Advances in Urology

Advanced Prostate Cancer: Local and Systemic Options

Guest Editors: Maximilian Burger, Christian Stief, Oliver Kölbl, and Christopher P. Evans

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Editorial Board

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Research Article

Predictive Value of Positive Surgical Margins after Radical Prostatectomy for Lymph Node Metastasis in Locally Advanced Prostate Carcinoma

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Introduction. Suspected locally advanced prostate carcinoma shows lymph node involvement in a high percentage of cases. For a long time, such patients were not radically prostatectomised. In recent years, however, this viewpoint has changed. *Material and Methods*. We analysed a single-centre series of 34 patients with suspected locally advanced prostate cancer to establish predictive parameters for lymph node metastasis. All patients underwent radical prostatectomy between 2007 and 2010. *Results*. Of the 34 patients, 26% showed pathological stage T3a, 59% pT3b, and 15% pT4. Median preoperative PSA level was 25 ng/mL, and five patients had had neoadjuvant antihormonal treatment. Positive margins were found in 76% of patients. Patients without neoadjuvant treatment showed it in 79%, and after preoperative antihormonal treatment the rate was 60%. Positive margins were associated with lymph node involvement in 85% of cases, complete resection was associated only in 50% of cases. *Conclusions*. Positive surgical margins play an important predictive role when estimating lymph node involvement in patients with locally advanced prostate carcinoma. Neoadjuvant antihormonal therapy is associated with a relevant reduction in the rate of positive margins but not with the rate of lymph node metastasis. As such, a combination of antihormonal and surgical treatment should be considered.

1. Introduction

According to the European Association of Urology (EAU) guidelines on prostate carcinoma, radical prostatectomy (RP) is the standard treatment for stage T2N0M0 prostate cancer, equivalent to radiation therapy. For locally advanced prostate cancer, recommendations are less concise. In selected patients RP in combination with extended pelvic lymphadenectomy may be feasible. A study by Gontero et al. showed no relevant differences in the rate of comorbidities, only transfusion and lymphocele rate appeared more often compared to T2N0M0 prostate carcinoma. Cancer-specific survival (CSS) was 90% for T3-4, N0, M0 prostate cancer, and 99% for organ-confined cancer [1].

In lymph node positive prostate cancer after RP and adjuvant hormonal treatment 10-year CSS reaches 80% [2]. However, known lymph node metastasis remains a contraindication for most urologists for radical prostatectomy, and antihormonal treatment is initiated. Since then, the standing of radical prostatectomy as a treatment in this indication has been promoted by the findings of Engel et al., even in cases of suspected or proven lymph node metastasis. They were able to show that the survival of patients with lymph node metastasis was improved by radical prostatectomy when compared to patients who broke off surgery [3]. Adjuvant radiotherapy combined with hormonal treatment in lymph node involvement is advantageous when compared with hormonal treatment alone [4]. Preoperative prediction of lymph node involvement is challenging, especially in current-era prostate cancer with high percentage of low-risk prostate carcinoma that do not fit with the Roach formula, which overpredicts lymph node metastasis [5, 6].

We analysed a single-centre collective of patients suspected for ≥cT3 prostate carcinoma after radical prostatectomy and pelvic lymphadenectomy in order to establish the predictability of lymph node involvement by virtue of histopathological parameters.

2. Material and Methods

We retrospectively collected clinical and histopathological data of 34 patients who underwent RP for suspected ≥cT3 prostate cancer. Open surgery took place between 2007 and 2010 in a German single centre.

Suspect digital rectal examination (DRE), elevated PSA level, lower urinary tract symptoms (LUTS) or hydronephrosis led to the suspicion of prostate cancer, respectively. Diagnosis was assessed by ultrasound-guided prostate biopsy. Locally advanced stage was indicated by suspect digital rectal examination and confirmed by computed tomography (CT). There was no evidence of lymph node involvement or organ metastasis in CT assessment. Before surgical therapy all patients underwent bone scans without detection of skeletal metastasis. To reduce local tumour mass, five patients were neoadjuvantly treated antihormonally.

We assessed pT and pN stage, the share of positive margins (R1) and compared bioptic and specimen Gleason scores as well as the predictive value of these parameters with regard to the existence of lymph node metastasis.

3. Results and Discussion

3.1. Clinical and Histopathological Patient Data. 34 patients with a median age of 65 years (range 55–75 years) and with suspected locally advanced prostate carcinoma had a median PSA level of 23 ng/mL (range 5–141 ng/mL) at the time of diagnosis. The day prior to surgery median PSA level was 25 ng/mL, but some patients only had one PSA testing run before surgery. Four out of five patients who underwent neoadjuvant antihormonal therapy had no further preoperative PSA testing; one patient's PSA level decreased from 98 to 2 ng/mL.

The median Gleason score from the prostate biopsy was 8 (range 6–10) and from the prostatectomy specimen 9 [7–9]. Only in 44% Gleason score of prostate biopsy and specimen was identical; underestimation in prostate biopsy score of one to three points was detected in 41% of patients and overestimation of one score point in 15%. Patients showed pathological stage pT3a in 26%, pT3b in 59% and pT4 in 15%. For details see Table 1. Residual tumour defined by cancer positive margin of the prostatectomy specimen was found in 76%. Neoadjuvant treatment seemed to have a protective effect, with positive margins in 60% of these patients whilst patients without preoperative antihormonal therapy showed residual tumour in 79% of cases. Whilst 85% of patients with positive margins had lymph node metastasis, only 50% of the patients without residual prostate tumour mass showed lymph node involvement (Table 2). Median number of dissected lymph nodes was 15 (range 6–32), in the case of lymph node metastasis, and the median number of metastasis was 2 (range 1–10).

3.2. Discussion of Predictive Factors for the Existence of Lymph Node Metastasis. In a multicentre series of 712 patients, Spahn et al. showed that PSA levels >20 ng/mL were associated with organ-confined tumour in 33%, with Gleason score ≤6 in prostate biopsy in 8%, with negative surgical margins in 54%, and with no lymph node involvement in 85% of cases, respectively [7]. Patients with PSA levels >20 ng/mL and suspected locally advanced prostate cancer had positive margins in 79% and lymph node invasion in 51% of cases. Our results confirmed these findings by showing residual tumour and lymph node metastasis in 76% of cases. Using the same series, Gontero et al. found that the PSA level was of prognostic relevance with 26% cured by surgery alone when PSA was 20–50 ng/mL but only about 7–9% with PSA >50 ng/mL [8]. A single-centre analysis of more than 2 600 patients with locally advanced prostate cancer after RP and adjuvant androgen deprivation revealed the Gleason score to be the most important prognostic factor [9]. In our much smaller series we did not attempt to show cancer-specific survival, but for the prediction of T stage and

Table 1: Characteristics of patients with locally advanced prostate carcinoma.

No.	Age	PSA	GS biopsy	GS specimen	pT stage	pN stage
1	60	77,3	6	7	pT3b	pN1
2	66	36,0	6	7	pT3a	pN1
3	68	30,2	6	7	pT3a	pN1
4	62	58,0	6	8	pT3b	pN0
5	64	35,6	6	9	pT3a	pN0
6	59	60,0	6	9	pT3b	pN1
7	60	31,5	7	7	pT3b	pN1
8	65	52,0	7	7	pT3b	pN1
9	70	56,0	7	7	pT3b	pN1
10	74	17,8	7	8	pT3b	pN0
11	63	21,4	7	8	pT3b	pN1
12	75	14,2	7	9	pT3b	pN1
13	55	5,8	7	9	pT4	pN0
14	61	100,0	7	9	pT3a	pN0
15	63	14,1	7	9	pT4	pN1
16	62	47,0	8	7	pT3b	pN1
17	74	23,3	8	7	pT3a	pN1
18	63	73,0	8	8	pT3b	pN1
19	68	11,5	8	8	pT3a	pN0
20	71	15,2	8	8	pT3a	pN0
21	70	9,5	8	8	pT3b	pN1
22	71	141,0	8	9	pT3b	pN1
23	65	138,0	8	9	pT4	pN1
24	64	34,7	9	8	pT4	pN1
25	70	7,2	9	9	pT3a	pN1
26	69	14,6	9	9	pT3b	pN1
27	60	13,0	9	9	pT3b	pN1
28	70	100,0	9	9	pT3b	pN1
29	58	25,0	9	9	pT3a	pN0
30	67	100,0	9	9	pT3b	pN1
31	61	22,0	9	9	pT3b	pN1
32	68	2,2	9	9	pT3b	pN1
33	56	15,1	10	9	pT3b	pN1
34	70	15,0	10	9	pT4	pN1

GS: Gleason score.

Table 2: Association of positive margins with lymph node metastasis.

No.	Age	Neoadj. HT	R stage	pN stage
1	60	No	R1	pN1
2	66	No	R1	pN1
3	68	No	R1	pN1
4	62	No	R1	pN0
5	64	No	R0	pN0
6	59	No	R1	pN1
7	60	Yes	R0	pN1
8	65	No	R1	pN1
9	70	No	R1	pN1
10	74	No	R0	pN0
11	63	No	R1	pN1
12	75	No	R1	pN1
13	55	No	R1	pN0
14	61	Yes	R1	pN0
15	63	No	R1	pN1
16	62	Yes	R0	pN1
17	74	No	R0	pN1
18	63	No	R1	pN1
19	68	No	R0	pN0
20	71	No	R0	pN0
21	70	No	R1	pN1
22	71	No	R1	pN1
23	65	No	R1	pN1
24	64	No	R1	pN1
25	70	No	R0	pN1
26	69	No	R1	pN1
27	60	No	R1	pN1
28	70	Yes	R1	pN1
29	58	No	R1	pN0
30	67	No	R1	pN1
31	61	No	R1	pN1
32	68	Yes	R1	pN1
33	56	No	R1	pN1
34	70	No	R1	pN1

HT: antihormonal treatment.

lymph node involvement, the Gleason score was not the most obvious parameter. Evidence of residual tumour presence on the surgical margins in our patient collective was the most important predictive parameter for lymph node metastasis. 76% positive margins corresponded with 76% stage pN1. Patients with positive margins had synchronous lymph node metastasis in 85%, and negative margins were only associated in 50% with lymph node metastasization. Another study on a collective of high-risk prostate cancer (stage ≥pT3 in 89%) showed positive margins in 83% but only in 28% pN1 disease [10]. Oh et al. showed that positive margins in stage pT2 prostate cancer lead to a worse outcome, similar to that of patients with locally advanced prostate carcinoma [11].

4. Conclusions

Alongside the Gleason score and pathological T stage, the presence of positive surgical margins is an important predictive factor in estimating lymph node involvement. Neoadjuvant antihormonal therapy does lead to a relevant reduction in the rate of positive margins, but not to a reduction in the rate of lymph node metastasis. As such, antihormonal and surgical treatment should be considered in combination for the therapy of locally advanced prostate cancer.

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Clinical Study

A Case of Definitive Therapy for Localised Prostate Cancer: Report of a Urological Nightmare

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Radical prostatectomy, external beam radiotherapy and permanent brachytherapy are the most common treatment options for nonmetastatic localised adenocarcinoma of the prostate (PCa). Accurate pretherapeutic clinical staging is difficult, the number of positive cores after biopsy does not imperatively represent the extension of the cancer. Furthermore postoperative upgrading in Gleason score is frequently observed. Even in a localised setting a certain amount of patients with organ-confined PCa will develop biochemical progression. In case of a rise in PSA level after radiation the majority of patients will receive androgen deprivation therapy what must be considered as palliative. If local or systemic progressive disease is associated with evolving neuroendocrine differentiation hormonal manipulation is increasingly ineffective; radiotherapy and systemic chemotherapy with a platinum agent and etoposide are recommended. In case of local progression complications such as pelvic pain, gross haematuria, infravesical obstruction and rectal invasion with obstruction and consecutive ileus can possibly occur. In this situation palliative radical surgery is a therapy option especially in the absence of distant metastases. A case with local and later systemic progression after permanent brachytherapy is presented here.

1. Case Report

A 65-year-old patient was referred to our urological clinic for a prostate biopsy indicated for a PSA elevation of 4,5 ng/mL. The patient presented without any previous morbidities in his medical or urological history and was entirely asymptomatic. Digital rectal examination (DRE) and transrectal ultrasound (TRUS) of the prostate were normal, the size of the gland was 36 mL. An octant biopsy was conducted in January 2002 by which adenocarcinoma of the prostate (PCa) was diagnosed in 1 out of 8 cores. The lesion was circumscribed with a length below 2 mm and a Gleason grade of 2, WHO grade was 1, all the other seven biopsies were classified as benign prostatic hyperplasia and chronic inflammation. Following discussion of all therapeutical options, the patient decided to undergo permanent brachytherapy with J^{125}. 62 seeds with 0,467 mCi/seed were implanted, total activity was 28,95 mCi, and postoperative course was without any complications.

During the early postoperative phase, the patient was free of complaints, there was neither a sign of incontinence nor any stool disorder, even the erectile function was assessed by an IIEF-score of 21. PSA was constantly decreasing to reach its nadir of 0,75 ng/mL 15 months after seed implantation.

