissection initiated from the sides of cervix. Cervical and vaginal uterine vessels were eventually identified, isolated, and coagulated. At the end of this time the transection of the round ligament was completed by dividing all the anterior leaf down to the vesicouterine peritoneal fold. This was finally mobilized from connections to the lower uterine segment. The infundibulopelvic ligaments were identified as high as possible out of the pelvis. While being grasped and elevated, an incision was bluntly made 1 cm beneath the ligament on the underlying peritoneum. This allowed to push away the ureter before coagulation. These ligaments were coagulated with bipolar over a 2 cm distance and were divided.

Afterwards, the posterior margin of the peritoneum was superficially incised towards the posterior vaginal apex and rectovaginal septum. By creating the avascular space the medial portion of the sacrouterine ligament could be safely drawn away from the isthmic portion of the ureter. The apical part of the rectovaginal septum was then opened. During this step parametrial tissue containing the vascular pedicles was coagulated and variably dissected as a function of the radicality required. A third operator was then enrolled to expose, by means of ring forceps, the anterior vaginal vault which was therefore incised and opened by the first operator. A vaginal tampon was then used to stop gas loss and maintain the pneumoperitoneum. While the second operator was grasping the anterior margin of the vagina, the first operator executed the retrograde incision of the vagina (circular culdotomy). This was facilitated by pulling up the cervix and dissecting the vaginal mucosa at variable distance from the portio as indicated by need of radicality. During this final step the sacrouterine ligaments were coagulated and transected. The retrograde direction of the culdotomy proceeded parallel and 2-3 cm above the course of the ureter. The vagina was then sutured laparoscopically by using 14 cm 0 Quill SRS suture (Angiotech, Vancouver, BC, Canada). Closure started at one angle of the vaginal cuff and prosecuted in a running fashion with a final stich securing one uterosacral ligament to the other. Finally, the pelvis was washed and hemostasis assured.

3. Results

The results are summarized in Tables 1, 2, and 3. Ninety-five patients affected by endometrial cancer at variable stage were consecutively referred to our attention. Clinical details of our patient population are given in Table 1. Conversion to laparotomy has never occurred. Endometrioid adenocarcinoma was the most common histological type found (70.5%). In the remaining 28 cases, rare histological subtypes associated with poor outcome were noted (29.1%). No invasion or less than one-half myometrial invasion was present only in 58.4% of the cases. A peritoneal cytology resulted positive in 12.6% of cases (12/95). In half of these cases the level of myometrial invasion resulted < of 50% (IA surgical stage). Cumulative prevalence of high grade (G2, G3) cases and advanced disease (IB, II, IIIA, IIIC stages) were 65.26% and 46.31%, respectively (Table 1). Always a total laparoscopic extrafascial hysterectomy coupled to bilateral annessiectomy was performed aside from 21 cases undergone radical hysterectomy (Table 2). This was decided based on preoperative information achieved throughout hysteroscopy or endocervical curettage or intraoperative surgical and pathological staging. Despite this, the surgical procedure here employed has basically remained unchanged for all the patients. Median operative time was 129.47 minutes (60–240). However, after excluding more complicated cases of fixed or enlarged uteri, the median operative time dropped significantly. In few instances a sudden bleeding in the pararectal space occurred but has always been promptly controlled by bipolar coagulation with no significant impact on the duration of the operation. In general, the blood loss was on average 125.15 mL (range 100–300). Mean length of patients hospitalization stay was 3.5 days (2–6) (Table 2). Three patients suffered short-term perioperative complications. One patient had an unintentional cystotomy that was recognized and repaired by laparoscopy while other two patients were found with ureteral injuries and undergone endoscopic positioning of a double J ureteral stent and one week hospitalization stay was needed. One patient required an intraoperative blood transfusion (1 U packed red blood cells) and another one received 2 U of packed red blood cells postoperatively. In 5 out of 96 cases, major postoperative complications occurred. This included one patient with advanced stage tumor who developed a vagina-enteral fistula (pelvic recurrence after 7 months and death), one with pelvic hematoma, one with pelvic abscess,

Table 1: Patients characteristics.

Patient's profile	
Number of cases	95
Age (years) mean (range)	63.46 (43–84)
BMI mean (range)	29.64 (20–46)
Other pathologies	
Hypertension	60
Diabetes	13
Thyroid	9
Other	13
Total (%)	95 (100%)
Previous surgeries	51
Histology	
Endometrioid	67
Adenosquamous	8
Serous-papillary	6
Villous-glandular	5
Undifferentiated	5
Mucinous	2
Carcinosquamous	1
Clear cell	1
Grading	
G1	33
G2	43
G3	19
Myometrial invasion	
No invasion	6
<50%	50
>50%	39
FIGO Staging	
IA	51
IB	26
II	3
IIIA	5
IIIC1	7
IIIC2	3
Positive washing cytology	12 (6/12 myom.invasion < 50%)

Table 2: Perioperative data.

	Number of cases
Hysterectomy + bilat. annessiectomy	95
Extrafascial	74
Radical	21
Operative time (min)	129.47 (60–240)
EBL (mL)*	125.15 (100–300)
Pelvic lymphadenectomy	65
Mean number of pelvic lymph removed	10.25 (1–28)
Para-aortic lymphadenectomy and omentectomy	13
Mean number of hospitalization days	3.5 (2–5)
Intraoperative complications (2 blood transfusions, 3 ureteral injuries)	5.2% (5/95)
Postoperative complications (fistula, lymphocyst, ascess, renal dilatation, hematoma)	5.2% (5/95)

*EBL: bleeding loss.

Table 3: Adjuvant therapy, followup, and survival.

	Number of cases
Adjuvant radiotherapy	20
Adjuvant chemotherapy	9
No adjuvant therapy	66
Mean followup (months)	49.09 (4–140)
Lost	6
NED*	75
ED°	1
Deaths	13
Recurrences	13 (12 deaths + 1 ED)
Vaginal	4
Pelvic	6
Peritoneal	3
Disease-free interval (months)	15 (7–34)

*NED: no evidence of disease.
°ED: evidence of disease.

one with septic lymphatic cyst, and another one with renal dilatation (Table 2). Adjuvant radio- or chemotherapy was administered in 29 patients (Table 3). A mean followup of 49.09 months (4–140) showed an important rate of 78.94% of patients with no evidence of disease (NED) (75/95). Thirteen had recurrences after a disease free interval of, on average, 15 months and all but one then died (12/13) (Table 3). These patients were suffering from advanced disease (abnormal histological subtypes and low grade). In our series, no port-site metastasis was ever observed.

4. Discussion

In this study we have reported about the method applied at our department for total laparoscopic hysterectomy in case of endometrial cancer. As shown in Table 1 patients characteristics were typical for this type of disease. Most of them were overweight, had a medical history of previous abdominal laparotomies, and all of them had some additional important health problem. Abdominal surgery therefore would have exposed them to increased risk of complications. As suggested by Vergote et al. (2009) [23] these patients might have benefit in many instances of vaginal hysterectomy or, better, laparoscopy assisted vaginal hysterectomy. We have been employing a retroperitoneal laparoscopic hysterectomy since a long time and believe about important advantages of laparoscopy particularly in case of uterine cancer staging. We agree with Magrina, (2001) [24] that in selected patients and in the hands of gynecologic oncologists experienced in advanced laparoscopic techniques the laparoscopic approach provides major patient advantages and should be used whenever feasible. In our opinion it is not any longer the case to doubt whether is it safe to treat endometrial carcinoma endoscopically [23]. Concerns raised about recurrence and survival rates are questionable since they appear comparable to those obtained by laparotomy [12]. Despite the poor surgical quality, on average, of our study population, we have been able not to convert any patient to laparotomy. This is contrary to that reported by GOG studies [10, 11] in patients having similar age and BMI. This is even more remarkable considering the high percentage of patients at advanced stage of disease undergone laparoscopic treatment and staging in our study. As it refers to the intra- and postoperative complication and survival rates observed in our retrospective study they are in agreement with those generally reported by most part of the studies. In particular a 78% of patients with no evidence of disease after on average of 49 months followup is noteworthy. Again this is of relevance since our patient population was largely far from being ideal and not comparable to patients studied so far by other authors (early endometrial cancers). In our study the prevalence of bad histological subtypes and high grade tumors was indeed very high (21% and 65%, resp.). In our series only 20% were true early endometrial cancers making our study not comparable to other studies. Once again we can conclude that in terms of operative time, expected blood loss and duration of hospitalization our data confirm that laparoscopic hysterectomy compares favorably to laparotomic hysterectomy. The technique here used for hysterectomy has in particular the advantage of being particularly cost saving and safe in terms of potential spread of tumor cells since the uterine manipulator is avoided. The technique is reproducible and has been performed by the same operators respecting consistently any single surgical step each time. Amount of parametrium to be resected and extension of lymphadenectomy were modulated on the bases of either preoperative data (grading) or intraoperative factors (FIGO 2009 surgical staging). This was made possible because of the accurate retroperitoneal preparation of the uterine vessels at their origin and retrograde dissection of paravesical tissue as well as retrograde incision of the vagina. By adopting a standard retroperitoneal approach in all the cases, it was easier to modify grade of radicality and decide for a pelvic and/or para-aortic lymphadenectomy.

In conclusion, we confirm adequacy and cost effectiveness of laparoscopy for surgical staging and treatment

of endometrial cancer. Specifically, our method of retrograde and retroperitoneal hysterectomy is particularly indicated and valuable in that it avoids the use of uterine manipulator and allows easy modulation of radicality. This last consideration is important since patients suitable for surgical treatment of endometrial cancer represent a quite heterogeneous population.

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Review Article

Fertility-Sparing Surgery for Early-Stage Cervical Cancer

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Nowadays cervical cancer is diagnosed in many women who still want to have children. This led to the need to provide fertility-sparing treatments. The main goal is to maintain reproductive ability without decreasing overall and recurrence-free survival. In this article, we review data on procedures for fertility preservation, namely, vaginal and abdominal trachelectomy, less invasive surgery and neoadjuvant chemotherapy. For each one, oncological and obstetrical outcomes are analyzed. Comparing to traditionally offered radical hysterectomy, the overall oncologic safety is good, with promising obstetrical outcomes.

1. Introdution

Cervical cancer is the second most common cancer in women in developing countries and the seventh in developed countries [1]. It affects women of all ages, including those in their prime childbearing years.

More than 500.000 new invasive cervical cancers are estimated to be diagnosed worldwide every year. Because of the effective and widespread use of cervical carcinoma screening, many women will be diagnosed at a relatively young age and early stage [2]. The postponement of childbearing accompanied with the comparatively young age at which many women are diagnosed with cervical carcinoma has posed new challenges in the management of this disease—there is a strong demand for fertility-sparing surgery.

Traditionally the recommended treatment for early cervical cancer is a radical hysterectomy (RH) with bilateral pelvic lymphadenectomy: removal of the uterus, cervix, radical resection of the parametrial tissue and upper vagina, and complete pelvic lymphadenectomy [3].

Cervical cancer spreads laterally to the parametria, inferiorly to the vagina and rarely superiorly to the uterus [4–6]. This is why it is possible to maintain the fundus and adnexa in most small cancers confined to the cervix and thus maintain the possibility of future childbearing.

Parametrial removal in early cervical cancer remais important to rule out parametrial spread, which would be an indication for further therapy, to prevent local recurrence; and to obtain a clear margin of the cervical primary.

There are several types of fertility-saving procedures, which differ in terms of surgical approach and extent of paracervical resection. The most widely accepted is radical vaginal trachelectomy (RVT), but in the last years there are increasing reports of an abdominal approach to perform radical trachelectomy. There are also some less invasive procedures under investigation, such as large conization and simple trachelectomy. Neoadjuvant chemotherapy is being studied as a possibility to downstage larger tumors and allow for these fertility-sparing procedures.