21 months after brachytherapy, the first increase of PSA up to 2,6 was observed. Presuming the possibility of a so-called "PSA bouncing" with an episode of prostatitis a cycle of antibiotic therapy with ciprofloxacin over three weeks was administered, after which PSA fell again to a level of 2,11. At the subsequent follow-up examination half a year later, the patient presented with obvious local and systemic progression: PSA rose up to 8,1 ng/mL with a doubling time of three months, and digital rectal examination showed a dense left lobe with a firm node on the contralateral side. At this time, the patient refused restaging and rejected the recommended LHRH agonist therapy. After prophylactic radiation to the breasts with a dose of 1500 cGy antiandrogen monotherapy with bicalutamide 150 mg per day was initiated. Receiving

this medication a drop of PSA to 2,4 ng/mL was achieved, the patient was furthermore feeling asymptomatic.

Due to a PSA progress up to 10,6 ng/mL after 15 months of antiandrogen treatment, reevaluation was conducted. While choline PET-CT showed an increased fluorocholine (FCH) metabolism in the right lobe of the prostate with no signs of lymph node or bone metastases, a rebiopsy of the gland yielded a dramatic upstaging and upgrading of the local disease: of 15 cores taken 13 were infiltrated by prostate cancer with Gleason Score 8 (4 + 4), WHO grade was 3. Antiandrogen therapy was stopped; the LHRH agonist leuprorelin acetate was administered. Due to the history of brachytherapy, any form of further external beam radiation was not feasible.

Only two months later, the patient had to be hospitalised again because of gross haematuria and clot retention. A CT scan showed local progression with a large solid tumour dorsal of the right side of the prostate and bladder with a diameter of 6 cm as well as pathologically enlarged lymph nodes in the pelvis up to 2 cm. Due to continuous bleeding under bladder irrigation palliative transurethral resection of the prostate had to be performed, 15 g of fragile tumour tissue were removed. The pathological report confirmed the diagnosis of an adenocarcinoma with a Gleason score of 8, but additionally larger areas with neuroendocrine differentiation were found.

After a period of the next three weeks, transurethral reintervention for severe haematuria had to be undertaken, and due to persistent bleeding transfusions of several red cell concentrates were necessary. Obstruction of the upper urinary tract led to bilateral nephrostomies. After discharge, several recurrent episodes of bleeding and clot retention occurred. The general health status deteriorated preventing the initiation of systemic chemotherapy.

Only two months following the previous CT scan, MRI showed a large solid local tumour with a diameter of now 9 cm infiltrating the trigone and the bladder floor on each side (Figure 1). Beneath lymph nodes, up to 3 cm disseminated bone metastases were diagnosed. Four years after the "first definitive" therapy, the patient received a palliative ileal conduit to control local symptoms. With regards to the limited life expectancy, the prostate and bladder remained in situ; recurrent bleeding was controlled by percutaneous transluminal angiography and coil embolization; additionally, instillations with formalin were performed twice. The patient's health status was declining rapidly and three weeks after the last surgery, he died due to dilatation of the right ventricle and pulmonary oedema. Beyond that, autopsy showed extensive pulmonary metastases.

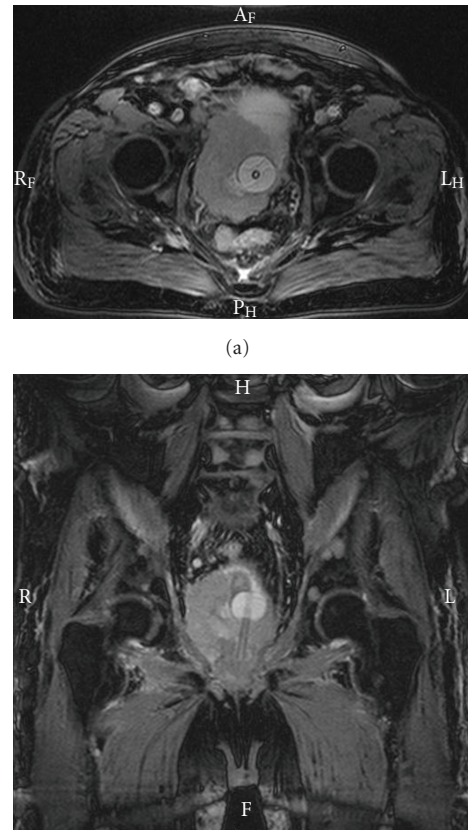

Figure 1: MRI demonstrating a local solid tumour with a diameter of 9 cm infiltrating the trigone and the bladder floor on each side.

2. Discussion

Accurate staging of prostate cancer on the basis of clinical features such as PSA, DRE, and histology of biopsy is difficult. The number of positive cores does not imperatively represent the extension of the cancer, furthermore, in about 50% an upgrading in Gleason score has to be observed after performing radical prostatectomy. Besides, radical prostatectomy and external beam radiotherapy, permanent brachytherapy is one treatment option of nonmetastatic-localised PCa [1]. Even in a localised setting, 10–20% of patients with organ-confined PCa will develop biochemical progression within 5–10 years; if the cancer is locally advanced at the time of treatment, the progression rate increases to up to 30–50% [2–4]. 70% of the patients with PSA relapse after brachytherapy, present with local persistence as the only site of recurrence, depending on the initial tumour stage [2, 5]. In case of a rise in PSA level after radiation therapy the majority of patients will receive androgen deprivation therapy. Since this must be considered as palliative, a reverse strategy is salvage radical prostatectomy (SRP). Heidenreich et al. reported a retrospective series of 55 men with biopsy-proven, locally recurrent PCa after primary radiotherapy. Predictors of organ-confined PCa with negative surgical margins were biopsy Gleason score prior to salvage radical prostatectomy, <50% positive biopsy cores, PSA doubling-time >12 months, and low-dose brachytherapy. SRP was judged as a surgically challenging but effective secondary local treatment with curative intent [2]. Furthermore, studies about cryotherapy, brachytherapy and high-intensity focused ultrasound (HIFU) with partly encouraging results but smaller numbers of patients were published [6].

If SRP was not performed after PSA relapse castration resistant PCa with local progression and associated complications such as pelvic pain, gross haematuria, infravesical obstruction, and rectal invasion with obstruction and consecutive ileus can possibly occur in the further course; each of those sequels impairs the patient's well-being significantly. Voiding problems may require lifelong indwelling catheters, obstruction of the ureters often results in long-term placement of nephrostomy tubes or ureteral stents, and despite those measurements renal failure may occur. In this situation, palliative radical surgery is a therapy option especially in the absence of distant metastases.

Leibovici et al. were looking at the effect of cystoprostatectomy for palliation of symptomatic bladder invasion by prostate cancer. 21 patients had previous local therapy, 17 were primary T4 tumours. During surgery, rectal injuries occurred in 13%, there were no perioperative deaths. In 79% (30/38 patients), local symptoms were relieved permanently after the operation. 3 patients (8%) suffered from persistent pelvic pain, another 3 patients from urinary incontinence, and 1 from on going haematuria. The average interval between surgery and clinical systemic disease was 26 months, median disease specific survival was 31 months [7]. Pfister et al. published a series of 20 patients with locally advanced prostate cancer. 70% had an indwelling catheter due to infravesical obstruction, 10% had nephrostomy tubes inserted, 30% recurrent gross haematuria with the need for blood transfusions, 25% suffered from rectal obstruction with consecutive subileus. 15 patients received cystoprostatectomy, median operation time was 260 min, blood loss was 500 mL. In 80%, durable symptom reduction was achieved, median symptom-free survival added up to 15,3 (6–25) months, median survival up to 20,4 (9–28) months [8].

Neuroendocrine differentiation. The number of neuroendocrine cells increases after puberty until an optimum level that persists between the age of 25 and 54, they represent the third epithelial cell type on normal prostatic tissue in addition to basal and secretory cells. Because of the lack of androgen receptors on these cells in normal and neoplastic prostates, they are androgen-insensitive, so hormonal therapy is not a true option for neuroendocrine prostate cancer [9]. In case of loco-regional disease, surgical resection with or without adjuvant treatment (chemotherapy, radiation) is recommended [10]. For prostate cancer with a Gleason score between 8 and 10, Krauss et al. reported inferior clinical outcomes for patients treated with primary radiotherapy if neuroendocrine differentiation exceeds >1%, 10-year distant metastases rates and cause specific survival were significantly lower. In this paper no differences in outcomes were seen for patients with 0% versus <1% neuroendocrine differentiation [11].

For patients with metastatic-stage disease, systemic chemotherapy with a platinum agent (cisplatin or carboplatin) and etoposide is recommended. However, due to aggressive histological features of neuroendocrine carcinomas response durations are often short [10]. In a study published by Culine et al., 41 patients were treated with a combination of docetaxel and cisplatin. PSA response rate was 48% and clinical benefit was observed in 45% of patients, median survival was 12 months [12]. Stein et al. published a cohort of 30 patients treated with cisplatin-based chemotherapy with or without pelvic radiotherapy. After an initial response, 25 patients succumbed to massive local and/or distant failure [13]. Based on the disappointing results with the established therapy strategies, novel approaches have to be implicated. Somatostatin analogues, serotonin and bombesin antagonists, and cytokines are under investigation [14]. Recently, Sciarra et al. reported a median overall survival superior to the 10-month median survival in patients with hormone refractory disease using a combination of estrogens and somatostatin [15].

The case presented here may have profited from a surgical approach once rapid progression had become obvious. It teaches that palliative radical tumour surgery should be considered in patients with locally advanced disease, especially when symptoms impair the patient's well being. Even in cases with widespread metastases, an effective local symptom control can be achieved for the last months of their lives.

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Clinical Study

Subcapsular Orchiectomy in the Primary Therapy of Patients with Bone Metastasis in Advanced Prostate Cancer: An Anachronistic Intervention?

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Background. The therapeutic impact of palliative androgen deprivation in metastatic prostate cancer is indisputable. Bilateral orchiectomy represents the traditional method of AD but was reduced during the last years in favor for treatment with LHRH analogues. Due to limited economic resources of the health care system, the economically priced definite surgical castration might experience a renaissance. *Methods*. In this single-center retrospective study, 83 consecutive patients with osseous metastasized prostate cancer were evaluated, who had primarily been treated by subcapsular bilateral orchiectomy. Response to therapy, time until therapy failure, overall survival time, psychological disorders due to loss of organ, and disease-associated and postoperative surgical complications were recorded. The median followup was 35 months (IQR: 26–46). *Results*. Patients' mean age at surgery was 72.1 (54–91) years. Six patients (7.2%) displayed immediate tumor progression after orchiectomy. Median time of tumor remission and overall survival time were 29 and 36 months, respectively. 14% of the study group showed minor postoperative complications. No psychological problems occurred following bilateral orchiectomy. *Conclusion*. Due to an effective and persistent oncological effectiveness, less morbidity, and absence of psychological implications, bilateral subcapsular orchiectomy seems to be a practicable and advisable alternative in the first-line therapy of metastasized PCa.

1. Introduction

In the pre-PSA era, one third of men with prostate cancer (PCa) presented with distant metastasis at time of diagnosis, and currently, it is about 5%–10% [1]. Despite these changes, PCa still represents the second most frequent tumor-associated cause of death. In 2006, 12000 men died from PCa in Germany [1].

Suppression of endocrine testicular function still represents the gold standard in palliative treatment in advanced stage or metastasized PCa. Already in 1941, Huggins and Hodges demonstrated control of PCa growth rate by androgens and showed that there is no better way to achieve temporary control of PCa growth than androgen deprivation (AD) [2]. Basically, AD treatment is able to induce a remission in 90% of PCa patients; the median progression-free survival ranges from 18 to 34 months [3].

The earliest method of AD is represented by the bilateral orchiectomy, which means a definitive therapy for the patient. Treatment with Diethylstilbestrol (DES) was de-scribed as to the first method of reversible castration. At present, medicinal castration is achieved either by LHRH analogues, which have been available since the 1980s or by GnRH antagonists being approved at the end of the last decade. The use of antiandrogens remains the limitation of initial increase of testosterone (flare phenomenon) under treatment with LHRH analogues. Alternatively, they can also be used as monotherapy, especially in patients with marginal metastatic load with consideration of a better quality of life but only slightly shorter progression-free and overall survival in comparison to castration [4].

Despite the fact that bilateral orchiectomy represents a proven method showing excellent oncological efficiency with

rapid onset of action, 100% compliance of surgical castration due to the definite character, and just minimal side effects, at present, priority is given to medical treatment [5]. One rational explanation for the avoidance of surgical castration might be the expectation of psychological consequences due to loss of testicles [6]. In 1942, Riba described subcapsular bilateral orchiectomy (OE-R) as a surgical method of avoidance of the "empty scrotum" without damage of the oncological effectiveness [7]. Furthermore, American and European studies could clearly prove that medical castration by LHRH analogues is considerably more expensive than surgical castration [8, 9].

In the present retrospective study, 83 patients with an osseous metastasized adenocarcinoma of the prostate undergoing OE-R in an 11-year period were analyzed with respect to progression-free and overall survival and discussed against the background of internationally available data on this topic. Furthermore, disease-related and postoperative surgical complications as well as psychological implications were evaluated and discussed.