2. Selection Criteria

The management of fertility sparing surgery must include a good selection of patients and complete information about them. They need to be informed about preoperative examinations, late complications, and especially the oncologic and obstetric outcomes related to the surgery as well as the alternative approaches [3]. There is no guarantee of fertility after

a radical trachelectomy and the standard treatment for early-stage cervical carcinoma is still radical hysterectomy. So, detailed informed consent is essential [7–11].

It is estimated that even with a careful patient selection for fertility-sparing surgery, 12–17% of the patients will have the procedure aborted due to nodal metastasis or positive endocervical margins [12].

The main selection criterion is a strong desire to preserve fertility. Preservation of uterus in women who does not plan pregnancy is controversial [12, 13] as it is in women with previously impaired fertility. Assisted reproduction techniques are widely used and many women did not even tried to conceive before the diagnosis of cervical cancer. Hence, it is not possible to estimate reproductive potential before surgery accurately.

Most centres do not also specify an upper age limit for fertility-sparing surgery. Regarding their inherent risk of infertility based on age alone, some centres exclude patients from 40 or 45 years [2, 14–16].

Tumor size is the most important risk factor for recurrence. It has been shown in many studies that tumors greater than 2 cm have a significant increase in the risk of recurrence [13, 17].

Appropriate candidates for fertility-sparing surgery are patients with tumors of FIGO stage IA1 with lymphovascular space involvement, IA2 and IB1. Most centres include stage IB1 tumors of less than 2 cm only.

Tumor size may not completely exclude a candidate for surgery. For instance, a patient with an exophytic tumor with more than 2 cm but with little stromal invasion may still be a reasonable candidate for radical trachelectomy [44].

Expert colposcopy is the standard examination before fertility-sparing surgery and is important in assessing the exocervical diameter and spread to the vagina [9, 15, 45].

A second histopathological examination is important for determination of type, grade, tumor dimensions, depth of invasion, and lymphovascular space involvement. There is controversy as to whether adenocarcinoma or adenosquamous histology is related to a higher risk of recurrence, compared to squamous cell carcinomas. In the largest series published, which compared early-cervical cancers with different histological subtypes, it was found that adenocarcinomas and squamous cell carcinomas had similar outcomes with fertility-sparing surgery [46, 47]. Small-cell neuroendocrine carcinoma is not suitable for fertility-sparing surgery since the prognosis for this aggressive tumor is worse than for other types [13, 48, 49]. For this kind of tumor, usual treatment includes radical hysterectomy and chemotherapy. It is unknown if radical trachelectomy followed by chemotherapy would have the same outcomes [44].

Lymphovascular space involvement is still the most commonly discussed risk factor. Although it is a negative prognostic factor for recurrence and nodal metastasis, its presence alone does not necessarily exclude the possibility of fertility-sparing surgery. There are reports in the literature of patients that underwent radical trachelectomy even with known lymphovascular space involvement, and only 5% of them were shown to have positive lymph nodes on specimen examination [50]. Patients should be informed of the risk of recurrence if lymphovascular space involvement is extensive [51].

Magnetic resonance imaging (MRI) volumetry is another preoperative diagnostic method, and its information can be further amplified by the use of an endovaginal receiver coil [52] or by creating an artificial saline hydrocolpos [53]. It is important for determination of exact tumor size, amount of cervical stroma infiltration, and amount of healthy stroma (determination of tumor growth in anterioposterior, craniocaudal, and transverse directions).

Estimation of lesion size is further complicated when a patient has undergone conization prior to presentation for definite treatment [54].

It has been shown that MRI has 100% positive and negative predictive value in assessing which patients are suitable for radical vaginal trachelectomy [55].

Many clinicians have suggested that infiltration of less than half of the cervical stroma is the limit for a safe trachelectomy, because it is necessary to have a 1 cm free margin [15, 56, 57]. Some clinicians suggest margins of only 5–8 mm to be sufficient but this is still debatable [20].

All forms of trachelectomy should save a good proportion of healthy stroma because the chance of successful pregnancy is higher. Preservation of the cervical stroma lowers the risk for cervical incompetence, ascending infection, premature rupture of membranes, and premature delivery [20].

MRI can also assess tumor involvement of paracervical tissues. In the literature [5, 58], parametrial involvement in IB1 tumors ranges from 6 to 13%. Factors which potentially correlate with parametrial tumor spread at the time of radical hysterectomy include lymph node status, size of tumor, deep stromal invasion, stage, lymph vascular space invasion, grade, histology, and presence of residual tumor in the surgical specimen [58, 59].

Patients with cervical cancer that has spread to the parametria require adjuvant chemoradiation and, therefore lose the benefit of the "fertility-sparing" aspect of the surgery [12, 54, 60]. In these patients, there may be an increased risk of complications. Unfortunately, most of the characteristics that increase the risk of spread (deep stromal invasion and vascular invasion) may not be determined reliably preoperatively [54].

MRI and computer tomography (CT) scans are insufficient for evaluation of microscopic pelvic lymph node infiltration [61, 62]. A new generation of PET-CT and MRI, which use ultra-small iron particles, seems to be feasible for preoperative assessment of lymph nodes [63, 64]. Vaginal or rectal ultrasonography is also used in some centres, with good results [65].

Usual clinical eligibility criteria for radical trachelectomy are listed on Table 1 [2].

3. Intraoperative Assessment

During surgery, extrauterine spread to the lymph nodes should be assessed and an adequate margin of healthy stroma assured. Perioperative pathological examination should be performed. When extrauterine spread or infiltration of

Table 1: Eligibility criteria for radical trachelectomy.

FIGO stage IA1 with lymphovascular space involvement, IA2 and IB1
Desire for future fertility
Age ≤ 40–45 years
Confirmed invasive carcinoma—squamous, adenocarcinoma, or adenosquamous
No previous documentation of infertility (+/−)
No evidence of pelvic lymph node metastasis and/or other distant metastasis
Patient being a candidate for surgery
4–6 weeks postconization with adequate resolution of acute inflammation

the cranial part of the specimen is found, it becomes necessary to perform a more radical surgery or to initiate chemoradiotherapy [20].

Perioperative assessment of regional lymph nodes includes removal of the nodes from external, internal iliac, and obturator regions. They can be examined by repeated frozen sections but recently this assessment was replaced by detection of sentinel lymph node in many centres [13, 15, 17, 66]. The technique of sentinel lymph-node mapping may help localize aberrant nodal metastasis spread and identify micrometastases that have been missed with conventional histopathological processing [50]. In the presence of micrometastases (<2 mm) or isolated tumor cells not diagnosed until the final histopathology, adjuvant chemotherapy or radiotherapy should follow surgery, but there are no randomized studies about the ideal modality of treatment [20].

4. Radical Trachelectomy

Radical trachelectomy, the removal of the uterine cervix and adjacent tissues, was originally introduced in 1987 by Dr. Daniel Dargent. He performed a laparoscopic pelvic lymphadenectomy and a VRT. In a short period of time, several centres presented studies regarding slightly modified VRT [45, 56, 67, 68] and also abdominal approaches [54, 69].

The choice for abdominal or vaginal route as well as laparotomy or laparoscopic approach depends mainly on the surgeon's preference and level of expertise [3]. Details about the performance of these techniques are well described elsewhere [3, 19, 27–30, 32, 34, 60, 66, 68]. Robot-assisted laparoscopy is also rapidly increasing as a possibility in fertility-sparing surgery for early cervical cancer [70–73].

The oncological safety of these procedures in the treatment of early-invasive cervical cancer is well established in many retrospective studies and is associated with an acceptable live birth rate [3, 9, 74].

There has not been any randomized controlled trial comparing fertility-sparing radical trachelectomy to radical hysterectomy for the treatment of early cervical cancer. Such a trial is not feasible, since offering young women who desire fertility preservation a trial in which they would be randomized to a radical hysterectomy may be exceedingly difficult and unacceptable to these patients. Moreover, a formidable sample size would be needed to do meaningful statistical analysis.

Instead, there are some case-control studies [2, 22, 75] and a meta-analysis on five of these previous studies has been recently published, comparing 303 patients who underwent VRT with 892 who underwent RH. No significant differences were found between VRT and RH in 5-year survival rate, 5-year progression-free survival rate, intraoperative complications, and postoperative complications. There were fewer blood transfusions, less blood loss and shorter hospital stays in patients undergoing VRT.

4.1. Surgical Complications. Several studies compared the surgical morbidity of VRT with RH [47, 50, 76]. Overall VRT has equal or less morbidity than RH in terms of blood loss, surgery duration, analgesic requirements, and hospital stay [75, 76]. The main drawback of radical trachelectomy is the operative time associated with the procedure, which is in part caused by a longer learning curve.

Combined data showed an average intraoperative complication rate of 4% and postoperative complication rate of 12% [50].

Bladder injury accounts for more than half of the complications; usually, it is easy to identify and repair, with no long-term sequelae. Vascular injuries are the second most common complications and occur mainly during lymphadenectomy or as a result of trocart insertion during laparoscopic procedures [50]. There are also reports of isolated cases of enterotomy, vaginal fornix laceration, and ureteral injury [27]. Lymphedema and lymphocyst formation are more common in RH [76]. However, there are two known cases of pelvic-obturator space lymphocysts infected by group B streptococcus associated with VRT [18].

Typical complications reported after radical trachelectomy include dysmenorrhea (24%), dysplastic Pap smears (24%), metrorragia (17%), problems with cerclage sutures (14%), excessive vaginal discharge (14%), isthmic stenosis (10%), amenorrhea (7%), and occasional reports of deep dyspareunia [76].

4.2. Followup after Radical Trachelectomy. There are no universal guidelines as to the optimal followup after radical trachelectomy.

Most authors suggested visits every 3–6 months for the first two years, then every 6 months for three years. Typically, more than three-fourths of recurrences will occur within the first 2-3 years after the initial treatment but there have been reports of recurrence even 7 years after RVT. Thus, followups may be extended to every year after the first 5 years [56, 75, 77].

Patients should be aware of symptoms of recurrence such as abdominal or pelvic pain, lymphedema, leg pain, vaginal bleeding or discharge, urinary symptoms, cough, and weight loss. They are present in 46–95% of the patients with recurrences [78, 79].

Physical examination is widely accepted for surveillance and accounts for the highest detection rate when compared with cytologic evaluation and imaging modalities [80, 81]. It should include a complete assessment of areas that are susceptible to the human papilloma virus and a thorough speculum, bimanual, and rectovaginal examination. Along with symptoms, physical examination will detect most cases of recurrent cervical cancer [77].

Although there is insufficient evidence, cytologic evaluation performance in retrospective studies showed low detection rates for recurrences and so it may not be mandatory. Nevertheless, most surveillance programs include cervical cytology, colposcopic examination, and eventually endocervical curettings. Follow-up cytology posttrachelectomy can have normal results interpreted as atypical so an experienced cytopathologist should be enrolled in interpreting results. It can also be important in detecting other lower genital tract malignancies [77, 82].

Some clinicians perform routine MRI at 6, 12, and 18 months, while others do so only if clinically indicated [56, 75]. MRI should be read by radiologists familiar with the procedure since anatomic changes can be misinterpreted as recurrences [83]. Anyway, there is still insufficient data to support its routine use in asymptomatic patients.

PET scans have high sensitivity (86%) and specificity (87%) for detecting disease recurrence. Its use as a surveillance tool is also being studied with promising results [84, 85].

5. Less Radical Procedures

Approximately 65% of patients do not have any residual cancer in the trachelectomy specimen after a diagnostic cone [7, 9]. Additionally, the rate of parametrial involvement in patients with tumor size ≤2 cm, negative pelvic nodes, and depth of invasion ≤10 mm is only 0,6%, so it might be safe not to resect parametrial tissue in these patients [58, 86–88]. This raises the question as to whether less radical surgery provides similar effectiveness to RVT.

Recently, some authors proposed less radical procedures for "low-risk" patients (tumor size <2 cm, low risk histology, absence of lymph vascular space invasion) [42].

Usual protocols perform pelvic lymphadenectomy first, and if there are no positive nodes (or if sentinel node is negative), a large conization or simple trachelectomy is performed after. Simple trachelectomy consists of amputation of the cervix approximately 7–10 mm above the lesion and then removal of the endocervical channel by use of loop electrosurgical excision. This technique keeps the risk of stenosis to a minimum [89].