2. Methods

In the time period between January 1990 and December 2000, OE-R was carried out in 98 patients with a metastasized PCa in the clinical center Berlin-Moabit. Based on electronic patient files of the hospital and from urologists in practice, clinical and oncological parameters of 83 patients with bone metastasis, out of whom 63% presented with multiple metastases, could be evaluated. In two out of 15 patients excluded, examination criteria were not completely documented, and in further 13 patients, the OE-R was not accomplished as primary therapy for osseous metastasized PCa. Accurate assessment of PSA kinetics (initial value and nadir) could be evaluated in 67 patients. Patients were offered OE-R in local anesthesia, and surgery was carried out according to the originally published surgical method [7]. Each patient received antibiotic single-shot application at the day of surgery. In all cases, postoperative pain could be managed with nonsteroidal anti-inflammatory drugs.

Oncologic course of disease was calculated by Kaplan-Meier method according to time of tumor remission and overall survival starting at the moment of OE-R. For the determination of the time until tumor remission, patients who died without tumor progression were censored by time of death. In 16 patients, preoperative PSA values were not known; however, following PSA values were assessed so that even in these patients the end of hormonal sensitivity could be defined by an increase of the PSA value and/or by newly established symptoms. The median followup was 35 months (IQR: 24–26).

Psychologically relevant disorders of the patient caused by loss of testicles were considered when information of psychological problems was indicated by the patient himself (criteria 1), in case of comedication with antidepressant drugs (criteria 2), or cotreatment by a psychiatrist (criteria 3). Information on this was taken by the electronic patient files noted by the ambulant urologist. Criteria 1 was proven by the ambulant urologist with the question: "Do you feel compromised in your well-being or body consciousness due to cosmetic or optical consequences caused by the operation?".

3. Results

3.1. Patients' Demography. Average age of patients at the time of OE-R was 72.1 (54–91) years, and general condition of patients according to ECOG criteria was median 0 ($n = 41$; 49.4%). Altogether 17 patients (20.5%) showed an ECOG performance status of ≥ 2. In all cases, histologically affirmed adenocarcinoma of the prostate was present. 70% ($n = 58$) of patients had an undifferentiated tumor (solitary Gleason pattern: ≥ 4). In 67 patients, preoperative PSA value was known, and the median value was 144 ng/mL (IQR: 68–259). In 9.6% patients ($n = 8$), AD primarily resulted in achievement of maximum hormone blockade (OE-R plus antiandrogen).

3.2. Operation Parameter. In 62 patients (74.7%), OE-R was performed in local anesthesia. The remaining 21 patients additionally received sedoanalgesia. Representing a surgical procedure mostly performed by residents ($n = 74$), the operation time was 25 minutes (11–47 minutes) with a median of 20 minutes.

Altogether, 12 postoperative complications (14.4%) were described, which were managed conservatively in 7 cases (3x hematoma and 4x wound infection). In 5 patients, surgical revision (2x massive hematoma and 3x abscess) was necessary.

3.3. Oncological Followup. Median time of hormonal efficacy was 29 months, whereby 11% of patients ($n = 9$) showed tumor remission until 5 years beginning from OE-R (Figure 1). Median overall survival of 36 months was analyzed. After 5 years, 16% ($n = 13$) of the patients were still alive. The mean PSA nadir achieved was 10.5 (0.01–212) ng/mL, but 45% patients ($n = 37$) achieved a PSA nadir under 2 ng/mL. Six patients (7.2%) showed immediate tumor progression after OE-R. Seven patients of the study group (8.4%) underwent chemotherapy for further treatment during castration-resistant status (different protocols, $n = 4$ with Mitoxantrone 12 mg/m^2 q3w).

During further disease progression, 12% of patients suffered from pathologic bone fractures ($n = 10$). According to electronic patient files received from the ambulant urologists, there was no patient with psychological problems (criteria 1–3, Section 2) concerning OE-R. More than one half of patients ($n = 48$, 58%) declared to suffer psychologically under general consequences of androgen withdrawal (disturbances, depression, tiredness, muscle wasting, osteoporosis, loss of libido, and erectile dysfunction).

4. Discussion

In 1895, White demonstrated the hormone sensibility of the prostate by treating 111 men with an obstructive prostate

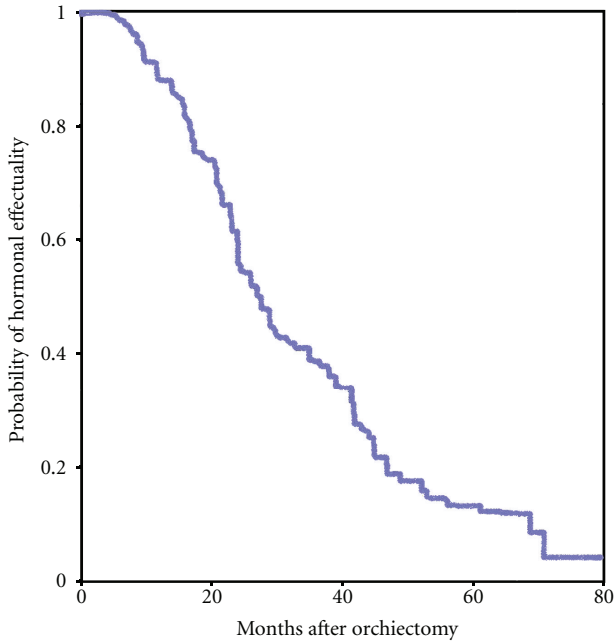

Figure 1: Time of tumor remission in 83 patients with osseous metastasized prostate cancer after subcapsular orchiectomy (Kaplan-Meier method).

hyperplasia by surgical castration [10]. In 1935, David et al. succeeded in isolating testosterone. Subsequently, Huggins and Hodges inaugurated the androgen deprivation as targeted therapy in advanced PCa [2]. For several decades, surgical castration displayed the gold standard in metastasized PCa. Huggins received the Nobel Prize for Medicine and Physiology in 1966 in appreciation of his scholarly achievements. Coy et al. and Labrie et al. first synthesized potent LHRH analogues in 1973. This new substance class has effectively been applied since the 1980s as standard therapy in metastasized PCa [11, 12].

Equivalence of surgical and medical castration with regard to remission and overall survival rate has been verified sufficiently [13, 14]. Median time of tumor remission in the present study was 29 months, which was in the upper range of the corresponding expectation values for PCa patients with primary AD therapy in tumor stage D2 [15].

One advantage of orchiectomy is rapid effectiveness, with achievement of castration level between 3 to 12 hours postoperatively [16]. This is an extremely important factor for symptomatic patients (ostealgia, imminent fracture, and compression of the spinal cord). A compromise of the oncological safeness with OE-R is not a matter of concern due to potential residual of testicular parenchyma. Postsurgical testosterone and LH level is comparable with values after bilateral radical orchiectomy [17, 18].

A second advantage is the definitive approach of surgical castration with respect to good compliance of patients. A disadvantage might occur when intermittent androgen deprivation (IAD) would be indicated [19]. In the basic studies, Goldenberg et al. added this form of therapy hoping for improvement of quality of life during the therapy-free interval and altogether for a prolonged duration of treatment during hormone sensitive status [20]. A large clinical study comparing a continuous with intermittent AD (SWOG 9346) showed no difference in overall survival [21]. In a recent study (SEUG), there was no evidence of better survival or an improvement of quality of life for IAD in comparison to continuous AD [22].

In 14% of patients in the present study, surgical side effects occurred; however, in only 5 patients, surgical revision was necessary. This high postoperative complication rate in comparison to an international level might eventually be based on the fact that in our study, the OE-R was mainly performed by residents (89%). Orchiectomy and the use of LHRH analogues or GnRH antagonists did only show slight differences concerning other side effects [23]. Hot flushes, lack of drive, loss of libido, and erectile dysfunction are the major side effects of castration therapy which were reported by patients. In our study group, 58% of patients suffered from psychical illness. In the long-time period, in approximately 50% of patients, osteoporotic changes occurred. In case of that, there seems to be a rationale to apply simultaneous therapy with bisphosphonates or RANK-ligand-inhibitors (Denosumab) [24, 25]. Due to the fact that prostate cancer mainly metastasizes into bones, a prevention of pathologic fractures is expected by the use of this co-medication.

A psychological strain caused by loss of testicles was not detectable in our study group (in accordance with criteria 1–3). Regarding this, a representative study by the Zoladex Prostate Cancer Group Study was initiated which compared quality of life and psychological status of patients with medical versus surgical castration [26]. In this study, including 147 PCa patients at tumor stages D1-D2 (Zoladex 115 and orchiectomy 32), patients were able to individually choose the kind of therapy, and, finally, an advantage was observed in the Zoladex arm concerning quality of life and psychological status. Especially in the sector of body awareness, patients with surgical castration reported detriment [26]. However, there are also studies with best evidence which report no difference in "body image" and "quality of life" between both treatment arms [27]. In the "Prostate Cancer Outcomes Study," there was significantly more gynecomastia (25% versus 10%) and a reduced general health condition (35% versus 28%) by treatment with LHRH analogues compared to patients with surgical orchiectomy [28]. Furthermore, patients taking LHRH analogues critically described to feel more often reminded of their treatment and their cancer disease. Due to this, they felt a negative impact in quality of life [28].

Concerning the general worse assigned body image of patients with orchiectomy, which is caused by loss of testicles, the paper of Issa et al. should be taken into consideration [29]. In this study on 88 orchiectomized patients pretreated by LHRH analogues ($n = 52$), the weight of testicles in study group 1 was compared with study group 2, comprising patients undergoing orchiectomy without medical pretreatment ($n = 36$). There was a significantly lower median weight of testicles in patients with pretreatment (7 versus 15 gr.; $P < 0.001$) [29]. In consideration of volume-protecting

effects after the surgical method described by Riba (OE-R), general data concerning deprivation of body awareness in patients after orchiectomy in comparison to medical castrated patients have to be interpreted more cautiously. In one study, Chadwick et al. showed that approximately 50% of men with advanced prostate cancer would have chosen orchiectomy if they had been offered this as a therapeutic option [30]. Furthermore, there is an extremely insightful study of Mariani et al., which again documents that 70% of patients with free option of treatment would choose LHRH analogue treatment [31]. However, in case of 20% self-maintenance in therapy costs, only 24% of patients would favor medical hormonal ablation [31].

Each study assessing cost efficiency of therapy clearly affirmed an advantage for orchiectomy in comparison to medical castration. Even older studies, that are describing definitely longer periods of hospitalization after orchiectomy, agree with this statement [32, 33]. In the study of Mariani et al. which already has been quoted, 96 patients were analyzed. Treatment with LHRH analogues was assessed to be 10.7x to 13.5x more expensive than surgical castration [31]. Deliberations concerning treatment should include the limited financial valences of the public health system, considering that in case of equality of treatment effects, an inadequate resource policy would be short-sighted and, furthermore, limit treatment options for other patients.

The present study shows some limitations, which have to be considered with regard to interpretation of the results. It is a retrospective study based on a limited number patients included in the study group (only 8 patients were added per year), who have been treated during a relatively long time span and by different surgeons. Period of examination (1990–2000) took place before the approval of Docetaxel; this might be one of the reasons for the worse median overall survival (35 months). Lacking availability of chemotherapy on the basis of evidence recommendation during the evaluation period, only 8% of patients were treated with chemotherapy at castration-resistant tumor stage (CRPC). Most patients only received best supportive care. In addition to that, only in 81% of patients, the preoperative PSA values were known. It has to be critically noted that the evaluation of psychological disorders, caused by loss of testicles, was not determined based on standardized and validated questionnaires.

In summary, the present study shows that subcapsular bilateral orchiectomy described by Riba (OE-R) remains a very effective procedure with few side effects in the primary treatment of metastatic PCa. This procedure combines a high patient comfort with the absence of mental disorders and low costs for a financial limited public health system.

5. Conclusions

Against the background of cost explosion in the health care system, OE-R might experience a renaissance as an effective therapeutic option of androgen deprivation and as a cost-effective method with only few side effects. Hence, OE-R could regain an increasing relevance in the primary therapy of metastasized PCa.

Conflict of Interests

The authors report no conflict of interests. The authors alone are responsible for the content and the writing of the paper.

Authors' Contributions

O. Rud and J. Peter prepared the data for statistical analysis and helped to draft the paper. R. Kheyri conceived the study, participated in its design and coordination, and carried out acquisition of data. C. Gilfrich and A. Ahmed supervised design and process of the study. W. Boeckmann and P. Fabricius participated in the design of the study and helped to draft the paper. M. May participated in the design and coordination of the study, carried out statistical analysis and interpretation of data, and drafted the paper. All authors read and approved the final paper. O. Rud, J. Peter, and R. Kheyri are contributed equally to this paper.

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Research Article

A Rare Location of Metastasis from Prostate Cancer: Hydronephrosis Associated with Ureteral Metastasis

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Prostate carcinoma is a very rare origin of metastatic disease in the ureter. We report a case of a 74-year-old man who presented in November 2008 initially with flank pain and lower urinary tract symptoms. Diagnostic investigation revealed a skeletal metastasizing prostate carcinoma, and the cause for the flank pain was a hydronephrosis due to ureteral metastasis diagnosed by biopsy. Antihormonal treatment led to disappearance of the hydronephrosis; however, further progress finally ended in acute liver failure with patient's death in July 2010.