6. Neoadjuvant Chemotherapy and Fertility Sparing Surgery

In women affected by larger cervical lesions (>2 cm tumor size), there is a higher risk of recurrence [90]. Some authors suggested the use of neoadjuvant chemotherapy prior to surgery in these patients [42], providing a more conservative endocervical tissue resection, diminishing the risk of central recurrence, and potentially improving obstetrical results.

Concerning the deleterious effects of chemotherapy on ovarian function, this treatment should be offered to women who normally have a good ovarian reserve, since alkylating agents such as ifosfamide and cisplatin can be detrimental to ovarian follicles.

Different chemotherapy protocols include (1) cisplatin 75 mg/m^2 plus ifosfamide 2 g/m^2 every 10 days. (2) cisplatin 75 mg/m^2 plus doxorubucin 35 mg/m^2 every 10 days; (3) TIP: paclitacel 175 mg/m^2 plus cisplatin 75mg/m^2 plus ifosfamide 5 g/m^2; (4) TEP: paclitacel 175 mg/m^2 plus cisplatin 75 mg/m^2 plus epirubicin 80 g/m^2, every 21 days; TEP is usually used in adenocarcinomas. In the future, less gonadotoxic regimens should be evaluated [21].

However, downstaging tumors larger than 2 cm by neoadjuvant chemotherapy is still an experimental procedure and will need multicentre cooperation to verify its oncological safety.

7. Oncological and Pregnancy Outcomes

The critical concern when treating patients with early-stage cervical cancer is whether conservative surgery is as effective as the standard radical hysterectomy.

In some instances, patients will be recommended to receive additional treatment due to the presence of positive lymph nodes, close or positive upper margins of the removed cervix, or unusual histological subtype as neuroendocrine carcinoma. Therapy can consist of radical hysterectomy or radiation, with or without chemotherapy; this depends on the center protocol and the timing of diagnosis—intraoperative versus postoperative [50]. Even after an appropriate patient selection, it is estimated that around 10% of the patients would require these additional treatments and thus will lose the fertility-sparing characteristic of the procedure.

There are some reports of patients who refused adjuvant therapy when indicated. Three women with nodal micrometastasis refused adjuvant treatment and none recurred. Four women with positive nodes on final pathology refused radiation therapy and did only chemotherapy and none recurred. Two patients with margins inferior to 5 mm on the superior cervical canal on final pathology also refused adjuvant therapy and none recurred [17, 90].

Yet, in other series, there are reports of one patient that had close margins and recurred in the uterine fundus after 3 months and another patient with invasive cancer after 10 months [17].

Until now, there have been many reports on oncological outcomes of RVT, which are described in Table 2.

In a total of 849 women, only 83 (9,8%) for whom a VRT was planned could not have their fertility preserved, mostly because of positive nodes.

Recurrence rate was 3,9%. Excluding one article which does not specify tumor size, a comparison of recurrences in tumors less than 2 cm in size—2,6%, with recurrences in bigger tumors—23,9%, shows that VRT might be a risky procedure for tumors larger than 2 cm.

Table 2: Characteristics and oncological outcome of RVT.

Authors	Planned surgeries	Fertility preserved	Positive nodes	LVSI	Histology			Recurrence		Deaths
					SCC	AC	O	≤2 cm	>2 cm	
Shepherd et al. [7, 8]	158	138	7	49	103	51	4	3**		4
Sonoda et al. [18]	43	36	2	NA	24	16	3	1/36	0/0	1
Pahisa et al. [14]	15	13	0	1	9	6	0	1/11	1/2	1
Chen et al. [19]	16	16	0	1	14	2	0	0/9	0/7	0
Hertel et al. [17]	108	106	2	38	74	33	1	3/105	1/1	2
Dargent et al. [2, 20]	135	118	9	43	90*	25*	3*	1/91	6/27	5
Plante et al. [21]	140	125	9	32	69*	48*	8*	3/111	3/14	2
Covens et al. [7, 22]	93	91	2	31	40	50	3	5/83	1/8	4
Burnett et al. [12, 23]	21	18	1	6	12	9	0	0	0	0
Schlaerth et al. [24]	12	10	0	1	4*	5*	1*	0/10	0/0	0
Mathevet et al. [13]	108	95	8	23	76*	18*	1*	0/85	4/8	3
Total	849	766	40	225	559	264	24	33		24

*Only after VRT; ** data not available for the number of recurrences > and ≤2 cm; NA: not available data.

Table 3: Pregnancy outcomes of VRT.

Authors	Fertility preserved	Pregnant women	Conceptions	Abortions		Deliveries		
				1st T	2nd T	Preterm	Term	On going*
Shepherd et al. [7, 8]	138	NA	88	22	12	10	37	7
Sonoda et al. [18]	36	11	11	3	0	0	4	4
Pahisa et al. [14]	13	3	3	0	0	0	1	2
Chen et al. [19]	16	5	5	0	2	1	1	1
Hertel et al. [17]	106	18	18	3 (2VIP)	0	8	4	3
Dargent et al. [2, 20]	118	33	56	14	8	5	29	0
Plante et al. [21]	125	58	106	25 (4VIP)	4 (1VIP)	19	58	0
Covens et al. [7, 22]	91	18	24	3	3	6	12	0
Burnett et al. [12, 23]	18	3	3	0	1	1	1	0
Schlaerth et al. [24]	10	4	4	0	2	1	1	0
Mathevet et al. [13]	95	33	56	14	8	5	29	0
Danska-Biazinska et al. [25]	14	2	2	1	0	0	1	0
Speiser et al. [26]	212	50	60	8 (2VIP) (1EP)	3	18	27	4
Total	992	238	436	93	43	74	205	21

*Ongoing pregnancies at the time of publication of each study; VIP: voluntary interruption of pregnancy; EP: ectopic pregnancy; NA: not available data.

Table 4: Characteristics and oncological outcome of ART.

Authors	Planned surgeries	Fertility preserved	Positive nodes	LVSI	Histology			Reccurrence		Deaths
					SCC	AC	O	≤2 cm	>2 cm	
Abu Rustum et al. [27, 28]	22	15	6	9	9	13	0	NA	NA	0
Pareja et al. [29]	15	14	1	5	11	4	0	0/14	0/0	0
Nishio et al. [30]	71	61	15	31	58*	2*	1*	1/48	5/13	NA
Cibula et al. [31]	24	17	4	2	14	10	0	1/14	0/3	NA
Ungará et al. [32]	33	30	2	8	26*	1*	3*	0/21	0/9	0
Olawaiye et al. [33]	10	10	0	1	3	7	0	0/9	0/1	0
Wan et al. [34]	2	2	0	0	2	0	0	0/2	0/0	0
Yao et al. [35]	10	10	0	NA	8	2	0	0/10	0/0	0
Li et al. [36]	64	62	2	4	50*	8*	4*	0/48	0/14	0
Total	251	221	30	59	181	47	8	2/166	5/40	0

*Only after ART; NA: not available data.

Table 5: Pregnancy outcomes of ART.

Authors	Fertility preserved	Pregnant women	Conceptions	Abortions		Deliveries		
				1st T	2nd T	Preterm	Term	On going*
Abu Rustum et al. [27, 28]	15	2	2	1	0	0	0	1
Pareja et al. [29]	14	3	3	0	0	1	2	0
Nishio et al. [30]	61	4	4	0	0	2	2	0
Cibula et al. [31]	17	6	6	1	0	2	3	0
Ungará et al. [32]	30	13	13	4	0	1	5	3
Olawaiye et al. [33]	10	3	3	1	0	1	1	0
Wan et al. [34]	2	0	0	0	0	0	0	0
Yao et al. [35]	10	2	2	0	0	1	1	0
Li et al. [36]	62	2	2	0	0	0	1	1
Total	221	35	35	7	0	12	15	5

*Ongoing pregnancies at the time of publication of each study.

Table 6: Characteristics and oncological outcome for less radical procedures.

Authors	Planned surgeries	Fertility preserved	Positive nodes	LVSI	Histology			Reccurrence	Deaths
					SCC	AC	O		
Rob et al. [15]	40	32	6	17	32	7	1	1	0
Landoni et al. [16]	11	11	0	NA	5	6	0	0	0
Bisseling et al. [37]	3	3	0	NA	0	3	0	0	0
Total	54	46	6	17	37	16	1	1	0

NA: not available data.

In women who underwent VRT, mortality rate was 3,1%.

There have been 436 pregnancies reported after fertility-sparing VRT, which resulted in 279 deliveries—see Table 3. Excluding ongoing pregnancies, delivery rate was 67,2%. The rate of first trimester miscarriage was 22,4%, which is similar to that of the general population. The rate of second trimester miscarriage was 10,3%—twice higher than that of the general population, mainly because of ascending infections and premature rupture of membranes. Premature delivery also had a higher rate and occurred in 74 of 279 deliveries—26,6%. Various authors suggested routine administration of antibiotics between 14–16 weeks, antepartum management with prophylactic antibiotics, bimonthly screening for infections, bed rest, steroids therapy, and even serial measurements of cervical length [91, 92]. It appears that none of these approaches are evidenced-based and all of them require further investigation, although it is a consensus that these pregnancies should be followed up as high-risk pregnancies [75].

There have also been reports on oncological outcomes of ART but data is less extensive—see Table 4. Of the 251 cases reported, fertility-sparing surgery was not possible in 12% of women because of lymph node involvement.

Oncological outcomes of ART were good and similar to those of VRT as there were only 7 recurrences reported (3,4%).

In a comparison of recurrences in tumors less than 2 cm in size—1,2% with recurrences in bigger tumors—12,5% shows that ART, as VRT, is also a risky procedure for tumors larger than 2 cm.

The obstetrical outcomes reported with ART—see Table 5—have been less than with VRT, as a result of less experience with this procedure, and also because of recommendations of some clinicians to wait 2 years prior to conception [32].

In all 221 women that have undergone ART, it was found that only 35 women achieved pregnancy, which is a dramatically lower rate of pregnancies than that found with VRT [8, 20]. The rate of pregnancy loss (23,3%) was similar to that in VRT, and preterm labor was slightly bigger (44,4%).

It is generally believed that the difference in pregnancy rates between vaginal and abdominal radical trachelectomies is due to the fact that in RVT the blood supply from the main uterine arteries is not affected, while the uterine artery is usually transected at its origin in ART [93].

However, some facts reported in other studies contradict this theory: healthy pregnancies at term have developed even with the uterus being perfused relying only on the ovarian vessels [94] and there is also an ART performed in a patient who was 15-week pregnant, and despite the need to completely transect the left uterine vasculature, the pregnancy reached term without evidence of any anomaly, including fetal growth restriction [95]. So, further data with long-term followup need to be gained to determine whether preserving the uterine artery is an important factor in improving pregnancy outcomes [73].

Preliminary findings for less invasive surgeries such as large conization or simple trachelectomy after pelvic lymphadenectomy (or sentinel node identification) are comparable to those achieved with abdominal or vaginal radical

Table 7: Pregnancy outcomes for less radical procedures.

Authors	Fertility preserved	Pregnant women	Conceptions	Abortions		Deliveries		
				1st T	2nd T	Preterm	Term	On going
Rob et al. [15]	32	17	23	5	3	12		3
Landoni et al. [16]	11	3	3	0	0	0	3	0
Bisseling et al. [37]	3	3	4	0	0	4		0
Total	46	23	30	5	3	19		3

Table 8: Characteristics and oncological outcomes for fertility-sparing surgery after neoadjuvant chemotherapy.

Authors	Planned surgeries	Fertility preserved	Positive nodes	LVSI	Histology			Reccurrence	Deaths
					SCC	AC	O		
Maneo et al. [38]	21	16	2	1	9	12	0	0	0
Kobayashi et al. [39]	1	1	0	0	1	0	0	0	0
Plante et al. [21]	3	3	0	0	3	0	0	0	0
Robova et al. [40]	15	12	0	9	9	3	0	3	1
Palaia et al. [41]	1	1	0	0	1	0	0	0	0
Marchiole et al. [42]	8	7	1	NA	6	2	0	0	0
Gottschalk et al. [43]	1	1	0	0	0	1	0	0	0
Total	50	41	3	10	29	18	0	3	1

NA: not available data.

Table 9: Pregnancy outcomes for fertility-sparing surgery after neoadjuvant chemotherapy.

Authors	Fertility preserved	Pregnant women	Conceptions	Abortions		Deliveries		
				1st T	2nd T	Preterm	Term	On going
Maneo et al. [38]	16	6	10	1	0	2	7	0
Kobayashi et al. [39]	1	1	1	0	0	1	0	0
Plante et al. [21]	3	2	3	0	0	1	2	0
Robova et al. [40]	12	7	7	0	0	1	5	1
Palaia et al. [41]	1	0	0	0	0	0	0	0
Marchiole et al. [42]	7	1	1	0	0	0	0	1
Gottschalk et al. [43]	1	1	1	0	0	0	1	0
Total	41	18	23	1	0	5	15	2

trachelectomies—see Table 6. In patients with negative lymph nodes and tumors less than 2 cm, results are promissing and comparable with the results of VRT and ART [20]. Prospective multicentric studies will be needed to confirm their oncological safety.

Of the 46 surgeries performed, there was only one recurrence reported; in this case adjuvant treatment with chemotherapy was performed, and there was no evidence of disease until now (5-year followup) [15, 89].

Half of the women become pregnant after surgery and there were reported 30 pregnancies, and 19 deliveries—see Table 7. These studies, although in a small scale, show that less-invasive procedures have good results and have the potentiality of performing even better than radical trachelectomy in selected patients.

Oncological and pregnancy outcomes after neoadjuvant chemotherapy and fertility-sparing surgery were reported in few series—Tables 8 and 9.

In a total of 41 fertility-spared women, there were only 3 recurrences registered, one of which occurred in the ovary and the patient died soon after. All recurrences occured in patients in whom the surgery performed was less radical than radical trachelectomy [40].

There were 23 pregnancies in 18 of the 41 women who undergone neoadjuvant chemotherapy before surgery—Table 9. There were one first-trimester loss, five preterm deliveries and 15 full-term babies.

Analysis on pregnancy outcomes for all different approaches revealed that ART performed worse than all the others and that less radical procedures had significantly better results as it would be expected [20].

The extent of the removed cervix, the technique of reanastomosis, and the formation of the neocervix are factors than will affect future fertility, because of shortening of the cervix length, diminished cervical mucus, and stenosis of the residual cervix. All techniques try to save as much

cervix as possible, leaving at least 1 cm of cervical stroma. Approximately 15% of patients develop cervical stenosis after RVT [96]; most are asymptomatic, but some develop menstrual disorders or hematometra, requiring dilatation of the cervical ostium to resolve. Another important factors that affect fertility are the higher risk of abdominal surgical adhesions, subclinical salpingitis and disruption of the uterus and tube innervation after pelvic lymphadenectomy, and parametrial resection [50, 75].

It was estimated that infertility rate after trachelectomy is between 25–30% [75].

In patients with difficulties conceiving after trachelectomy, a complete infertility workup should be done, and patients may require assisted reproductive techniques as any other case. In 75% of the cases, a cervical factor appears to be the cause for the infertility [75].

There is no consensus as to the timing of pregnancy after RT. Some suggest a 6 months to 1-year followup period before attempting pregnancy [9, 44], but others do not establish any period [56].

8. Conclusion

The management of early-stage cervical carcinoma in young women who desire future fertility remains a challenge to gynecologic oncologists.

Tumor size, presence of positive nodes, lymphovascular space involvement, deep stromal invasion, and unfavorable histology are the most important risk factors for recurrence and should be carefully evaluated preoperatively.

Nowadays, radical vaginal trachelectomy is a well-established safe procedure on early cervical cancer with large experience to date. It has good oncological and obstetrical outcomes with low morbidity and mortality, especially in tumors less than 2 cm in size.

Experience with abdominal open or laparoscopic approach is increasing, and it is now possible to select patients for less radical fertility-sparing procedures such as large cone biopsy or simple trachelectomy. Neoadjuvant chemotherapy before fertility-sparing surgery is an innovative approach, which can extend the possibility of a conservative treatment to many young women affected by larger cervical lesions.

New data from these techniques is currently being studied, and in the future more options will be safely available for early cervical cancer such as the use of robotic surgery in large institutions, which will result in surgeries performed safer, better, faster, and at a lower cost.

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Review Article

Total Pelvic Exenteration for Gynecologic Malignancies

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Total pelvic exenteration (PE) is a radical operation, involving en bloc resection of pelvic organs, including reproductive structures, bladder, and rectosigmoid. In gynecologic oncology, it is most commonly indicated for the treatment of advanced primary or locally recurrent cancer. Careful patient selection and counseling are of paramount importance when considering someone for PE. Part of the evaluation process includes comprehensive assessment to exclude unresectable or metastatic disease. PE can be curative for carefully selected patients with gynecologic cancers. Major complications can be seen in as many as 50% of patients undergoing PE, underscoring the need to carefully discuss risks and benefits of this procedure with patients considering exenterative surgery.

1. Introduction

Pelvic exenteration (PE) describes a radical surgery involving the en bloc resection of the pelvic organs, including the internal reproductive organs, bladder, and rectosigmoid. Indications include advanced primary or recurrent pelvic malignancies, most commonly centrally recurrent cervical carcinoma, but also other gynecologic tumors and urologic and rectal cancers. Distant metastasis has traditionally been a contraindication to PE with curative intent. As the best chance for disease-free survival is surgical resection of regional disease, this procedure is an opportunity to cure advanced and recurrent cancers confined to the pelvis. PE has also been used for palliation of symptoms related to radiation necrosis or extensive tumor burden. Both total and partial PE require extensive reconstruction and surgical recovery with significant associated morbidity and mortality. Careful patient selection is required to balance the potential goal of cure or symptom palliation with surgical risk.

The first cases of total PE were described by Brunschwig in 1948 as a palliative procedure for symptoms caused by locally advanced gynecologic cancers. This demonstrated proof of concept for PE, with a postoperative survival of up to 8 months, and a 23% surgical mortality rate [1]. Subsequent data demonstrated that the technique could offer a chance of cure for centrally located tumors, not just palliation, and the focus of the surgery shifted to one of curative intent. Various surgical approaches both for sparing uninvolved pelvic organs and removing extraperitoneal structures such as the sacrum were attempted. Major breakthroughs included separate stomata for urine and fecal diversion and the use of omentum to protect the empty and denuded pelvic space and reduce abscess formation and intestinal obstruction [2, 3]. More recently, techniques to resect tumor involving the pelvic sidewall, previously a contraindication to PE, have been described offering more patients a chance at curative surgery [4]. PE may also be combined with intra-operative radiation therapy for improved disease control at the pelvic sidewall or possible positive margins [5, 6].

Since 1948 several developments in perioperative care and surgical technique have improved survival, morbidity, and mortality, with recent mortality rates quoted <5%. Development of continent urinary conduits and orthotopic neobladders, as well as low rectal anastomoses has led to the completion of PE without formation of stomata [7]. Various techniques for functional neovaginas have been described, allowing patients to maintain sexual function if they desire. Advances in laparoscopic and robotic assisted technology applied to PE have improved operative recovery. Despite these significant advances and five-year survival rates of approximately 50%, PE remains a radical procedure with significant complications (31–92%; see Table 1), both

Table 1: Recent series of pelvic exenteration for gynecological malignancies.

Author	Year	*N*	Cervical	Uterine	Vulvar	Vaginal	Ovarian	Early complications	Late complications	Severe morbidity	Operative mortality	5-year survival
Benn et al. [60]	2011	54	40	9	5	0	0	50%	61%	44%		34%
Maggioni et al. [61]	2009	106	62	10	9	21	4	48%	49%		0%	
Marnitz et al. [12]	2006	55	55	0	0	0	0	11%	75%	38%	6%	37%
Goldberg et al. [11]	2006	103	95	2	1	0	0			25%	1%	47%
Sharma et al. [62]	2005	48	39	2	3	2	2	27%	75%	45%	4%	30%
Berek et al. [10]	2005	75	67*	8	0	*	0			23%	4%	54%

*Combined cervical and vaginal cancers.

physical and psychological [8]. Given the nature of this procedure, appropriate patient selection and counseling remain paramount.

2. Indications and Outcomes

2.1. Cervical Cancer. Traditionally PE has been used for centrally recurrent cervical carcinoma, both squamous and adenocarcinoma, with well-documented salvage potential. Up to 25% of women with FIGO stage IB-IIA cervical cancer may recur after initial therapy [9]. Frequently, these recurrences may be treated with radiotherapy; however, radical surgery may offer an alternative for curative treatment. Survival rates ranging from 16 to 60% are reported for these patients [10, 11]. Long-term survival is directly correlated with complete tumor resection [12, 13], so establishing resectability is a key aspect of preoperative planning. Time from primary treatment, with radiation or chemoradiation, to time of PE has also been shown to be related to survival and disease-free interval [12], with women requiring PE for recurrence less than 2 years following primary therapy demonstrating an 8-month survival versus 33 months in women who recurred more than 2 years following initial treatment in one study [14], though this has not been shown in all series [10]. PE has also been utilized as a potentially curative primary treatment for locally advanced cervical cancer (FIGO stage IVa), a practice exercised more frequently in Germany than the United States [15]. For example, in their series, Marnitz et al. reported a 52.5% five-year survival [12].

2.2. Uterine Cancer. Cases of PE for a variety of histologic types of uterine cancer have been reported, with outcomes similar to PE for other indications. Most recurrent uterine cancers spread beyond the pelvis, given their propensity for diffuse abdominal or heterogenous spread, making PE appropriate intervention for only a select group of patients with recurrent uterine malignancies. Women with only locoregional recurrence, however, may be candidates for PE with curative intent. Khoury-Collado et al. [16] described a series of 21 women with recurrent uterine cancers who underwent PE and demonstrated a five-year survival of 40%. The study also noted varying outcomes dependent on histology, with endometrioid adenocarcinoma (50% five-year survival rate) and sarcoma (66% five-year survival rate) demonstrating improved survival over a group of women with tumors with serous, mixed, and carcinosarcoma-histology (14% five-year survival rate). Morris et al. [17] reported a five-year survival rate of 45% following PE for recurrent endometrial cancer. Given the similarity of complication rates (48–60%) and survival to PE for cervical cancer, patients with locally recurrent uterine cancer may be considered candidates for the procedure.

2.3. Vulvar Cancer. Vulvar cancer has a propensity for regional metastases. For patients with advanced primary or recurrent vulvar cancer who do not have the option of treatment with radiation therapy, PE may be appropriate. Forner and Lampe [18] published a series of 27 patients undergoing PE. The authors demonstrated results similar to other gynecologic malignancies, with a five-year survival of 62%. Complete resection with no evidence of residual disease was associated with improved outcomes, a five-year survival rate of 74%, compared to 21% in patients without complete resection. Absence of tumor lymph node invasion was also associated with an improved five-year survival rate (83% versus 36%). In contrast, combination therapy with vulvectomy and radiotherapy has been described for locally advanced vulvar cancer with the goal to spare the pelvic organs, with five-year survival in two series of 45% and 72%, and sparing of the pelvic organs in 62.5% and 89% of patients [19, 20].

2.4. Ovarian Cancer. Given the propensity of ovarian cancer to spread throughout the abdomen, women with this disease are rarely candidates for PE with curative intent. Supralevator PE has been reported when needed for optimal cytoreduction, combined with standard staging procedures and for recurrent disease. Two series of modified posterior PE for ovarian cancer demonstrated median survival 33 and 37.4 months after initial surgery. Optimal cytoreduction was achieved in 46% and 58% of patients in the series [21, 22], demonstrating this technique may be used to achieve optimal cytoreduction in patients with disease requiring rectosigmoid resection.