1. Introduction

The ureter is a rare location of metastasis for primary tumors of any kind. In 1909, Stow described the first case of a truly metastatic ureteral lesion from a lymphosarcoma [1]. The most common malignant tumors metastasizing to the ureter are breast cancer followed by stomach cancer and colorectal cancer. Only 43 cases of metastasis in the ureter by primary adenocarcinoma of the prostate have been reported during the last century [2–7]. We present the first case of such a patient since the last 2 years.

2. Case Report

A 74-year-old man in November 2008 first presented at an outpatient urologist, due to lower urinary tract symptoms and intermittent pain of the right flank. The digital rectal examination revealed an enlarged, palpatory suspicious prostate gland with an endured left lobe. The PSA level was initially at 52 ng/mL. The subsequent prostate biopsy showed a low differentiated adenocarcinoma of the prostate gland (Grade 2, Gleason score 7 = 3 + 4). Further diagnostics with bone scan and ultrasound provided the evidence of diffuse skeletal metastasis as well as an hydronephrosis of the right kidney. Because of the findings, an antihormonal therapy with LHRH-analogues was initiated.

As further diagnostics, an intravenous pyelography showed a delayed excretion of the right kidney and a significant hydronephrosis with a dilated ureter. Cause of the prestenotic dilatation was a stricture of the lower part of the ureter (Figure 1). Due to the unclear nature of the stricture, a computer tomography was performed, detecting a suspicious intraluminal ureteral mass at the height of the bifurcation of the A. iliaca (Figures 2 and 3). An extraluminal compression of the ureter, as shown with lymph nodes or other solid masses, could not be demonstrated. In addition, there was no evidence of suspicious enlarged subdiaphragmal or pelvic lymph nodes. The blood and urine counts were except for a microscopic hematuria inconspicuous. Ureterorenoscopy with biopsy of the ureteral mass was the next step in the diagnosis of the patient. In ureterorenoscopy, the reported intraluminal mass was found in the distal ureter, as well as in the middle ureter. After collecting urine for cytology, each of the intraluminal lesions underwent biopsy. Histology by immunohistochemical analysis revealed a metastasis of the ureter by a prostate adenocarcinoma. Cytology did not reveal pathological result.

Because of the symptomatic hydronephrosis and suspected ureteral tumor, we first placed a nephrostomy after ureterorenoscopy. Postoperatively, there were no complications, but at the fourth postoperative day, the nephrostomy

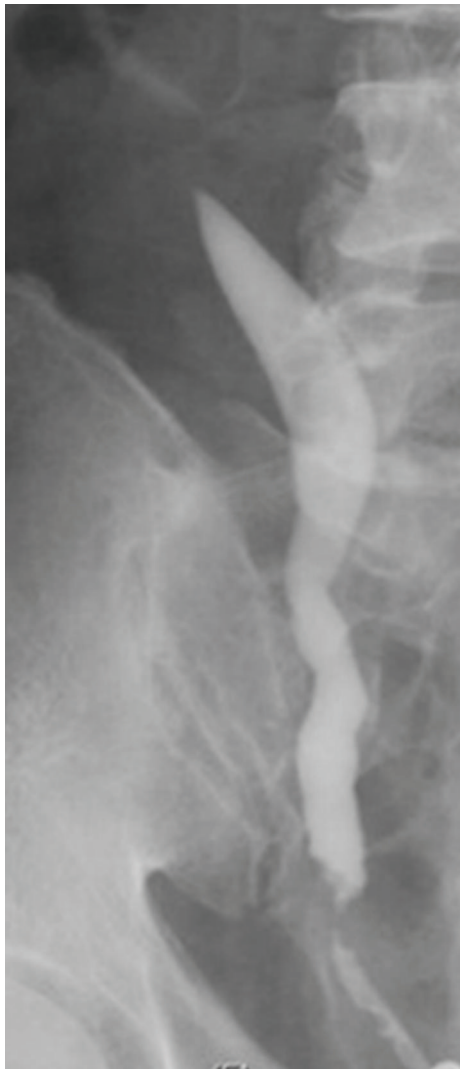

Figure 1: Retrograde pyelography showing an obstruction of the lower part of the right ureter.

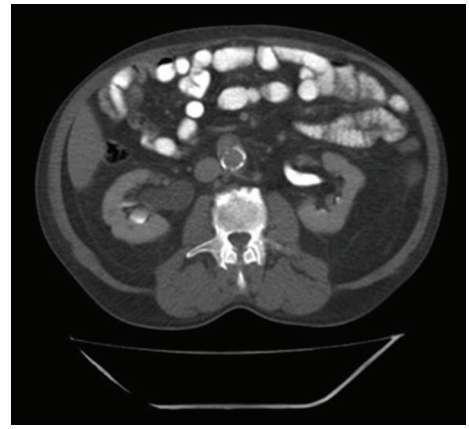

Figure 2: Computer tomography with hydronephrosis of the right kidney.

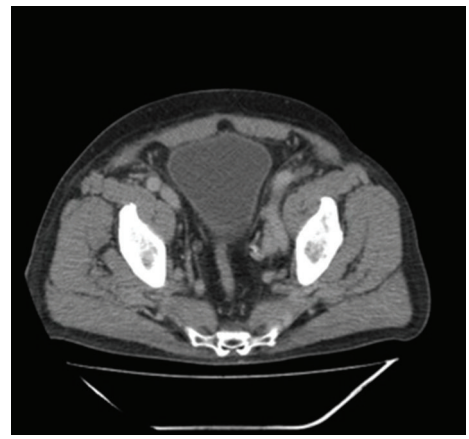

Figure 3: Presentation of an intraluminal ureteral mass of the right upper urinary tract in computer tomography of the pelvis.

dislocated. Since then, however, no relevant hydronephrosis existed and the patient remained pain-free, so that no further insertion of a nephrostomy was indicated.

The following procedure in case of multiple skeletal metastasis by prostate cancer was a continuation of the therapy with LHRH analogues in combination with zoledronic acid infusions once a month. In June 2009, PSA progress led to maximum antihormonal therapy with LHRH analogues and antiandrogene. Further progress in January 2010 indicated docetaxel chemotherapy that was prematurely stopped by appearance of liver metastases. In July 2010, the patient died of acute liver failure without having experienced further hydronephrosis.

3. Discussion

In 1999, Haddad described over all 38 cases of prostate carcinoma with at least one ureteral metastasis. For this paper, the authors considered data from the last century until 1987 [2]. For example, McLean showed 1956 of 10,223 cancer patients with only 18 cases of ureteral metastasis, and even only one of them related to a prostate carcinoma [8]. Kirshbaum et al., 1933, also demonstrated the rarity of ureteral metastasis by a series of 4,860 autopsies. They found in these patients only 5 ureteral metastasis, and only 2 of them were metastatic from adenocarcinoma of the prostate gland [9]. In a case report, Hulse and O'Neill described a true ureteral metastasis of a prostate carcinoma associated with a ureteral stone [3]. Cohen et al. underlined in 1974 the uncommon way of metastasis to the ureter from a prostate carcinoma. They showed 3,200 autopsies with 31 cases of ureteral metastasis but none of them with a prostate cancer as origin [10]. Singh et al. presented in 2009 a case report of a man with a locally advanced prostate cancer and bone metastasis with ureteral metastasis in both ureters [4]. In 2007, Marzi described another case with undifferentiated prostate cancer and neoplastic metastasis of prostatic origin in both ureters too [5]. Jung et al. showed a ureteral metastasis from prostate adenocarcinoma after bilateral orchiectomy in 2000, and Yonneau et al. presented in 1999 a patient with an episode of renal colic and a ureteric

tumor with a history of prostatectomy for prostate cancer. They performed ureterectomy, and histology examination revealed a metastasis from prostatic adenocarcinoma to the ureter [6, 7]. Altogether, only 43 cases of an adenocarcinoma of the prostate metastatic to the ureter have been reported in the last century [2–7]. In the first half of the last century, these ureteral metastases have been only developed by incidental finding during autopsy. Later ultrasonography and ureteroscopy have been established, so that also clinical cases were reported. However, only a few patients with ureteral metastasis are identified, because up to 85% patients are staying asymptomatic [3]. In case of disorders, the most frequently is flank pain (15–50%), hematuria is rather rare (16%) [3, 11].

In our case, the patient complained intermittent right flank pain together with a hydronephrosis of the right upper urinary tract. During medication with LHRH analogue, hydronephrosis disappeared completely.

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Review Article

Circulating and Disseminated Tumor Cells in the Management of Advanced Prostate Cancer

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Management of prostate cancer is recognized as one of the most important medical problems. Latest findings concerning the role of circulating (CTC) and disseminated tumor cells (DTC) have provided new insights into the biology of metastasis with important implications for the clinical management of prostate cancer patients. Most of the established methods of circulating/disseminated tumor cell enrichment use density-gradient centrifugation and immunomagnetic procedures. Reverse transcriptase polymerase chain reaction is another used detection technique. Novel methods, the CTC-chip and the epithelial immunospot assay already showed promising results. For localized and metastatic prostate cancer, significant correlations between spreading tumor cells and well-established indicators of disease activity have been demonstrated. Careful randomized prospective trials will be required to justify the routine use of CTCs/DTCs for therapy decision making.

1. Introduction

While significant therapeutic advances have been made for primary curative procedures, there still remains a significant risk of prostate cancer recurrence after therapy. Between 27% and 53% of all patients will develop local or distant recurrences within 10 years of initial curative-intended therapy. In addition, 16%–35% of patients will receive second-line treatment within 5 years of initial therapy [1]. Despite recent advances in treatment of advanced prostate cancer, the majority of patients with metastatic disease will die. In many cases, effective treatment of metastatic disease is delayed due to diagnostic failure of early detection by standard clinical or radiographic evaluation [2]. The presence of disseminated tumor cells at the time of primary diagnosis is assumed to be an important determinant for subsequent successful treatment and has been examined for a variety of human malignancies [3, 4]. However, the process of metastatic spread from the primary tumor site into distal organs is still not well understood. Recent studies suggest an early spread of tumor cells to lymph nodes or bone marrow (BM) referred to as "disseminated tumor cells" (DTCs) or as "circulating tumor cells" (CTCs) when present in the peripheral blood (PB) [5, 6]. Even after complete removal of the primary tumor, DTCs/CTCs can cause later development of distant metastases. There is growing evidence that spreading tumor cells indicate metastatic disease and poor prognosis [7, 8]. Although the first report on circulating tumor cells had been published in 1869 by Asworth, the lack of technology precluded further investigations on their clinical use until recently [9]. Today, technological advances in immunological and quantitative real-time PCR-based analysis enable clinicians to detect, enumerate, and characterize DTCs and CTCs in cancer patients. The monitoring of CTCs and DTCs has the potential to not only improve therapeutic management at an early stage, but also to identify patients with increased risk of tumor progression or recurrence before the onset of clinically evident metastasis. In addition, the molecular characterization of CTCs and DTCs can provide new insights into prostate cancer biology and systemic treatment in neoadjuvant or adjuvant settings.

2. Detection Methods of CTCs/DTCs in Urogenital Cancer

Unfortunately, the clinical applicability of most CTC/DTC detection techniques is restricted due to their high complexity, methodological limitations, and lack of standardization.

DTCs and CTCs can be found in the peripheral blood and bone marrow samples of cancer patients [10]. The rare presence of CTCs in the blood system (estimated as one tumor cell per billion normal blood cells) requires the use of advanced bioengineering tools for tumor cell identification and enumeration. The sampling from the BM is more invasive and is difficult to implement in daily clinical practice. Current methods of CTC detection in the PB are limited because of comparatively lower CTC concentration rates [11, 12]. Several methods of CTC/DTC enrichment have been investigated to increase the sensitivity [7]. The most established tumor cell enrichment methods for BM and PB samples use density-gradient centrifugation and immunomagnetic procedures [13]. Cell density-based enrichment methods are based on the principle of differential cell migration according to their buoyant density. In contrast, antibody-related techniques use specific antigen patterns on the tumor cell surface to separate tumor and blood cells. For example, tumor cell-specific cell adhesion protein EpCAM is overexpressed in many types of cancer. Many approaches with EpCAM antibodies conjugated with magnetic particles followed by separation in a magnetic field have been described in literature [14, 15]. After tumor cell enrichment immunological and PCR-based molecular assays are used for the detection of CTCs/DTCs. Some methods use only detection assays without further enrichment steps to minimize tumor cell loss due to limited cell separation. Immunological approaches are based on either specific epithelial (i.e., EpCAM) or organ-specific antigens (i.e., PSA) which are exclusively expressed on tumor cells and can be analyzed by simplified automated scanning devices. Automated digital ultraspeed microscopy and the use of laser scanning have opened up new opportunities for immunocytochemical approaches in this field [16]. Due to the aforementioned methods being highly labor and time consuming, a semiautomated immunomagnetic system (CellSearch) was developed to combine both detection and enrichment of tumor cells. This technique uses ferro fluids coupled to EpCAM antibodies followed by cytokeratin staining and separation. CellSearch has already been introduced into clinical trials to monitor CTC in patients treated with new targeted therapies and was approved by the US Food and Drug Inspection Agency [17]. In addition, this measuring method has been effectively used to evaluate prognostic influence on cancer progression in various types of human cancers [18–20]. However, EpCAM-based enrichment is limited by the wide variety of protein expression levels in different tumor types [16]. Reverse transcriptase polymerase chain reaction (RT-PCR) is one of the most commonly used techniques for CTC detection and has been successfully applied in many cancer types.