2.5. Vaginal Cancer. As vaginal cancer is rare, this review could not identify any literature specifically addressing PE for this indication. Several cases of vaginal cancer, both primary and recurrent, undergoing PE have been included in larger studies, most frequently including the results for these

patients combined with results for cervical cancer [10, 23]. It may be hypothesized, that results following PE for vaginal carcinoma would be similar to those for cervical cancer provided the same other parameters for patient selection apply.

2.6. Palliative PE. PE has been described for palliation rather than for curative intent, most frequently in the setting of severe radiation necrosis. Indications have also included intractable hemorrhage due to tumor invasion and fistulae. Both morbidity and mortality were shown to be higher in this group of patients as opposed to those undergoing PE with curative intent, though improvements in quality of life are reported [24, 25]. PE is thus only considered for palliation if there is no reasonable alternative, though with the development of minimally invasive surgical technology, PE may become a more feasible option [26].

3. Patient Selection and Preoperative Screening

PE is a major surgery with significant morbidity, and as such selecting appropriate patients is essential. If the surgery is undertaken with curative intent, the tumor should be fully resectable with negative margins. Recurrence should be biopsy-proven. Classically, disease burden was required to be limited to the central pelvis, but with new surgical developments candidates for curative PE may now also include patients with positive lymph nodes, pelvic sidewall involvement, and local bone invasion.

Regardless of the indication, patients undergoing PE must be in otherwise good medical health to be able to tolerate a long surgical procedure with extensive fluid shifts and prolonged hospital stay. Major medical comorbidities may be a potential contraindication to PE. Preoperative evaluation includes a complete history, physical exam, and, if necessary, an exam under anesthesia, biopsy of any suspicious lesion such as an enlarged lymph node, evaluation of specific patient concerns suggesting metastatic spread, such as unilateral leg pain, chest radiograph or computed tomography (CT). In general, cystoscopy and sigmoidoscopy are not necessary unless the bladder or rectum is to be spared. In this case, careful evaluation of these structures is imperative to rule out occult metastatic disease.

Laboratory tests should include a complete blood count, platelet count, comprehensive metabolic panel, including hepatic and renal function, as well as clotting factors and urinalysis. Elevated liver function tests require further evaluation to rule out liver metastasis. Patients with a bleeding diathesis and any anemia should have their anemia corrected preoperatively. Any infectious process should be fully evaluated and whenever possible resolved preoperatively. Patients with underlying diabetes should have their glucose control optimized before PE. Patients should be offered testing for human immunodeficiency virus, which may be a contraindication to PE.

Patients being considered for pelvic PE need to be carefully counseled. Given the nature of the surgery, patients should be counseled about changes in body image and function. Specifically, patients should have an understanding of anatomical changes involving creation of colostomy and urinary conduit and need to be accepting of major changes in body image even in the setting of reconstructive surgery. Patients require significant family support, intact mental capacity and access to continued and long-term medical care. We recommend sharing printed literature and illustrations depicting ostomies and conduits, as well as offering patients the opportunity to speak with other women who have undergone the procedure. Patients should meet with ostomy nursing staff to begin the education process preoperatively and gain confidence with management of the ostomy and conduits. During these visit, patients can be marked for optimal placement of the ostomy and conduit. Part of the counseling sessions should focus on sexual function and how this will change for both patients choosing to have creation of a neovagina, as well as for those declining this part of the reconstruction. A formal psychiatric consultation may be appropriate for some patients.

Patients should be informed of all possible perioperative complications, including infectious, thromboembolic, gastrointestinal, urinary, psychiatric, readmission, and reoperation. Women being considered for PE should be informed of a 3–5% risk of operative mortality. Importantly, as noted by Khoury-Collardo et al. [16] some of these complications occur more frequently in the remote postoperative period (days 31–90) than in the immediate one (0–30 days). Patients should expect frequent visits to the hospital during this time given the risk not only of immediate but also delayed complications. Of note, part of the preoperative counseling should include the impact aborting the operation for unexpected surgical findings may have on the patient. That is, patients should be informed that even with the use of state-of-the art, preoperative imaging, the possibility of finding metastatic disease continues to exist, and a minority of exenterative procedures are aborted at the time of surgical exploration. It is critical that patients have sufficient medical and emotional support to manage the physical and psychological challenges central to the operation [27].

3.1. Imaging. The presence of metastasis outside the pelvis is an absolute contraindication to PE. Therefore, the goal of diagnostic techniques is to find evidence of unresectable or metastatic disease; thus, making the woman an unsuitable candidate for PE. A number of diagnostic techniques can aid in assessing unresectable disease in a patient who is believed to have central pelvic disease. Computed tomography (CT) and magnetic resonance imaging (MRI) can be helpful in assessing the presence of lateral pelvic wall invasion or liver metastasis. However, major limitations of CT and MRI lie in their inability to assess minimally enlarged nodes to detect microscopic peritoneal disease and to distinguish fibrosis from tumor in recurrent disease, and the fact that most patients have usually received extensive radiation makes distinguishing radiation fibrosis from malignant tumor extremely difficult [28].

F-fluorodeoxyglucose positron emission tomography (FDG PET) has been shown to perform better in this population. The only prospective study to date in which all patients

underwent surgical exploration with curative intent and in which almost all PET positive sites were biopsied showed that sensitivity and specificity of PET imaging in metastatic disease in patients being considered for PE was 100 and 73%, respectively. Despite a negative predictive value of 100%, positive predictive value was 55%. The high false positive rate found in this study makes surgery obligatory for all PE candidates [29]. Bone scans are usually not indicated unless there is a history of recent bone pain and concern for bony metastases.

3.2. Explorative Phase. The procedure begins with the patient in low lithotomy position to allow for abdominal and perineal portions of the surgery. Combined epidural and general anesthesia may be considered for additional postoperative pain control. PE is traditionally performed as an open abdominal procedure, but recent developments in laparoscopy and robotics have allowed for the minimally-invasive adaptation of the technique. Open technique will be described here. The abdomen is opened with a vertical midline incision to allow for maximum ability to explore the upper abdomen as well as the pelvis. The abdomen and pelvis are then thoroughly examined for evidence of metastatic disease. Washings may be sent for cytology. Any suspicious lesion is biopsied and sent for frozen section to exclude the possibility of distant metastatic disease that would preclude complete resection or alter the surgical plan. For recurrent cervical cancer, low para-aortic and pelvic lymph node dissection may be performed again to preclude metastatic spread beyond the pelvis. Lateral involvement of disease to the pelvic sidewall should be assessed at this time. Once the disease has been confirmed to be resectable, the operation may proceed [8, 30, 31].

The round ligaments are divided, and the paravesical and pararectal spaces are developed. At this time the pelvic sidewalls may again be examined. At this point, the extent of PE must be determined. Total PE includes removal of the bladder and distal ureters, portions of rectum and sigmoid colon, internal reproductive organs (if still present), and vagina. In well-selected patients, this procedure generally ensures complete negative margins from the tumor specimen. Occasionally, if the anatomic location of the recurrence is only the anterior or posterior compartment of the pelvis, the colon or bladder may be spared and only an anterior exenteration or posterior exenteration may be necessary.

3.3. En Bloc Resection. Removal of the specimen begins with the ligation and division of the fibrovascular pedicle containing the uterine vessels, cardinal ligament, and the ureter bilaterally. The uterine artery is ligated at is origin from the hypogastric, lateral to the ureter. The infundibulopelvic ligaments are ligated above the level of the common iliac vessels. The sigmoid is then mobilized and transected with a gastrointestinal anastomotic stapler (GIA), and the sigmoid vessels are identified and ligated. Care must be taken to preserve blood flow to the remaining colon—usually the sigmoid artery is left intact and the superior hemorrhoidal artery is ligated. The avascular plane between the sigmoid and the sacrum is developed to the level of the levator ani muscles. The prevesical space is extended bluntly. At this point, the specimen should be freely mobile in the pelvis.

The perineal portion of the procedure is then performed (or may be performed synchronously with an additional surgeon). An incision is marked to include the urethra, vaginal opening, anus, and possibly the vulva. The muscles of the pelvic floor are transected circumferentially. The pubococcygeal and anococcygeal ligaments are identified and divided. Upon completion of the dissection, the entire specimen is free to be removed.

3.4. Alternative Types of PE

3.4.1. Anterior PE. Anterior PE involves the removal of the bladder and internal reproductive organs but spares the gastrointestinal tract. The rectosigmoid, anus, and lower portion of the posterior vagina are left intact. After division of the cardinal ligaments, uterine vessels, and ureters, the rectum is separated from the upper vagina. The rectum is retracted posteriorly by rectovaginal bimanual exam to ensure the space is clear of tumor and resectable. The uterosacral ligaments are dissected and divided. An incision is made into the peritoneum of the cul-de-sac, and the rectum is dissected sharply off the upper vagina. The incision into the posterior vagina at its midportion is made. Biopsies of the vagina or margins may be sent for frozen section.

3.4.2. Posterior PE. Posterior PE removes the internal reproductive organs and the rectosigmoid but spares the anterior vagina, urinary bladder, and ureters. In previously irradiated pelves, it is important to consider the possibility of urinary fistulae developing following a posterior PE given the possibility for devascularization. The uterovesical peritoneum is incised after the paravesical and pararectal spaces have been developed. The ureters are identified and dissected as in a radical hysterectomy, and the uterine arteries and cardinal ligaments ligated. The anterior vagina is incised and dissected sharply. The perineal phase of the operation spares the urethra and the anterior vagina.

Modified posterior PE, as for cytoreduction in ovarian cancer, is a supralevator dissection. There is no perineal phase to the operation. If enough rectum remains (more than 6 centimeters), a low rectal anastomosis may be made, sparing the patient a stoma.

3.4.3. Supralevator PE. If the tumor does not involve the vulva or lower third of the vagina, the patient may be a candidate for a supralevator PE [10]. After the specimen is mobilized as in a total PE, an incision is made into the posterior vaginal wall below the tumor, ensuring an adequate margin. The rectum is isolated and divided with a stapling device, leaving an anorectal stump and possibility for low rectal anastomosis.

3.5. Reconstruction

3.5.1. Urinary Diversion. Brunschwig initially designed reconstruction after PE with an ureterosigmoidostomy, known

as a wet colostomy, with urine and feces emptying through one stoma [1]. This was complicated by infection and patient dissatisfaction. Subsequently, Bricker developed the isolated ileal loop conduit [2]. In current practice, both incontinent ileal and colonic conduits are used, as well as a variety of continent urinary reservoirs, most commonly the Miami pouch [30, 31]. The standard ileal conduit is formed by an isolated segment of distal ileum with its vasculature. The ureters are anastomosed directly to the ileum at one end, and the other end is brought to the skin as a stoma. A drainage bag must be worn over the stoma.

The Miami pouch was first reported by Bejany and Politano in 1988, a modification of prior continent colonic pouches designed to reduce incontinence [32]. A segment of distal ileum and ascending colon are used for the pouch. The ileum is transected 10 to 15 centimeters proximal to the ileocecal valve, and the transverse colon is transected distal to the middle colic artery. An appendectomy is performed. To form the bulk of the pouch, the colon is opened along the tenia, and the open edges are approximated by folding the colon segment into a u-shape conduit and the edges closed with a stapling device. This formation of the colon creates a reservoir and interrupts the ability of the bowel to peristalse and increase the pouch pressure. For the ureteral anastomoses, the distal ends of the ureters are flayed and then sutured with fine, absorbable suture to the colonic submucosa. Ureteral stents are placed and secured. Attention is then turned to the ileum, which is tapered distally to support the ileocolic valve and prevent reflux. The free end of the ileum is brought to the skin surface as a stoma. The patient will be required to self-catheterize this stoma, but she is spared a drainage device if the procedure is successful. Penalver et al. [33] in a follow-up study of the Miami pouch reported 92% continence and reservoir volume of average 650 mL, allowing for a reasonable catheterization interval. Another recent series reported 89% of women were continent of urine [11].