This method can detect tumor-associated molecular markers with a higher sensitivity than protein-based assays [21–23]. CTC detection by PCR depends on gene-specific oligonucleotide primers and has already been used to detect prostate cancer cells in the PB [24]. However, PCR has low specificity due to the lack of cancer-specific molecular targets in the overall majority of urogenital malignancies. In addition, tumor-associated proteins like prostate-specific antigen (PSA) are also expressed in normal cells. Therefore, PCR is extremely susceptible to errors in quantification and needs high methodical standardization, which limits its wide clinical use. A new detection method, the so called "CTC chip," can separate tumor cells from whole blood by EpCAM-antibody-coated microspots. After this first step, CTCs are stained with antibodies against cytokeratin or tissue-specific markers, such as PSA in prostate cancer, and are visualized by automated scanning. The CTC chip demonstrated high sensitivity and specificity with doubled detection efficiency in comparison to currently available technologies such as CellSearch [25]. In patients with metastatic prostate cancer, the CTC chip identified 16 to 292 CTCs per milliliter. The CTC chip enables cell separation without harming the cellular integrity of tumor cells and allows subsequent molecular analysis. Another novel antibody-based technique is the epithelial immunospot (EPISPOT) assay, an adaptation of the enzyme-linked immunospot assay. This test is highly sensitive and detects only viable protein-excreting cells. Detection of CTCs/DTCs has shown promising results in kidney and bladder cancer patients with advanced disease. In various studies, CTCs have been detected in renal cell carcinoma patients in the PB by immunocytochemistry and PCR. Immunocytochemical methods have reached CTC detection rates between 32% and 53% in patients with metastatic disease [10, 26–28]. For PCR-based CTC analyses in renal cell carcinoma, the detection rates range between 37.5% and 49% [29–33]. In addition, Buchner et al. studied 256 BM samples of nonmetastatic RCC patients and reported a detection rate of DTCs in 25% but without any prognostic relevance [34]. The prognostic relevance of cytokeratin-positive BM DTCs was demonstrated in 55 patients with metastatic RCC compared with 256 patients without systemic involvement with significantly more DTCs being detected in metastatic disease (42% versus 25%, resp.). Multivariate analysis revealed that the presence of more than 3 DTCs was an independent prognostic factor [35]. Bluemke et al. evaluated the presence of CTCs in 233 PB samples from 154 patients with RCC after magnetic cell sorting followed by immunocytochemical staining against cytokeratin. In preliminary studies, the authors established a CD45 depletion protocol and identified 29%–42% of CTCs in patients with RCC. The frequency of cytokeratin-positive CTCs and "tumor-like" blue-stained cells without cytokeratin expression showed a significant correlation to lymph node status and presence of synchronous metastases in RCC.

CTCs were identified in 41% of the samples, corresponding to 53% of patients. In multivariate analysis, cytokeratin-stained CTCs were identified as an independent prognostic factor for a reduced overall survival. Interestingly, postoperative blood samples (40% of sample size) showed a higher rate of CTCs compared to preoperative ones indicating increased tumor cells dissemination during surgery [27]. The role of CTCs has also been studied in patients with urothelial cell carcinoma. Urothelial cancer cells express the cell surface molecule EpCAM and can therefore be detected by iron particles coated with anti-EpCAM antibodies. Naoe et al. demonstrated that the sensitivity of the CellSearch assay

was approximately 79% for the detection of CTCs derived from established urothelial cancer cell lines and mixed with peripheral blood mononuclear cells. In this study, in contrast to patients with localized disease, CTCs were only present in patients with metastatic disease [36]. CTCs might therefore represent an important tool to monitor the efficacy of chemotherapy in metastatic disease or addressing the risk of undiscovered micrometastatic disease when considering adjuvant chemotherapy for patients with locally advanced bladder cancer. In this respect, the feasibility of using the CellSearch system was recently demonstrated in patients with locally advanced nonmetastatic or metastatic disease. Moreover, the presence of CTCs in these patients was associated with a significantly reduced progression-free and cancer-specific survival [37]. Recently, Gradilone et al. showed that the bladder cancer cell marker survivin was expressed in 92% of patient with high-grade pT1 bladder cancer and the presence of survivin-expressing CTCs was an independent predictor for decreased disease-free survival [38].

3. CTCs and DTCs and Their Relevance in Prostate Cancer

Until now, prostate-specific antigen (PSA) has been the most investigated biomarker across all prostate cancer disease stages. However, in many cases, PSA is inadequate to document status of metastasis and risk of progression. The high concentration of CTCs/DTCs reported in prostate cancer patients provides novel opportunities for alternative therapeutic approaches and monitoring concepts [39]. In addition, recent data have shown that CTCs can be found at high frequency in metastatic disease underlining their potential use as surrogate markers to predict clinical outcomes and survival [17, 40–46]. Chen et al. correlated CTCs in 84 advanced prostate cancer patients with PSA, prostate-specific membrane antigen expression, and clinical parameters. Beside a high rate of intact CTCs, the authors found significant correlations between CTCs and established disease indicators (i.e., PSA), but no significant correlation for Gleason score or the type of therapy and metastasis [46]. In 2007, Shaffer et al. isolated and analyzed CTCs from PB samples of patients with advanced prostate cancer and showed that 65% of patients had five or more CTCs per 7.5 mL PB with an average CTC count of 16. In this study, CTCs were available for further epidermal growth factor receptor (EGFR) expression, chromosome ploidy, and androgen receptor (AR) gene amplification analyses [45]. The role of CTC baseline threshold value critical for survival was evaluated after immunomagnetic separation in 120 patients with progressive castration-resistant prostate cancer. Higher CTC numbers were identified predominantly in patients with bone compared to patients with soft tissue metastases and with prior chemotherapy. In univariate analysis, baseline CTCs and PSA were associated with survival without showing a threshold value [41]. Nagrath and coworkers established a microfluidic platform, the so-called CTC-chip for CTC detection and demonstrated a sensitivity rate of more than 99%. In early-stage prostate cancer, CTCs were isolated in all seven patients [25]. In a large trial leading to the FDA approval of the CellSearch system for therapeutic monitoring of castration-resistant prostate cancer, 231 patients were stratified in two prognostic groups according to CTC count (<5 or ≥ 5 per 7.5 mL of PB). During a follow-up period of up to 36 months under mainly docetaxel-based chemotherapies, CTC based prediction of overall survival was better than with PSA [17]. A recent study examined potential tumor-specific aberrations in the blood of cancer patients and their use as surrogate markers for the presence of CTCs. Samples were analyzed in 81 prostate cancer patients by immunospot assay and PCR-based fluorescence microsatellite analysis. Authors showed correlations between DNA plasma levels and the differentiation between tumor stage, localized and systemic disease. Moreover, CTCs correlated with tumor stage and higher Gleason scores [47]. Recently, Scher and colleagues showed a strong association between survival and CTC changes after systemic therapy in metastatic castration-resistant prostate cancer patients receiving first-line treatment [44].

However, the low rate of CTC in the prechemotherapy setting limits the use of CTCs as a potential biomarker for prostate cancer detection. Multiple ongoing phase III studies aim to clarify the role of CTC changes and their potential to replace established biomarkers in the monitoring of chemotherapy treated-prostate cancer patients.

4. Conclusion

Advanced technologies offer nowadays the opportunity to detect tumor cells in the peripheral blood and bone marrow and to estimate the risk of progression after intended curative surgery in prostate cancer patients. Despite the relatively scarce data available, DTCs/CTCs have the potential to specifically address currently controversial issues in the management of advanced prostate cancer. However, before detection of CTCs/DTCs becomes the standard of care, there is a need for further prospective randomized studies.

Authors Contribution

Both S. Kruck and G. Gakis contributed equally to the paper.

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Clinical Study

The Role of ^{11}C-Choline-PET/CT-Guided Secondary Lymphadenectomy in Patients with PSA Failure after Radical Prostatectomy: Lessons Learned from Eight Cases

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Introduction. ^{11}C-choline-PET/CT is a promising technique for detection/restaging of patients with biochemical failure (BF) after curative therapy for prostate cancer (PCA). The aim of this paper was to evaluate the PSA response in patients with BF after radical prostatectomy (RP) who underwent secondary lymphadenectomy (LAD) due to ^{11}C-choline-PET/CT findings. *Material and Methods*. Eight patients with BF and positive lymph nodes in ^{11}C-choline-PET/CT after RP were retrospectively included in the study. Extended LAD until the common iliac arteries was performed in all patients. *Results*. Six of 8 patients had histologically proven lymph node metastases. Four patients showed an initial PSA reduction after LAD, and in 4 patients the PSA increased. Two of the latter had no histological lymph node metastases. *Conclusions*. Because 50% of our patients showed an initial PSA response, our data suggest that positive ^{11}C-choline-PET/CT after RP and BF could help to select patients that could benefit from secondary LAD.

1. Introduction

The incidence of recurrent disease after the initial curative treatment of local PCA ranges from 30 to 50% after RP [1, 2] and up to 80% after extracorporal radiotherapy [3]. An increasing PSA is the most certain indicator for relapse, but it does not always help in differentiating between local recurrence and systemic spread of the disease [4]. PSA kinetics and imaging techniques play an important role in the diagnostic of PCA recurrence after primary treatment.

Positron emission tomography/computed tomography with choline tracer (^{11}C-choline-PET/CT) has emerged as a promising technique for restaging patients with BF. Tumor cells are known to have a higher turnover of essential cell membrane components, such as phosphatidylcholine, [5]. After uptake by tumor cells, radioactive choline is phosphorylated in high concentration and built into the cell membrane and can be recognized by PET [6]. PCA or its metastases can be detected by ^{11}C-choline-PET/CT [7]. The aim of this paper was to retrospectively evaluate the PSA response after secondary LAD in patients with a BF and positive lymph nodes in ^{11}C-choline-PET/CT after RP.

2. Material and Methods

Eight consecutive patients between 2009 and 2011 with BF and positive lymph nodes in ^{11}C-choline-PET/CT were retrospectively included in the study. Because of a PCA, 5 patients had initially undergone a retropubic RP with a pelvic LAD and 3 a perineal RP without LAD. Local recurrence was excluded by transrectal ultrasound and digital rectal examination. All patients were informed of the pure diagnostic value and the risk of a surgical intervention. ^{11}C-choline-PET/CT imaging results were analysed by a nuclear medicine specialist in all 8 cases. The patients subsequently underwent a secondary open extended LAD, performed by

Table 1

Patient	Age	Primary treatment	Initial tumor stage	Gleason score	Hormonal therapy after primary treatment	Radiotherapy after primary treatment
1	57	RP	pT3aN0MxR1	9 (4 + 5)	+	+
2	54	RP	pT2cN0MxR0	8 (4 + 4)	+	+
3	62	RPP	pT2bNxMxR1	6 (3 + 3)	–	–
4	65	RP	pT3bN0MxR0	7 (4 + 3)	–	+
5	59	RP	pT2aN0MxR0	7 (4 + 3)	–	+
6	68	RPP	pT3aN0MxR1	6 (3 + 3)	+	+
7	68	RPP	pT3bN0MxR1	9 (5 + 4)	–	+
8	75	RP	pT4N1MxR1	7 (4 + 3)	–	+

RP: radical prostatectomy; RPP: Radical perineal prostatectomy.

Table 2

Patient	PSA 1 (ng/mL)	PSA 2 (ng/mL)	PSA 3 (ng/mL)	PSA 4 (ng/mL)	Lymph nodes resected *n*	Lymph nodes positive *n*
1	6.14	0	1.38	1.6	24	3
2	5.54	0.64	1.57	0.1	3	1
3	8.56	0	0.17	0.2	17	0
4	8.32	0	1.66	1.74	5	1
5	7.62	0	2.92	1.34	20	1
6	6.94	0.53	2.93	4.1	11	0
7	5.23	0	2.43	0.66	12	1
8	9.81	0.13	1.5	0.11	1	1

PSA 1: initial PSA at time of cancer diagnosis; PSA 2: PSA after primary treatment; PSA 3: PSA at time of PET imaging; PSA 4: PSA after lymphadenectomy.

2 of our experienced department surgeons. The extended LAD consisted of the dissection of lymph nodes from the obturator fossa, the internal and external iliac artery, the paravesical lymph nodes, and the common iliac artery. In one patient, only the ^{11}C-choline-PET/CT-positive lymph node around the external iliac artery was resected. Three to five weeks after the LAD, the PSA value was determined and then determined again at 3-month intervals.

3. Results

Patient characteristics are summarized in Tables 1 and 2. The median PSA value at the time of ^{11}C-choline-PET/CT was 1.62 ng/mL (IQR 1.47 ng/mL–2.56 ng/mL). Definitive histological lymph node metastases could be found in 6 of 8 patients with positive ^{11}C-choline-PET/CT. In 2 of the 6 patients with histological lymph node metastases, the localization was not concordant with the ^{11}C-choline-PET/CT findings. Regarding PSA response after LAD, 4 patients showed a PSA increase: two of them showed no sign of histological lymph node metastases, and the other two had an increase of the PSA value, despite the resection of the positive nodes. Three of them underwent androgen deprivation therapy (ADT), and one patient has been under observation with a stable PSA (0.21 ng/mL) after LAD for the last 29 months. Out of the 4 patients with decreasing PSA, one patient had an undetectable PSA after 29 months of followup. A second patient showed a decrease in PSA from 2.43 ng/mL to 0.66 ng/mL and remained stable after 34 months of followup. After a period of 5 months maintaining initial PSA response, the third patient showed disease progression. He subsequently underwent an ADT, and 31 months later he became castration resistant. He then received chemotherapy with docetaxel. At 4 months of followup, the fourth patient has not yet shown any increase in PSA value.

4. Discussion

When BF occurs after a radical treatment for PCA, being able to differentiate between local recurrence and distant metastases plays a crucial role in choosing the appropriate course of treatment. The functional imaging modality PET/CT has been proven to be useful for restaging patients with a PSA value which increases after RP. However, differing figures can be found in the literature with regard to the sensitivity and specificity of this approach.

De Jong et al. analyse the role of the ^{11}C-choline-PET/CT for preoperative staging in 67 patients with histologically proven PCA. This work gave a sensitivity of 80%, a specificity of 96%, and an accuracy of 93% for the detection of lymph node metastases using ^{11}C-choline-PET/CT. They conclude that this tracer has a higher sensitivity than standard CT and magnetic resonance imaging (MRI) [8].

In patients with BF after RP, Scattoni et al. reported a lower sensitivity 64% and a specificity of 90% for the ^{11}C-choline-PET/CT for the detection of lymph node metastases [9].

The sensitivity of choline-PET/CT in patients with BF after radical treatment for PC could range between 38 and 98% as was recently reported by Picchio et al. in their review article. Such variability is to be attributed to differences among patient cohorts [10]. The type of tumor and primary treatment, extension of the LAD, and particularly the PSA value at the time of choline-PET/CT could influence the sensitivity and specificity of this imaging technique. Some authors have stated that no positive lymph nodes could be detected using ^{11}C-choline-PET/CT in patients with BF and PSA level <5 ng/mL [11], but others have shown positive PET/CT findings in patients with PSA values <5 ng/mL, albeit with a sensitivity reduction [12], and indeed this is in concordant with our experience. For example, Picchio et al. concluded that the routine use of choline-PET/CT cannot be recommended for PSA values <1 ng/mL [10]. Castellucci et al. evaluated the role of ^{11}C-choline-PET/CT in the restaging of 102 patients after RP with only a slight PSA increase <1.5 ng/mL during followup. ^{11}C-choline-PET/CT showed positive findings in only 28% of the cases: local relapse in 7 patients, bone metastases in 13 patients, and lymph node metastases in 9 patients. PSA doubling time and initial node status were found to be significant and independent factors in a multivariate analysis for positive ^{11}C-choline-PET/CT. PSA doubling time in patients with positive PET findings was 4.3 months and in PET-negative patients 13.3 months ($P = 0.0001$). They concluded that the optimal threshold for PSA doubling time was 7.2 months, providing ^{11}C-choline-PET/CT 93% sensitivity and 74% specificity [13].

In our cohort, 2 patients with BF showed no signs of lymph node metastases in the final histological analysis but instead exhibited inflammatory altered tissue, and, in 2 further patients, no positive nodes where found were these were indicated by ^{11}C-choline-PET/CT giving a positive predictive value (PPV) of 50%. Schilling et al. found a PPV of 70% in a retrospective work similar to ours [14]. Inflammatory node disease and small bowel activity (adherence and hernias) seem to imitate positive lymph nodes. This is a known phenomenon and can be explained by the high proliferation activity of intestinal mucosa [8]. Our study showed a PSA reduction in 4 patients (50%), and, in 3 cases (37.5%), this response persisted at 29, 34, and 4 months of followup in the respective patients.

Our results agree with the findings of Winter et al. In their study, 3 of 8 patients with single lymph node metastases reached a complete PSA remission without adjuvant therapy. They concluded that a selected patient group seems to benefit from secondary LAD [15]. Weckermann et al. also showed that especially low-risk patients profit from the resection of the lymph node metastases and that 60% of patients with resected metastases were free of relapse without adjuvant therapy after 18 months [16]. It should also be determined whether patients that benefit from a secondary LAD had an optimal LAD at the time of primary treatment. In fact, data in the literature affirm that microscopic metastatic pelvic node disease could be cured by means of surgery and extended LAD. Bader et al., for example, found that 38.5% of the patients with one positive lymph node, 10% with two, and 14% with multiple lymph node metastases remained relapse-free for 45 months in a cohort of post-RP and extended LAD patients [17].

5. Conclusions

Extended LAD should be carefully performed at the time of the first treatment.

In case of BF without local recurrence, ^{11}C-choline-PET/CT could be performed if the PSA value is >1 ng/mL, to select patients that may benefit from a secondary LAD.

Since positive lymph nodes have been found outside the regions indicated by ^{11}C-choline-PET/CT, a complete extended secondary LAD should always be performed.

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Review Article

Prostate-Specific Membrane Antigen-Based Therapeutics

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Prostate cancer (PC) is the most common noncutaneous malignancy affecting men in the US, leading to significant morbidity and mortality. While significant therapeutic advances have been made, available systemic therapeutic options are lacking. Prostate-specific membrane antigen (PSMA) is a highly-restricted prostate cell-surface antigen that may be targeted. While initial anti-PSMA monoclonal antibodies were suboptimal, the development of monoclonal antibodies such as J591 which are highly specific for the external domain of PSMA has allowed targeting of viable, intact prostate cancer cells. Radiolabeled J591 has demonstrated accurate and selective tumor targeting, safety, and efficacy. Ongoing studies using anti-PSMA radioimmunotherapy with ^{177}Lu-J591 seek to improve the therapeutic profile, select optimal candidates with biomarkers, combine with chemotherapy, and prevent or delay the onset of metastatic disease for men with biochemical relapse. Anti-PSMA monoclonal antibody-drug conjugates have also been developed with completed and ongoing early-phase clinical trials. As PSMA is a selective antigen that is highly overexpressed in prostate cancer, anti-PSMA-based immunotherapy has also been studied and utilized in clinical trials.

1. Prostate-Specific Membrane Antigen

Prostate-specific membrane antigen (PSMA) is the single most well-established, highly specific prostate epithelial cell membrane antigen known [1–6]. The PSMA gene has been cloned, sequenced, and mapped to chromosome 11p [2, 7]. Pathology studies indicate that PSMA is expressed by virtually all prostate cancers [7–10]. Moreover, PSMA expression increases progressively in higher-grade cancers, metastatic disease and castration-resistant prostate cancer (CRPC) [3, 4, 11, 12]. Although first thought to be entirely prostate-specific [1–3], subsequent studies demonstrated that cells of the small intestine, proximal renal tubules, and salivary glands also express PSMA [5]. Importantly, the expression in normal cells is 100–1000-fold less than in prostate tissue [6], and the site of expression is not typically exposed to circulating intact antibodies [5]. In addition, PSMA is expressed on the neovasculature of the vast majority of solid tumor malignancies, but not on the normal vasculature [13]. In contrast to other well-known prostate-restricted molecules such as prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) that are secretory proteins, PSMA is an integral cell-surface membrane protein that is not secreted, thereby making PSMA an ideal target for monoclonal antibody (mAb) therapy.

Prostate-specific membrane antigen has been found to have folate hydrolase and neurocarboxypeptidase activity [14]. Although its role in prostate cancer (PC) biology is unknown, the consistent finding of PSMA upregulation correlating with increased aggressiveness of the cancer implies that PSMA has a functional role in PC progression. Inhibition of enzymatic activity *in vitro* or in xenograft models has not demonstrated significant growth inhibitory effect (N. H. Bander et al., unpublished data). Nevertheless, the expression pattern of PSMA makes it an excellent target for mAb-based targeted therapy of PC.

Prostate-specific membrane antigen was initially validated as an *in vivo* target for imaging utilizing radiolabeled mAb 7E11 (CYT-356, capromab) [15, 16]. Capromab pendetide imaging was approved to evaluate the extent of disease in patients presenting with Gleason sums greater than 6 and those who experience a rising PSA after prostatectomy.

Though improvements have been made with single-photon emission computed tomography (SPECT) and SPECT/CT imaging, because of suboptimal sensitivity and specificity of capromab pendetide, this imaging tool has not been widely adopted [17, 18]. Molecular mapping revealed that 7E11 targets a portion of the PSMA molecule that is within the cell's interior and not exposed on the outer cell surface [5, 19, 20] and cannot bind to viable cells [1, 20]. Recognition of these features by Bander and colleagues at Weill Cornell Medical College led to the development of mAbs to the exposed, extracellular domain of PSMA. In theory, the bound mAbs to the PSMA molecule would have the potential to significantly improve *in vivo* targeting and likely result in enhanced imaging and therapeutic benefit [20–22]. After testing, these antibodies (J591, J415, J533, and E99) did indeed demonstrate high-affinity binding to viable PSMA-expressing LNCaP cells in tissue culture and were rapidly internalized [20, 21]. Amongst these antibodies, the deimmunized IgG monoclonal antibody known as J591 was the most highly developed antibody clinically [23].

2. Radioimmunotherapy: Background and Rationale for Prostate Cancer

Radioimmunotherapy (RIT) is a technique by which a radionuclide is linked to a mAb or peptide and is typically delivered in a systemic fashion. In clinical practice, mAbs and peptides can be labeled with radionuclides that are usually beta-emitters. This "targeted" form of RT allows radiation delivery to tumors while sparing normal organs. The initially investigated form of RIT utilized radiolabeled antibodies against carcinoembryonic antigen for solid tumors. To date, the most studied form of RIT targets the CD20 antigen (^{131}I tositumomab or ^{90}Y ibritumomab tiuxetan) in non-Hodgkin's lymphoma, demonstrating safety and efficacy in phase I–III trials, which led to FDA approval. RIT for solid-tumor malignancies has been slower to develop. Reasons for this are multifaceted, including lack of specific antigens and antibodies optimized for RIT, difficulties in stably linking radionuclides to existing mAbs, shortfalls in existing (and readily available) radionuclides, and difficulty in clinical use (coordination between different specialties) [24]. However, clinical trials utilizing RIT in solid-tumor malignancies have been increasing.

The most common radionuclides employed have been ^{90}Y and ^{131}I, with ^{177}Lu being used more recently. Based on the physical properties, each radionuclide may have an optimal tumor type and perform unique functions in clinical situations [25] (Table 1).

Prostate cancer is an ideal solid tumor malignancy for the utilization of RIT; the tumor is radiosensitive with high exposure to circulating antibodies (bone marrow and lymph nodes) through typical distribution. Although sometimes clinically problematic, early readouts of efficacy can be examined using serum prostate-specific antigen (PSA) levels. In preclinical and clinical PC settings, radionuclides have been linked to antibodies and/or peptides against mucin, ganglioside (L6), Lewis Y (Le^y), adenocarcinoma-associated antigens, and PSMA [26–36]. Of these, PSMA is the most specific and has been extensively studied in clinical trials.

Radioimmunotherapy can be delivered in a single dose or in multiple fractions. The degree of antitumor response following the administration of radiolabeled mAbs depends on several variables, specifically total (cumulative) radiation dose to the tumor, dose-rate, and tumor radiosensitivity. As with conventional external beam ionizing radiotherapy, dose fractionation may result in the ability to deliver a higher tumor dose with less toxicity. At the optimal dose-rate, fractionated dose RIT may decrease the amount of radiation to bone marrow while increasing the cumulative radiation dose to the tumor [37–39]. Preclinical data have shown that dose fractionation or multiple low-dose treatments can decrease toxicity while increasing the efficacy [40–42]. Early clinical studies have supported the ability to increase the cumulative maximum tolerated dose by dose fractionation [43–45].

Studies have shown that external beam RT can be combined with cytotoxic chemotherapy and, though toxicity may be increased, efficacy of concurrent chemoradiotherapy may be superior to sequential use. This may be especially true when utilizing chemotherapeutic agents with radiosensitizing effects. Combining RIT with cytotoxic chemotherapy has also been investigated [30, 31, 46]. These combinations have the possibility of increasing the therapeutic yield of RIT, particularly in the face of bulky, metastatic solid tumors.

With "targeted" therapy in general, patient selection can be significant. While our ability to preselect optimal PC patients based upon expression of a target has been limited, in other tumor types, reviewing targeted expression can be helpful in selecting patients more likely to respond or eliminating patients with a very low chance of response. For example, although epidermal growth factor receptor (EGFR) expression as measured by immunohistochemistry is not helpful in selecting patients for anti-EFGR mAb therapy in advanced colorectal carcinoma, excluding those with mutated K-ras has become helpful in clinical practice [47]. Specifically for PSMA expression, use of quantitative imaging, such as anti-PSMA-based positron emission tomography (PET) [48], may be more effective in selecting the best candidates (or ruling out poor candidates) for a PSMA-targeted therapeutic. When performing studies aimed to develop and examine predictive biomarkers, one must remember that prospective validation is important, as development of a "targeted" therapy may be thwarted by a suboptimal biomarker [49].