3.5.2. Fecal Diversion. For patients whose disease requires infralevator dissection posteriorly, permanent end colostomy will be required because the anal sphincter is compromised or excised. If the sphincter and enough rectum may be spared without compromising the chance at complete disease resection, low rectal anastomosis may be considered to restore continence. Direct end to end anastomosis with circular staplers is a reasonable option if enough healthy tissue remains. To improve frequency of stooling by improving the reservoir of the rectum, a colonic J-pouch may be used, particularly in patients with very little rectum remaining (less than 5 centimeters). Some authors, however, cite the frequency of recurrence of disease near the site of rectal anastomosis (45%) as a reason to perform complete resection and end colostomy in all patients [11]. Other authors strongly support low rectal anastomosis for a chance at preserved function and avoidance of undesirable colostomy for the patient [10].

3.5.3. Neovagina. After vaginectomy, construction of a neovagina for restoration of sexual function should be offered to patients undergoing PE. Several options exist for the creation of a neovagina, including split-thickness skin grafts, myocutaneous grafts, and colon. Rectus abdominus myocutaneous (RAM) flaps have been reported routinely in the literature, with 93% viability in the series from UCLA [10]. The flap also serves to fill and vascularize the pelvic dead space.

The RAM flap may be harvested from the same midline vertical incision used for the PE, improving cosmetic outcomes for the patient. Consideration must be made in the selection of the flap, such as previous Maylard incision or other compromise to the inferior epigastric artery. A transverse or vertical flap may be constructed, at least 10 to 12 centimeters in length, maintaining the blood supply from the inferior epigastric artery. The flap is freed, elevated, and sutured into a tube with the skin at the interior, which will serve as the neovagina. The tube is then secured in the pelvis at the vaginal introitus. A mold with estrogen cream is left in the vagina to maintain the lumen for 5 to 7 days. The donor site is closed with the primary abdominal incision. Results are positive, with high flap viability [31]. Patient satisfaction and coitus rates are quoted as 58–78% [34, 35].

3.5.4. Pelvic Floor Coverage. If a neovagina has been created with a myocutaneous flap, such as a RAM flap, this graft is usually sufficient to fill the pelvic dead space and ensure adequate vascularity. If no such procedure has been performed, it minimizes complications such as bowel obstruction and maximizes hemostasis to close the pelvic dead space. The most common mechanism for coverage is with the omental J-flap. The omentum is detached at the greater curvature of the stomach while preserving its origin containing the left gastroepiploic artery, which will supply the flap. The omentum is then brought into the pelvic dead space and sutured into place. Other options, such as mesh and pelvic packing, were attempted with poor outcomes [11].

4. Laparoscopic and Robotic-Assisted Surgery

Laparoscopic surgery has advanced considerably in recent years. The indications for its use have widened, and the superseding of open surgery seems inevitable in many areas of surgery. This revolution in surgery is in part associated with the technological advancement and a concomitant acquisition of advanced minimally invasive surgical skills by many gynecologic oncologists. Laparoscopy is now a well-accepted tool in the armamentarium of the treatment of gynecological cancer, and data have been published by various centers [36–39]. Minimal invasive surgery is generally associated with less intraoperative blood loss, postoperative pain, and shorter hospital stay.

Pomel et al. [40, 41] were the first group to report two cases of laparoscopic PE for gynecological cancer. The authors demonstrated in these reports the feasibility of this procedure. Both patients enjoyed the other well-known advantages of laparoscopy including minimal blood loss and quick ambulation, all contributing to a better postoperative quality of life. Subsequently, Lin et al. [42] reported a case of laparoscopy-assisted transvaginal total PE. In addition,

Ferron et al. [43] published a series of five patients that underwent a laparoscopic assisted vaginal PE. Their series reports the first application of a rational combination of laparoscopic, perineal, and hand-assisted surgery, with the goal of limiting the potentially long laparoscopic time to a strict minimum. Of note, the authors elected to perform a hand-assisted Miami pouch through a minilaparotomy (5 cm) in order to reduce the operative time, safely perform the ureteral anastomosis, restore bowel continuity and, in addition, build the omental cylinder for vaginal reconstruction. The use of a perineal or vaginal approach allowed to quickly and safely free the specimen well above the pelvic floor. In a subsequent report by the same authors, with a mean follow-up of 14 months, four patients died of the disease (three were metastatic), one patient presented a local recurrence, and two patients are disease free [44].

Puntambekar et al. [45] reported in a series of 16 consecutive patients, the technique, feasibility, and safety of laparoscopic anterior PE as primary treatment for locally advanced pelvic cancers. Thirteen patients underwent anterior PE with ureterosigmoidostomy, while two patients required total PE with wet colostomy. The authors described a low rate of morbidity in their series. Two patients suffered from subacute intestinal obstruction and were treated conservatively. One patient had a ureteric leak that resolved with conservative management. Of note, after a mean follow up of 15 months, all patients were disease free. Puntambekar et al. [46] also described the feasibility of doing a laparoscopic total PE for palliation in advanced cervical cancer. Of the 7 patients included in their series, no patients required conversion to open surgery. The mean postoperative hospital stay was 8 (7–21) days. The mean followup was 11 (4–24) months and mean symptom free period was 8 (3–24) months. There was no major and unanticipated postoperative morbidity. There was no immediate postoperative mortality. In all patients, the pathology specimen had tumor free margins. The mean followup of the patients was 11 months (range 4 to 24 months); and the mean symptom free survival period was 8 months (range 3 to 24 months). Four patients subsequently died secondary to distant metastases. Three patients are now disease-free for more than a year.

The development of robotic technology has facilitated the application of minimally invasive techniques for the treatment and evaluation of patients with gynecological cancers. Robotic surgery offers several advantages over laparoscopy: a three-dimensional vision system, wristed instrumentation, and ergonomic positioning for the surgeon while performing surgical procedures. The enhanced visualization gives the gynecologic surgeon an improved ability to identify tissue planes, blood vessels, and nerves while performing the surgical procedure [47–49].

Since the first report of robotic-assisted radical hysterectomy by Sert and Abeler in 2006 for cervical cancer, there have been some reports of robotic-assisted laparoscopic PE [50–52]. The first cases of robotic-assisted laparoscopic PE were described by Pruthi et al. [53] in 12 women for clinically localized bladder cancer. Urinary diversion was performed extracorporeally (9 ileal conduit diversion, 3 orthotopic neobladder). Lim [54] reported the first case report of robotic assisted total PE with an ileal loop urinary diversion and an end colostomy for treatment of recurrent cervical cancer. Subsequently, Lambaudie et al. reported a case series of three patients that underwent robotic assisted total PE. Of note, the urinary diversion was made extracorporeally by a transrectal laparotomy. The authors reported that concerning hospital stay, there was no benefit comparing to laparotomy, essentially due to urinary diversion management (catheterization) and to self catheterization patient's autonomy.

Despite the apparent encouraging early results suggesting an advantage of minimally invasive surgery for PE, questions remain about the surgical effectiveness of this approach. Further study of minimally invasive techniques to perform a PE is needed prior to widespread clinical application of these techniques.

5. Complications

As it is a radical surgery performed in the setting of advanced tumor growth and frequently on irradiated tissue, PE is associated with a significant rate of complications, quoted about 40–50% for major complications and about 80% for minor complications. Mortality is quoted from 1–16%, with disparate causes including sepsis, thromboembolic disease, and cardiopulmonary failure. Despite significant advances in the last fifty years, the extensive nature of the surgery, including blood loss, fluid shifts, and operative time, have led to unavoidable risks. Infection is the most frequent morbidity (19–86%), with urinary infections and wound infections most commonly reported. Anastomotic leaks and fistulae from either diverting system are also relatively frequent, cited at 8–36%. Small bowel and ureteral obstructions also occur in about 5–10% of patients. Most of these complications can be managed conservatively, but significant numbers of patients require operative revision [10, 11, 55]. Death in the perioperative period occurs in fewer than 5 percent of patients, with women over the age of 65 at highest risk [10].

6. Postoperative Period

Given the radical and prolonged nature of this procedure, patients and providers must be prepared for a long and potentially complicated hospital course. Many patients require a stay in the intensive care unit immediately postoperatively for close monitoring, particularly in the setting of potentially dramatic fluid shifts. Blood loss may be high with transfusion required in most patients [14]. Special attention to thromboembolism prophylaxis, respiratory care, and nutrition is required. While no longer routine, some patients will require total parenteral nutrition due to prolonged inability to eat postoperatively, as ileus is relatively common [56]. A team-based approach, including case managers, dedicated nurses, and social workers, may help patients as they heal both mentally and physically postoperatively.

7. Quality of Life

As a portion of preoperative counseling and postoperative support, the changes in a woman's body image following PE must be reviewed. Some patients, particularly those undergoing this surgery for palliative management of pain or fistulae, do report improved quality of life following surgery, with decreased narcotic requirements and malodorous discharge [25]. Most women, however, note a decline in specific areas of quality of life. Most commonly sexual quality of life is diminished from preoperatively. Notably, body image, physical ability, and social function have all be reported decreased in questionnaires compared to patients' preoperative answers. These changes are more pronounced in younger patients and those who do not undergoing vaginal reconstruction. Interestingly, overall function and mental and emotional quality of life are comparable [57–59].

8. Conclusions

PE is a radical operation, involving en bloc resection of pelvic organs, including reproductive structures, bladder, and rectosigmoid. In gynecologic oncology, it is most commonly indicated for the treatment of advanced primary or locally recurrent cancer. Patients need to be carefully selected and counseled about risks and long-term issues related to the surgery. A comprehensive evaluation is required in order to exclude unresectable or metastatic disease. Total PE is associated with significant surgical morbidity, a fact that underscores the importance of careful patient selection and counseling. The emergence of minimally invasive surgery and application of this technology to radical pelvic surgery including PE may result in a reduction operative morbidity and mortality. Further studies are necessary prior to a widespread adoption of this technology to exenterative procedures.

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Review Article

Intersphincteric Resection and Coloanal Anastomosis in Treatment of Distal Rectal Cancer

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In the treatment of distal rectal cancer, abdominoperineal resection is traditionally performed. However, the recognition of shorter safe distal resection line, intersphincteric resection technique has given a chance of sphincter-saving surgery for patients with distal rectal cancer during last two decades and still is being performed as an alternative choice of abdominoperineal resection. The first aim of this study is to assess the morbidity, mortality, oncological, and functional outcomes of intersphincteric resection. The second aim is to compare outcomes of patients who underwent intersphincteric resection with the outcomes of patients who underwent abdominoperineal resection.

1. Introduction

Colorectal cancer is the third most common cancer and the fourth leading cause of cancer death worldwide. It is also the second most common cancer in women and the third most common in men within European countries [1]. Although colon cancer and 2/3 proximal rectal cancer are treated more easily, treatment of distal rectal cancer involves challenges even colorectal surgeons. Abdominoperineal resection (APR) has been the usual treatment option for distal rectal cancer since Miles reported this technique in the 1920 [2]. However, APR inevitably includes permanent colostomy. Total mesorectal excision technique was described by Heald and Ryall and this is the gold standard management of middle and distal thirds of rectal cancer now. This technique both reduced the recurrence rate and increased the survival of the rectal cancer [3]. In addition, further studies suggested that distal intramural spread of rectal cancer rarely extends more than 1 cm beyond the distal margin of the tumor [4, 5]. Therefore, along with advances in preoperative chemoradiation therapy, a 1 cm distal margin has increased the incidence of successful sphincter-saving surgery [6]. Schiessel et al. first reported the intersphincteric resection (ISR) technique which has been used to increase sphincter preservation by achieving necessary distal margin for patients with distal rectal cancers [7]. Today, ISR and coloanal anastomosis are commonly preferred surgical treatment options of distal rectal cancer. The aim of this paper is to evaluate the mortality and morbidity, oncologic and functional outcomes after ISR for distal rectal cancer.

2. Materials and Methods

A literature search of Medline, Embase, Ovid, and Cochrane database was performed to identify relevant articles in the English language associated with ISR for rectal cancer for the years 1960 to 2012.

3. Surgical Technique

MRI and EUS are commonly used preoperative staging rectal cancer. In addition these two modalities, in evaluating whether a distal rectal cancer is eligible for ISR surgeons, use rigid proctoscopy and digital assessment of the level of the tumor in relation to the anal sphincter. Neoadjuvant treatment is performed T3, T4, and N positive rectal cancer for down staging and increase of possibility of sphincter-saving surgery. Common practice is performed to surgery within 6 weeks after neoadjuvant therapy [8].

The indication for ISR is any type of distal cancer extending or involving the anal ring. The internal anal sphincter involvement is also included. The tumors invading external anal sphincter or levator ani muscle and T4 cancers did not respond to neoadjuvant therapy, involving the prostate or vagina, preoperative poor sphincter functions are contraindications of ISR. The most common indication for ISR is cancer within 1 cm of the anorectal ring. ISR and coloanal anastomosis are performed as both abdominal and perineal approach. Abdominal part of the operation is performed either as open or laparoscopic technique [9–11].

The first step of abdominal part is high ligation of inferior mesenteric artery and left colonic mobilization including takedown of splenic flexure almost all patients. Second step is total mesorectal excision, with sharp dissection along an embryologic plane between the mesorectal fascia and the fascia of the pelvic sidewall and preserving hypogastric plexus nerves according to the method described by Heald [12]. The dissection is performed as distal as possible and the puborectal muscle surrounding lateral and posterior wall of the rectum is exposed at the pelvic floor to facilitating the perineal dissection. The first step of the perineal part of the operation is good exposition of the anal canal via self-retaining retractor (Lone Star Retractor; Lone Star Medical Products Inc., Houston, TX, USA). After injecting 1 mg diluted epinephrine in 20 mL of saline solution which minimized bleeding and facilitating intersphincteric dissection, the mucosa and internal sphincter are circumferentially incised at least 1 cm distance from the distal edge of the tumor. The anal orifice is then closed transanally with purse-string sutures to prevent tumor cell dissemination during the perineal approach. There are 3 types of ISR, called total, subtotal, and partial. When the tumor spread beyond the dentate line, total ISR should be done. The internal sphincter is completely removed, and the distal margin of resection is at the intersphincteric groove. If the distal edge of the tumor is more than 2 cm far from dentate line, subtotal ISR is performed instead of total ISR. The distal resection margin of subtotal ISR is between dentate line and the intersphincteric groove. If the surgeon has a enough distal surgical margin, the distal line of the resection can be on or above the dentate line. This is called parial ISR. The descriptions of 3 type of ISR are shown in Figure 1. Dissection continues through intersphincteric plane to connect with dissection from abdomen.

After the rectum is totally separated from prostate or vagina, the specimen is removed per anally. Frozen-section histopathology should confirm the lack of tumor cells in the distal margin. Colonic J pouch, transverse coloplasty, or straight coloanal hand-sewn anastomosis can be performed according to surgeons preference. However, the latter associated with high incidence of tenesmus, urgency, and incontinence [13]. Pelvic drain is placed, and defunctioning stoma is created in most of patients.

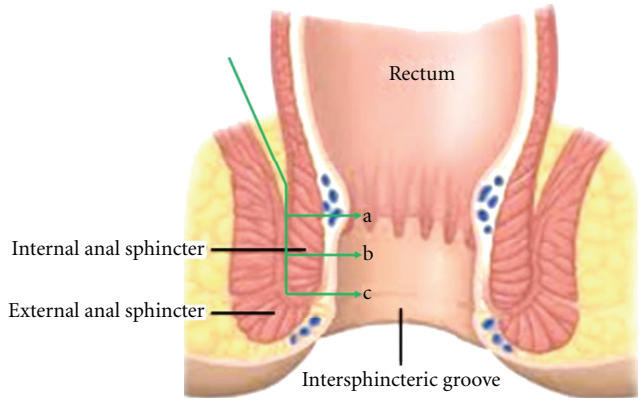

Figure 1: Type of ISR according to amount of excision of the internal anal sphincter. a: partial ISR, b: subtotal ISR, and c: total ISR.

4. Results

4.1. Morbidity and Mortality. ISR and coloanal anastomosis associate with complications and mortality like any other colorectal operations. Mortality rate of within postoperative 30 days was reported between 0 and 6 percent of patients in the different studies and is shown in Table 1. The common causes of death both surgery related factor (e.g., anastomotic leak) and consequence of comorbid medical conditions (myocardial infarction, pulmonary embolus) have been reported in the recently published meta-analysis [14].

The common complications of ISR are anastomotic leakage, stricture, fistula, pelvic sepsis, bleeding, bowel obstruction, and wound infections, which have been reported in different studies and are shown in Table 1. Anastomotic leaks are inevitable complications that have been previously reported to affect 2.6% and 24% of patients undergoing colorectal surgery [39, 40]. Likewise, the most serious complication of ISR and coloanal anastomosis is anastomotic leakage. Anastomotic leakage was defined by the presence of a pelvic abscess and was confirmed by a computed tomography scan or clinical peritonitis. Once the anastomotic leakage is diagnosed, prompt management has a vital significance. Although diverting loop ileostomy is a common surgical choice to secure an anastomosis or to divert feces from a distal affected intestinal segment, it has become clear that an anastomotic leak cannot be prevented by a proximal diversion, but septic symptoms can be reduced [41]. Anastomotic leakage has been reported 0.9–13% of ISR surgery in the different studies. The rate of pelvic sepsis is reported up to 5 percent, majority of these originate from an anastomotic leak [25]. Intraoperative blood transfusion and pulmonary disease were found to be independent risk factors for anastomotic leakage in the recent study [28].

Anastomotic leakage is managed by diverting ileostomy (if not perform initial operation) or percutaneous drainage. If the cause of anastomotic leakage is ischemic distal segment, pouch excision and reanastomosis or stoma creation with APR may be required.

Intestinal obstruction was defined by a combination of the following findings: abdominal distention, abdominal pain, vomiting, and the presence of air-fluid levels on a plain abdominal radiograph during the postoperative period.

Postoperative intestinal obstruction is presented between 0–16% according to various studies, and most of the patients manage conservatively [21, 32]. Failure of the conservative management requires further surgery in a few patients.

Wound infection is the most common minor complication of the ISR surgery. Wound infection is defined by the presence of purulent discharge, erythema, and induration of the wound. Wound infection has been reported up to 9 percent (Table 1). All of the wound infections were treated successfully by open wound care.

4.2. Oncologic Outcomes

4.2.1. Locoregional Recurrence. The local recurrence rates of different studies regarding intersphincteric resection are summarized in Table 2. The rates of isolated local recurrence reported are between 2% and 31% in these studies.

Various studies have shown that intersphincteric resection does not increase local recurrence rates [31].

Recurrence rate of the distal rectal cancer was radically reduced by total mesorectal excision technique which was first reported by Heald et al. Today the most of local recurrence is considered as being incomplete of surgical excision. However, involvement of circumferential resection margin is associated with high recurrence rate even if TME is properly performed [36]. In addition, some authors argue that involvement of lateral pelvic lymph node is responsible up to 22% of locoregional recurrence [47].

Another important point of local recurrence is tumor shedding. Cancer cells have been found on the peritumoral tissue and doughnuts after stapling anastomosis [48]. Because handling of the rectum during surgery causes increased number of cancer cells shed, no touch technique can be beneficial [49].

4.2.2. Survival. Range of the 5-year overall survival rate of intersphincteric resection was 62%–97%, and disease-free survival was 66%–87% in the different studies. (Table 2). Recently published study has reported that 5-year overall survival for patients after ISR was 80%, and disease-free survival was 69.1%. These results considered better than 5-year overall survival of APR but not 5-year disease-free survival [31].

Kuo et al. analyzed the comparison between low anterior resection and stapled colorectal anastomosis, radical proctectomy with ISR and APR. The authors found significantly differences in overall survival among three groups and APR had statistically shorter survival than others [46]. All these results suggest that intersphincteric resection is a safe procedure in terms of oncologic outcomes.

4.3. Functional Outcomes. Preservation of the sympathetic and parasympathetic nerves is one of the most important part of the TME in the rectal cancer surgery. There are four zone nerve damages that can occur. First, the root of the inferior mesenteric artery (damage of sympathetic hypogastric nerve); second, posterior rectal plane (damage of sympathetic hypogastric nerve); third, lateral rectal plane (sympathetic and parasympathetic nerves); fourth, anterior rectal dissection (cavernous nerve). Damage of these nerves causes urinary dysfunction or impotence in most of patients [50].

Functional results of different studies are shown in Table 3. Jorge and Wexner incontinence score, the Kirwan classification system, and other institutional questionnaires are usually used to evaluate patients' functional results. Postoperative functional outcomes seem to be acceptable. Incontinence was a record of the number of bowel movements in 24 hours almost in all studies. The bowel movement rates from 2.2 to 3.7 per 24 hours and fecal soiling rate from 11% to 59% are reported. Rullier et al. show that if more than half of the internal sphincter is resected, incontinence is worse but remains normal in 50% patients [8]. Denost et al. investigated risk factors fecal incontinence after ISR in 101 rectal cancer patients and they found that the only independent predictors of incontinence were distance of the tumor lower than 1 cm from the anal ring ($P = 0.004$) and anastomoses lower than 2 cm above the anal verge ($P = 0.037$) [51]. It should be considered that functional outcomes may be improved by use of J pouch or coloplasty [52]. Before surgery, the patient must be informed about possible functional outcomes of intersphincteric resection.

4.4. ISR versus APR. Although there are numerous studies comparing sphincter-saving surgery and APR [44, 53], few studies were found regarding comparison of ISR and APR due to heterogeneity of the sphincter-saving surgery groups. These studies are summarized in Table 4.

The study of Weiser et al. concluded that patients undergoing APR were elder ($P = 0.0006$) and have more poorly differentiated tumors ($P = 0.03$). Although there was no statistical significant difference in the pretreatment endorectal ultrasound stage, APR was associated with poorer outcome in this study. Saito et al. reported that though a significant difference in overall survival was observed, there was no significant difference in disease-free survival between ISR and APR groups. The authors concluded that ISR appears to be oncologically acceptable and can reduce the number of APRs [31].

5. Discussion

Multimodality treatment has brought advances in treatment of locally advanced rectal cancer during the last two decades. The Swedish Rectal Cancer Trial, assessing preoperative short course radiotherapy, found a benefit in overall survival compared to surgery alone [54]. In addition to this benefit, preoperative radiotherapy provides downsizing and downstaging which increase possibility of sphincter-saving surgery in patients with distal rectal cancer. Preoperative radiotherapy or chemoradiotherapy should be recommended for T3-4 or N1 rectal cancers [8].

Distal rectal cancer is considered surgical challenge even by colorectal surgeons. The ISR technique is a valuable sphincter-saving surgical treatment in patients with distal rectal cancer. Patients selection for ISR is based upon careful

Table 1: Complications and mortality after ISR.