3. Anti-Prostatic-Specific Membrane Antigen-Based Radioimmunotherapy

Based on its apparent clinical ability to target some sites of disease, treatment studies were initiated utilizing radiolabeled capromab (CYT-356). In a phase I dose-escalation study, 12 patients with metastatic CRPC received ^{90}Y-CYT-356 after biodistribution studies with ^{111}In-CTY-356 [26]. As expected with RIT, myelosuppression was the dose limiting toxicity (DLT). No objective responses (PSA or radiographic)

Table 1: Radionuclide properties.

Radionuclide properties	^{131}I	^{90}Y	^{177}Lu
Physical half-life (days)	8.05	2.67	6.7
Beta particles (mEv)			
max	0.61	2.280	0.497
average	0.20	0.935	0.149
Range in tissue (mm)			
max	2.4	12.0	2.20
average	0.4	2.7	0.25
Gamma emission (mEv)	0.364	None	0.113–0.208
Optimal size of tumor when targeted for curability [25]	3–5 mm	28–42 mm	1–3 mm
Comments	Cannot be used with internalizing mAb's	Lacks gamma emissions (cannot use for imaging)	

were noted. A subsequent phase II study utilizing ^{90}Y-CYT-356 was performed in men with biochemically recurrent prostate cancer [30], yet the study was stopped after significant toxicity (myelosuppression) and lack of efficacy (no PSA decline) were seen in the first 8 patients.

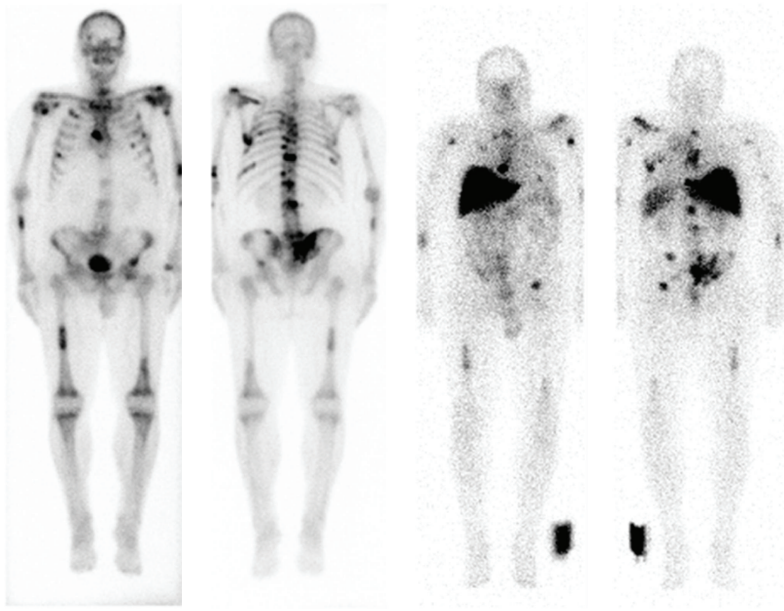
After determining that capromab was not capable of binding to viable PC cells, phase I clinical trials were performed linking Yttrium-90 (^{90}Y) or Lutetium-177 (^{177}Lu) to J591 via a DOTA chelate in patients with metastatic CRPC [25, 37]. Each of these studies was designed to deliver a single-dose of radiolabeled J591 intravenously followed by planar gamma camera imaging ± SPECT (in the case of ^{90}Y-J591, imaging was performed after ^{111}In-J591 administration). These trials defined the DLT and maximum tolerated dose (MTD) and further refined dosimetry, pharmacokinetics, and HAHA of the radiolabeled mAb conjugates and demonstrated preliminary evidence of antitumor activity. The vast majority of patients demonstrated good tumor targeting by radiolabeled J591. A representative planar gamma camera image of radiolabeled J591 is displayed in Figure 1. As expected, based on the physical properties as described above, the MTD of single-dose ^{177}Lu-J591 was higher (70 mCi/m^2) than that of ^{90}Y-J591 (17.5 mCi/m^2) [34, 35].

A phase II study was subsequently performed with ^{177}Lu-J591, confirming safety, efficacy, and tumor-targeting ability [50]. In a dual-center study, men with progressive metastatic CRPC received a ^{177}Lu-J591 intravenously followed by gamma camera imaging one week later. The results are promising and majority of patients demonstrated accurate targeting of known sites of metastatic disease, and PSA declines. All subjects experienced reversible hematologic toxicity without significant hemorrhagic complications. No serious drug-related nonhematologic toxicity occurred in either cohort.

In aggregate, based on the phase I and phase II data, these trials provide support that radiolabeled J591 is well tolerated with reversible myelosuppression, accurately targets PC metastatic sites, has antitumor activity, and is nonimmunogenic. However, as previously discussed, there are limitations to RIT for solid tumors, and the physical properties of ^{177}Lu should be suboptimal in treating the population treated to date (men with progressive metastatic CRPC were treated, many of whom had bulky disease). Additional studies to improve the therapeutic profile are in progress.

Based upon the rationale above, a US Department of Defense sponsored study utilizing fractionated dose ^{177}Lu-J591 has recently been completed with initial results of the primary endpoint presented [51]. Men with progressive metastatic CRPC received 2 fractionated doses two weeks apart. Doses were escalated in cohorts of 3–6 subjects, with cohort 1 receiving 20 mCi/m^2 x2 and each successive cohort undergoing dose escalation by 5 mCi/m^2 per dose (10 mCi/m^2 cumulative dose increase per cohort). The primary endpoint was to determine DLT and the cumulative MTD of fractionated ^{177}Lu-J591 RIT with pharmacokinetics and dosimetry, and the secondary endpoint was efficacy. Dose limiting toxicity was defined as severe thrombocytopenia (platelet count <15 or need for >3 platelet transfusions in 30 days), grade 4 neutropenia >7 days, febrile neutropenia, or grade >2 nonhematologic toxicity. Twenty-eight subjects received treatment with cumulative doses of up to 90 mCi/m^2 (highest planned dose). The median age was 72 years with median baseline PSA of 49 ng/mL; the majority of subjects had Eastern Cooperative Oncology Group (ECOG) performance status of 1 and had bone metastases. The study confirmed the hypothesis that fractionated dosing would allow higher cumulative doses of ^{177}Lu-J591 be administered with less toxicity.

Following progression on primary hormonal therapy, chemotherapy can offer symptomatic improvement as well as incremental survival benefit [52, 53]. However, responses are transient and all men eventually suffer from progression of disease as described above with single-agent anti-PSMA based RIT. The combination of taxane chemotherapy with RT has been used in several diseases because of the radiosensitizing effects of taxane-based chemotherapy [54–56]. In addition to favorable results from fractionated RIT and the radiosensitizing effects of taxane-based chemotherapy, it is hypothesized that the additional debulking by chemotherapy will overcome some of the limits imposed by the physical characteristics of ^{177}Lu. Based upon this theory, a phase I



(a) (b) (c) (d)

Figure 1: Radiolabeled J591 imaging. Left panels: Anterior (a) and posterior (b) images of pretreatment bony metastases on ^{99m}Tc-MDP bone scan. Right panels: Anterior (c) and posterior (d) total body images obtained via dual-head gamma camera of sites of uptake 7 days after ^{177}Lu-J591 administration. (note, antibody is partly cleared via the liver resulting in nonspecific ^{177}Lu localization).

trial of docetaxel and prednisone with escalating doses of fractionated ^{177}Lu-J591 is ongoing [57].

As discussed above, the most studied form of RIT to date targets the CD 20 antigen (^{131}I tositumomab and ^{90}Y ibritumomab tiuxetan) in non-Hodgkin's lymphoma. While approved in the relapsed setting, it appears that these therapies have their greatest impact in the minimal disease setting [58–63]. The vast majority of relapses after local therapy for PC are initially "biochemical" only, that is, with a rising PSA despite no evidence of cancer on imaging, affecting approximately 50,000 men per year in the United States alone [64, 65]. Although there is no proven overall survival benefit in a prospective randomized trial, radiotherapy as a salvage regimen can lead to long-term survival in selected individuals [66–69]. Unfortunately, most individuals subsequently suffer systemic progression because of subclinical micrometastatic disease outside of the radiation field.

Based on the demonstrated ability of J591-based therapy to successfully target known sites of disease and apparent clinical efficacy in the advanced setting, it is now under investigation in the salvage setting (clinicaltrials.gov NCT00859781). "Targeted radiotherapy" in the form of RIT is an attractive option with the possibility being a higher yield therapy in the minimal disease (biochemical only) setting. The primary objective of this trial is to prevent or delay radiographically evident metastatic disease. Radiolabeled J591 imaging will also be explored as a possible way to detect sites of disease in those patients with biochemical relapse and no evidence of disease on standard scans (^{99m}Tc-MDP bone scans and computed tomography or magnetic resonance imaging) [70].

4. Anti-Prostatic-Specific Membrane Antigen Antibody-Drug Conjugates

Rather than linking a radionuclide to an mAb, a drug or toxin can also be linked, forming an antibody-drug conjugate (ADC) [71]. In this form of therapy, drugs may be delivered to target cells, sparing normal cells from toxicity. Many advances have been made in ADC technology. Gemtuzumab ozogamicin is an anti-CD33 mAb conjugated to calicheamicin which was approved by the US FDA in 2000 for older patients with relapsed acute myeloid leukemia, though it has recently been withdrawn from the market. Many others are in late-stage development, including trastuzumab-DM1 (anti-Her2 for breast cancer), inotuzumab, ozogamicin (anti-CD22 for non-Hodgkin's lymphoma), and brentuximab vedotin (anti-CD30 for Hodgkin's lymphoma).

MLN2704 is an ADC with maytansinoid 1 (DM1), which is a potent microtubule-depolymerizing compound conjugated to J591. Preclinical activity with MLN2704 was demonstrated [72] leading to a phase I trial designed to explore single ascending doses of the conjugate to define DLT, MTD, and PK [73]. Twenty-three subjects with metastatic CRPC received MLN2704 at doses ranging from 18–343 mg/m^2 in an accelerated dose escalation scheme; 18 received at least 3 doses. Grade ≥3 toxicities occurred in 2 subjects, including 1 episode of uncomplicated febrile neutropenia and transient grade 3 elevation of transaminases. One subject (treated at 343 mg/m^2) achieved a >50% decline in PSA, and another (treated at 264 mg/m^2) experienced a PR by RECIST along with a >50% decline in PSA.

A subsequent multicenter phase I/II study was initiated based on the above results [71]. Sixty-two subjects received

multiple doses of MLN2704. Four regimens were tested, with PSA declines most frequent at 330 mg/m^2 every 2 weeks (2/6 had PSA decrease >50%, 2/6 had PSA stabilization). Although response was modest, and treatment was limited by toxicity, utilizing a PSMA mAb may be delivered in the clinic, and work is in progress and work is in progress utilizing new linkers to J591 designed to improve selective targeting.

Based on the PSMA selective expression in PC and the principle above, additional researchers have initiated further clinical work with toxin-conjugates that target PSMA. In the preclinical setting, A5-PE40 and D7-PE40 are recombinant anti-PSMA immunotoxins tested *in vivo*. Huang et al. inhibited the tumor growth in mice bearing subcutaneous LNCaP tumors with an immunotoxin consisting of the anti-PSMA mAb E6 and deglycosylated ricin A [74]. Russell et al. coupled the melittin-like peptide 101 to anti-PSMA mAb J591 and obtained a significant tumor growth inhibition in mice [75]. Henry et al. used MLN2704 for the treatment of CWR22 xenografts [76]. Elsässer-Beile et al. reviewed other targeted systems against PSMA including RNA-aptamer-based immunotoxins [77]. Preclinical activity has been demonstrated in another mAb conjugated to monomethylauristatin E (MMAE) that recognizes the external domain of PSMA [78]. This work has led to a phase I dose-escalation study that has shown to be tolerated at the initial dose levels [79]. Additional early-stage clinical work has involved utilizing enzymatic activation to release cytotoxic substances in PSMA positive cells [80].

5. Anti-Prostatic-Specific Membrane Antigen Immunotherapy

Immunotherapy has been utilized in oncology over many decades, but only relatively recently has an autologous cellular immunotherapy agent (sipuleucel-T) been approved for clinical use in prostate cancer [81]. Though many attempts at utilizing immunotherapy in PC have focused on PSA [82, 83], as discussed, PSMA is an attractive target based on its restricted sites of expression. Multiple vaccine approaches have been utilized in preclinical models and have moved to early-stage clinical trials [83–88].

In addition to the deimmunization process in the transition from murine to human antibody, mAb J591 was engineered to interact with human immune effector cells and trigger antibody-dependent cell-mediated cytotoxicity (ADCC). In some of the initial studies with "cold" or "naked" J591 (unconjugated J591 with or without small doses of trace-labeled ^{111}In-J591 for imaging purposes), stabilization of previously rising PSA occurred [89, 90]. Evidence of a dose-response relationship between mAb mass delivered and induction of ADCC was observed in a dose-escalation study enrolling patients with progressive CRPC [91]. One patient who received 100 mg of J591 had a >50% reduction in PSA.