Reference	Anastomotic leak (%)	Anastomotic stricture (%)	Fistula (%)	Pelvic sepsis (%)	Wound complications (%)	Bleeding (%)	Bowel obstruction (%)	Rectal mucosal prolapse (%)	Mortality (%)
Braun et al. [15] (1992)	10	3	0	0	8	0	3	NR	6
Bannon et al. [16] (1995)	0.9	0.9	0.9	0.9	1.8	0.9	0.9	1.8	1.0
Köhler et al. [17] (2000)	48	10	19	0	6	3	10	NR	0
Kim et al. [18] (2001)	6.2	6.2	4.2	NR	NR	NR	8.3	NR	NR
Tiret et al. [19] (2003)	11	NR	NR	3.8	NR	3.8	NR	NR	0
Luna-pérez et al. [20] (2003)	9.4	6.25	6.25	9.3	6.25	NR	6.25	NR	NR
Rullier et al. [21] (2005)	11	0	2	3	0	7	0	NR	0
Schiessel et al. [22] (2005)	NR	NR	5.1	NR	NR	0.8	NR	NR	0.8
Hohenberger et al. [23] (2006)	NR	NR	NR	NR	NR	NR	NR	NR	3
Saito et al. [24] (2006)	10.1	0	1.3	4.4	0	1.3	0	1.3	0.4
Chamlou et al. [25] (2007)	9	0	1	5	1	2	0	NR	0
Dai et al. [26] (2008)	NR	8.7	8.7	NR	NR	NR	NR	NR	0
Akasu et al. [27] (2008)	13.0	NR	NR	NR	NR	NR	NR	NR	0.8
Akasu et al. [28] (2010)	13	0.8	NR	NR	6.6	NR	5	0.8	0.8
Han et al. [29] (2009)	3	0	0	0	5	0	0	NR	0
Krand et al. [30] (2009)	4	2	0	2	9	0	2	NR	0
Saito et al. [31] (2009)	NR	NR	NR	NR	NR	NR	NR	NR	0
Weiser et al. [32] (2009)	5	16	5	0	7	0	16	NR	0
Yamada et al. [33] (2009)	4.7	8.4	0	0	3.7	0	8.4	3.7	0
Han et al. [34] (2010)	1.6	2.5	0.6	NR	NR	NR	NR	NR	NR
Park et al. [35] (2011)	6.2	1.3	NR	NR	NR	NR	2.5	NR	1.3
Lim et al. [36] (2011)	1.8	6.3	0.9	2.7	NR	NR	4.5	1.8	0
Bennis et al. [37] (2012)	7	NR	NR	NR	NR	1.6	2.69	NR	0.4
Reshef et al. [38] (2012)	NR	NR	NR	2.9	4.5	NR	NR	NR	0.7

Table 2: Oncologic results of ISR.

Reference	Year	*N*	Median followup	Local recurrence	5-year survival (overall)	5-year survival (disease free)
Braun et al. [15]	1992	63	80	11	62	NR
Marks et al. [42]	1993	52	50	14	85	NR
Bannon et al. [16]	1995	109	40	11.0	87	NR
Mohiuddin et al. [43]	1998	48	48	15	82	NR
Köhler et al. [17]	2000	31	82	10	79	NR
Kim et al. [18]	2001	48	26	4.1	NR	NR
Tiret et al. [19]	2003	26	39	3.4	NR	NR
Nakagoe et al. [44]	2004	184	47.4	9.5	NR	73.6
Rullier et al. [21]	2005	92	40	2	81	70
Yoo et al. [45]	2005	29	57	31	86.2	65.7
Schiessel et al. [22]	2005	121	94	5.3	88	NR
Hohenberger et al. [23]	2006	65	70	23	NR	NR
Saito et al. [24]	2006	228	41	3.6	92	83
Chamlou et al. [25]	2007	90	56	7	82	75
Dai et al. [26]	2008	23	31.5	8.7	NR	NR
Akasu et al. [27]	2008	120	42	6.7	91	77
Krand et al. [30]	2009	47	68	2	85	82
Han et al. [29]	2009	40	43	5	97	86
Yamada et al. [33]	2009	107	41	2.5	92	87
Weiser et al. [32]	2009	44	47	0	96	83
Saito et al. [31]	2009	132	40	10.6	80	69
Han et al. [34]	2010	310	84	11.6	66	NR
Lim et al. [36]	2011	111	29.4	5.4	NR	NR
Kuo et al. [46]	2011	162	55	7.7	83	76
Reshef et al. [38]	2012	986	60	3	71	69

preoperative staging. The level of the transection of the internal sphincter should be decided before surgery. Detection of preoperative external sphincter invasion or fecal incontinence is all contraindication of ISR. In addition, some authors argue that ISR is contraindicated to poorly differentiated or mucinous cancer [7, 55].

Recently published systematic review reported that the overall mortality associated with ISR is 0.8%. The overall morbidity rate reported is 25.8%. Anastomotic leak was experienced after a mean of 9.1% and the pelvic sepsis rate was of 2.4% [14].

Postoperative overall morbidity rate varies between series from 8% to 64%. Anastomotic leak rates are reported of 0.9–48%. (Table 1) this difference arises from some studies that include the asymptomatic leakage which is radiologically detected. Akasu et al. reviewed 120 patients who underwent ISR and reported risk factors for anastomotic leakage following ISR. This study suggests that intraoperative blood transfusion, pulmonary disease, and colonic J-pouch are independent risk factors for leakage following ISR [28].

One of the main targets of surgical treatment of rectal cancer is as possible as long disease-free survival. Therefore, the most important question to answer is ISR technique carries an increased risk local recurrence or decline survival. In the various studies, range of the 5-year overall survival rate of intersphincteric resection was reported from 79% to 97%, and disease-free survival was reported from 69% to 87%. (Table 2).

Tilney and Tekkis reported review, including 21 studies accumulating a total of 612 patients who underwent ISR for distal rectal cancer. The mean 5-year survival following ISR was reported in 81.5%. Locoregional recurrence rate was available from all of the studies evaluated for oncologic outcomes, with 51 of 538 patients (9.5%) experienced local recurrence [56].

Akasu et al. investigated risk factors for local and distant recurrence in 122 patients. Local recurrence rate found 6.7% and distant recurrence rate was found 13%. Positive resection margins, dedifferentiation of tumor, and elevated preoperative levels of CA19-9 (>37 U/mL) were reported risk factors of local recurrence. Pathological N1, N2 tumor, poor differentiation, and the tumor close to anal canal less than 2.5 cm were reported risk factor for distant recurrence [27].

The current systematic review and meta-analysis which included 14 studies reported that the mean distal margin free from tumor was 17.1 mm, CRM-negative margins were achieved in 96% of patients, RO and the overall local recurrence rate were 6.7% (range: 0–23%). The 5-year overall and disease-free survival rate was 86.3% and 78.6%, respectively [14]. The authors conclude that available datas with potential for selection bias, oncological outcomes after ISR are affected negatively.

There are limited studies in the literature about functional outcomes after ISR (Table 3). Jorge and Wexner incontinence score and the Kirwan classification system were generally used for evaluating patient' functional outcome

Table 3: Functional results of ISR.

Reference	Year	*n*	Anal manometry	Functional tool	Bowel movements per 24 hours	Complete incontinence (%)	Incontinence to flatus (%)	Faecal soiling (%)	Urgency (%)
Braun et al. [15]	1992	63	No	Mayo clinic classification	2.2 (1–3)	75	17	15	22
Köhler et al. [17]	2000	31	Yes	General questionnaire	3.3 (NR)	30	11	63	NR
Kim et al. [18]	2001	48	No	Kirwan classification	4.4 (3–6)	NR	NR	NR	NR
Tiret et al. [19]	2003	25	No	NR	2.5 (NR)	50	23	27	19
Schiessel et al. [22]	2005	121	Yes	Williams and johnston classification	2.2 (1–9)	86.3	NR	13.7	NR
Yoo et al. [45]	2005	17	No	Cleveland clinic incontinence score	5.0 (2–9)	NR	17.6	41.2	58.8
Saito et al. [24]	2006	228	No	Jorge and wexner incontinence score and kirwan score	NR	32.7	29.1	29.1	NR
Chamlou et al. [25]	2007	90	No	Jorge and wexner incontinence score	2.3 (NR)	41	25	59	19
Yamada et al. [33]	2009	107	No	Jorge and wexner incontinence score and Kirwan score	3.7 (2–6)	42.3	NR	27.9	NR
Han et al. [29]	2009	40	No	Kirwan classification	2.7 (NR)	43	29	29	31
Krand et al. [30]	2009	47	No	Kirwan classification	2.3 (2–5)	80	9	11	2
Kuo et al. [46]	2011	22	No	Wexner incontinence score	4.7 (NR)	NR	NR	NR	19

after ISR. Although neoadjuvant chemoradiotherapy has a beneficial effect downsizing and downstaging in patients undergoing ISR, it probably has a negative effect on functional results. Canda et al. showed that neoadjuvant chemoradiotherapy was associated with significantly lower maximal squeeze pressures and worsening of Wexner scores who had received neoadjuvant chemoradiotherapy [57]. This data support that counseling patients about expected functional outcomes is important.

Current metaanalysis of 8 studies demonstrated that the mean number of bowel motions in a 24 h period was 2.7, 51.2% patients experienced "perfect incontinence", 29.1% patients experienced fecal soiling. Incontinence to flatus is reported by 23.8% in this study [14]. However, Bretagnol et al. reported that the Wexner score and the Fecal Incontinence Severity Index (FISI) were significantly improved following colonic j-pouch reconstruction compared with straight coloanal anastomosis [58].

Quality of life after ISR has been rarely reported. Bretagnol et al. demonstrated that fecal incontinence-related QoL scores were poorer than LAR after ISR. However, SF 36 scores were similar [58]. Barisic et al. showed that fecal incontinence improved by the time and 11.1% patients had fecal incontinence after 1-year ISR. Moreover, most of patients had acceptable QoL scores according to all functional and symptom components of the European Organization for Research and Treatment of Cancer QoL-C30 questionnaire [59].

Kuo et al. reported functional outcomes of ISR in 162 patients; 38% had stool fragmentation, 23.8% had nocturnal defecation they reported and one-third needed antidiarrheal medications. However, 90.8% of patients was satisfied with functional results of ISR [46].

A few studies were found in the literature regarding comparison of ISR and APR (Table 4). Almost all studies reported low local recurrence rate and better survival for ISR

Table 4: Comparison ISR versus APR in terms of morbidity and oncologic outcomes.

References	No of patients			Overall morbidity			Local recurrence			Overall survival			Disease free survival			Median followup (months)
	ISR %	APR %	*P*	ISR %	APR %	*P*	ISR %	APR %	*P*	ISR %	APR %	*P*	ISR %	APR %	*P*	
Braun et al. [15] 1992	65	77	NR	30	NR	NR	11	17	NR	62	53	NR	NR	NR	NR	79
Kasper et al. [54] (1998)	85	81	NR	NR	NR	NR	8.7	17	NR	71	55	NR	NR	NR	NR	60
Saito et al. [31] 2009	132	70	0.18	30.3	28.6	0.30	10.6	15.7	0.29	80	61	0.03	69%	63%	0.714	48
Weiser et al. [32] 2009	44	63	NR	38.6	34.9	NR	0	9	NR	96	59	NR	83%	47%	NR	47
Kuo et al. [46] 2011	26	23	NR	NR	NR	NR	0	3.8	NR	83	46	0.006	76%	42%	0.029	55

technique. All of these studies have retrospective characters, and there could be bias about selection of the patients. However, only one study reported significant difference between ISR and APR by stage of rectal cancer [46]. Among these studies, 5-year survival was compared between ISR and APR by only one study regarding the stage of tumor. This study reported that according the Dukes' classification, 5-year survival rates for stages A, B, and C are 84%, 58%, and 27%, respectively, for ISR patients and 83.5%, 53%, and 37%, respectively, for APR patients [15]. Saito et al. published the well-designed-study in this area. Although there were no difference in patients' age ($P = 0.662$), gender ($P = 0.187$), and preoperative T ($P = 0.798$) and N ($P = 0.521$) stage, significant difference in overall survival was observed ($P = 0.033$) but no significant difference in disease-free survival between two groups ($P = 0.714$). There is one weak point in this study that the most of the APR was performed between 1995 and 2002. Only 11 patients underwent APR between 2000 and 2006. The authors conclude that acceptable oncologic outcomes were gained with ISR, and the use of ISR can reduce the number of APRs in patients with distal rectal cancer [31].

6. Conclusion

The ISR technique provides an opportunity to perform sphincter-saving surgery in treatment of distal rectal cancer. The favorable tumor is early stage, well differentiated or has a good regression after neoadjuvant therapy. This technique performs with acceptable functional outcomes. Moreover, if the adequate distal margin is provided, the local recurrence and survival rates after ISR may even be better than those of APR. The ISR technique should be considered as a safe procedure and a valuable alternative to APR in selected patients with distal rectal carcinomas.

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