Interleukin 2 (IL-2) promotes the proliferation and enhances the secretory capacity of all major types of lymphocytes, including T, B, and NK cells [92]. In addition, through its effects on NK cells, IL-2 stimulates antigen-nonspecific host reactions that involve interplay between NK cells and monocytes. Based on these functions, IL-2 may be useful as an immune stimulant, particularly in the setting of cancer immunotherapy [93]. Within two weeks of low-dose IL-2 treatment, selective expansion of human CD3$^-$, CD56$^+$ NK cells was seen with a plateau after 4 to 6 weeks of therapy [94, 95]. Based on the hypothesis that J591 plus IL-2 would work together to effect a positive immune response against prostate cancer, a combination study was initiated [96]. Seventeen patients with recurrent prostate cancer received continuous low-dose subcutaneous IL-2 (1.2×10^6 IU/m^2/day) daily for 8 weeks with weekly intravenous infusions of J591 (25 mg/m^2) during weeks 4–6. Therapy was well tolerated with a trend for those with significant NK cell expansion to be nonprogressors.

6. Conclusion

In summary, PSMA is the most highly specific PC cell-surface protein known. Prostate cancer represents an ideal disease for mAb-directed therapy, with PSMA as an optimal target. Current strategies aim to improve upon past successes in utilizing anti-PSMA mAbs to deliver toxic payloads specifically to PC cells, minimizing damage to normal organs. Clinical use to date include developments with anti-PSMA RIT and ADC. Additional work in early stages of development includes anti-PSMA vaccines and utilizing PSMA-targeted therapy with or without other immune modulators to stimulate anti-PSMA ADCC.

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Research Article

Complete PSA Remission without Adjuvant Therapy after Secondary Lymph Node Surgery in Selected Patients with Biochemical Relapse after Radical Prostatectomy and Pelvic Lymph Node Dissection

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Introduction. To evaluate whether secondary resection of lymph node (LN) metastases (LNMs) can result in PSA remission, we analysed the PSA outcome after resection of LNM detected on PET/CT in patients with biochemical failure. *Materials and Methods*. 11 patients with PSA relapse (mean 3.02 ng/mL, range 0.5–9.55 ng/mL) after radical prostatectomy without adjuvant therapy were included. Suspicious LN (1–3) detected on choline PET/CT and nearby LN were openly dissected (09/04–02/11). The PSA development was examined. Histological and PET/CT findings were compared. *Results*. 9 of 10 patients with histologically confirmed LNM showed a PSA response. 4 of 9 patients with single LNM had a complete permanent PSA remission (mean followup 31.8, range 1–48 months). Of metastasis-suspicious LNs (14) 12 could be histologically confirmed. The additionally removed 25 LNs were all correctly negative. *Conclusions*. The complete PSA remissions after secondary resection of single LNM argue for a feasible therapeutic benefit without adjuvant therapy. For this purpose the choline PET/CT is in spite of its limitations currently the most reliable routinely available diagnostic tool.

1. Introduction

In prostate cancer the long relapse-free survival of patients with 1-2 LNM even without adjuvant therapy in the primary situation [1, 2] argues for a feasible therapeutic benefit by resection of LNM especially in case of minimal lymphatic dissemination. To evaluate whether the sole secondary resection of LNM can result in a prostate-specific antigen (PSA) remission, we analysed the PSA outcome after targeted resection of LNM detected via choline positron emission tomography (PET)/computed tomography (CT) in patients with biochemical failure after radical retropubic prostatectomy.

In our first studies of PET/CT-guided secondary LN surgery, we reported on the outcome of all in all 8 patients with LNM detected by using [^{11}C]choline PET/CT without adjuvant therapy [3, 4]. 3 of 6 patients with single LN recurrence showed a complete PSA remission without adjuvant therapy up to 32 months. Now we wanted to update the results of secondary LN dissection in consideration of more patients and a longer followup. Moreover, in our present study patients with LNM detected by using [^{18}F]fluoroethylcholine were included too.

Former studies of others could give no evidence for PSA-remission after the sole secondary resection of LNM, whereas a resection of LNM was followed by adjuvant therapy [5, 6] and patients without adjuvant therapy were monitored for only a short time, respectively [7].

The integrated [^{11}C]choline and [^{18}F]fluoroethylcholine PET/CT provides the opportunity to detect small LNM (>5 mm) in prostate cancer with exact topographic allocation and so the targeted resection of LNM. In contrast, the

computed tomography (CT) and the conventional magnetic resonance imaging (MRI) are not applicable for early detection of LN recurrence. The lymphotropic nanoparticle-enhanced MRI can detect smaller LNM (>2 mm) [8] but has not been approved for routine diagnostics.

2. Materials and Methods

2.1. Patients. 11 consecutive patients (mean age 62 years, range 49–78 years) with 1–3 LNM detected by using [^{11}C]choline PET/CT ($n = 9$) or [^{18}F]fluoroethylcholine PET/CT ($n = 2$) in case of PSA failure (mean 3.02 ng/mL, range 0.5–9.55 ng/mL) were included. All had a PSA increase or persistence after operative therapy which was performed between 3 months and 9 years ago. In 10 patients a radical retropubic prostatectomy with pelvic LN dissection (PLND) and in one patient only a radical retropubic prostatectomy were carried out. One patient had received a sentinel guided PLND (sPLND) on both sides of the pelvic and also an extended PLND (ePLND) on the right side because of an advanced tumor and another one only sPLND in our clinic. The remaining patients had received conventional PLND, carried out by other institutions. There had to be negative margins and no clue for a local relapse or distant metastasis. The patients were informed that there is no conclusive data concerning survival benefit after secondary LN surgery in written and oral form, and signed an informed consent.

2.2. Choline PET/CT Imaging. All [^{11}C]choline or [^{18}F]fluoroethylcholine PET/CT studies were performed with integrated PET/CT systems externally in four centres with a high level of expertise. Experienced radiologists and nuclear medicine specialists evaluated the images to anatomically localize the sites of pathologic choline uptake. The diagnosis of tumor positive LN on PET/CT images was based on the visual evidence of the presence of focal increased choline uptake on PET images, whose location corresponded to LN on CT images (Figure 1).

2.3. Surgical Procedure, PSA Development, and Histological Evaluation. The LN/LNM detected by use of choline PET/CT and the nearby LN were openly dissected by two high-volume surgeons (09/2004–02/2011). The PSA development was monitored up to 48 months (mean 18.6, range 1–48 months) postoperatively. The primary histological diagnosis was made on hematoxylin and eosin-stained sections. Immunohistochemical staining of cytokeratins was performed to verify micrometastases. In one case, additional antibodies against PSA, prostate specific acid phosphatase, p504s, and the proliferation marker Ki67 were employed for typing of the metastatic tissue. The histological findings were compared with the PET/CT results.

3. Results

A summary of the patient characteristics is shown in Table 1. The mean PSA value at the date of the choline-PET/CT examination was 3.02 ng/mL (range 0.5–9.55 ng/mL).

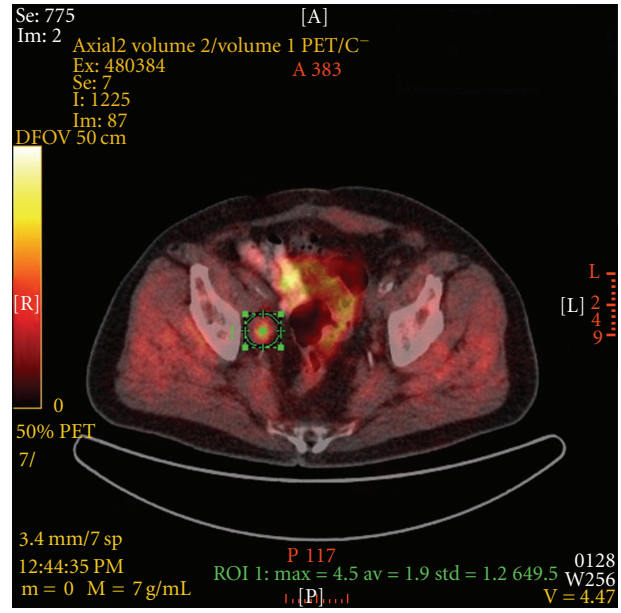

Figure 1: Integrated [^{11}C]choline PET/CT shows a single LNM in the right iliac region. The LNM was confirmed histopathologically after secondary resection. (Source: Clinic of Nuclear Medicine and Institute of Clinical Radiology, University Hospital Muenster, Germany).

In 10 of 11 patients the metastasis-suspicious LN detected by means of PET/CT could be completely removed. They were also histologically positive. In one patient with two metastasis-suspicious LN detected on PET/CT, only one histological negative LN could be resected because of severe cicatrization. A further 25 (mean 2.3, range 0–10) adjacent PET/CT negative LNs were dissected and negative for cancer. In one case, neighbouring LN could not be removed, because only three months ago this patient received a sPLND and ePLND on the concerning side in our clinic. In another patient only cicatricial tissue could be removed in addition to one LNM after radiotherapy. In the same patient a small lesion of the ureter necessitated a secondary ureteral stenting. In all other cases the intra- and postoperative courses were without complications.

After the secondary LN resection, 9 of 10 patients with histologically confirmed LNM showed a PSA response. 4 of 9 patients with single metastases had a lasting complete PSA remission (<0.01 ng/mL ($n = 3$), <0.03 ng/mL ($n = 1$)) without adjuvant therapy. The maximum followup of these patients was 48 months (mean 31.8 months, range 1–48 months). The other 5 patients with single LNM initially showed a PSA remission, 4 of them a partial incomplete remission. In one of these cases, a local recurrence was detected in the course of the study by means of PET/CT and MRI. In two other patients with incomplete remission already a tumorous infiltration of the adjacent tissue was histologically detected. In the patient without PSA response, 3 LNMs were histologically confirmed. The PSA development of all patients can be seen in Table 2 and Figure 2.

Table 1: Summary of the patient characteristics.

Patient	Age (yr)	Primary treatment	Initial tumour stage	Gleason score	Hormonal therapy after primary treatment	Radiotherapy after primary treatment	PSA initial (ng/mL)	PSA1 (ng/mL)	PET/CT positive LN
1	61	RPE + PLND	pT3a pN0 cM0 R0	3 + 4	−	−	4.13	0.92	1
2	59	RPE + PLND	pT2c pN0 cM0 R0	4 + 3	+	−	26.7	4.09	1
3	64	RPE + Splnd + ePLND right	pT3a pN1 cM0 R0	4 + 3	−	−	16.0	2.45	1
4	68	RPE	pT3a pN0 cM0 R0	?	−	+	9.9	1.64	1
5	78	RPE + PLND	pT3b pN0 cM0 R0	3 + 4	−	−	3.2	1.62	1
6	59	RPE + PLND	pT3a pN0 cM0 R0	4 + 3	+	−	7.6	4.51	1
7	49	RPE + PLND	pT3b pN0 cM0 R0	4 + 5	−	−	4.0	0.67	1
8	61	RRP + PLND	pT3a pN0 cM0 R0	5 + 5	+	+	?	9.55	3
9	53	RRP + PLND	pT3a pN0 cM0 R1	4 + 4	−	+	36.0	3.54	1
10	75	RRP + sPLND	pT3a pN0 cM0 R1	4 + 3	−	+	5.94	3.77	1
11	55	RRP + PLND	pT3b pN1 cM0 R0	4 + 3	−	−	5.08	0.5	2
mean	62							3.02	

PSA initial: PSA at primary diagnosis; PSA1: PSA at time of PET/CT diagnosis.

Table 2: PSA development after secondary resection of LNM without adjuvant therapy.

Patient	PSA1 (ng/mL)	PSA2 (ng/mL)	Follow up (month)
1	0.92	<0.03	48
2	4.09	<0.01	48
3	2.45	<0.01	30
4	1.46	<0.01	1
5	1.62	2.7	27
6	4.51	1.5	6
7	0.67	0.03	5
8	9.55	54.46	12
9	3.54	0.4	7
10	3.77 (6.51*)	10.3	2
11	No LNM histologically confirmed		

PSA1: PSA at time of PET/CT diagnosis; PSA2: PSA after resection of LNM; *preoperative, 3 months after PET/CT.

4. Discussion

The studies dealing with the secondary resection of LNM existing so far could give no evidence concerning the PSA response. The patients were either treated postoperatively with hormones or radiation [5, 6] or were monitored without adjuvant therapy for a maximum of four months, respectively [7]. In our present study 4 patients with single LNM even showed a complete and lasting PSA remission, over a maximum followup of 48 months, without an adjuvant treatment. These results confirm our previous data of the complete PSA remission in patients with single LN recurrence after secondary LN dissection [4].

Whether patients can benefit therapeutically by the removal of LNM in prostate cancer is still inconclusive. In our group the complete PSA remissions after secondary resection of single LNM argue for a feasible therapeutic benefit. Nevertheless, the small number of cases and the comparative short followup is a limitation of our study. The long-term outcome of patients undergoing PET/CT guided secondary resection of LNM remains to be seen. However, observations in the primary situation support a therapeutic benefit especially for patients with minimal lymphatic dissemination. Several reports suggest that ePLND increases the likelihood of finding positive nodes and improves biochemical relapse free survival [1, 9]. In the study of Daneshmand et al. [1] LN-positive patients had a progression-free survival of 70% (one positive LN), respectively, 73% (two positive LNs) after ten years. von Bodman et al. showed [2] that the time (median) to relapse without adjuvant therapy was 59 months (1 LNM), 13 months (2 LNMs), and 3 months for

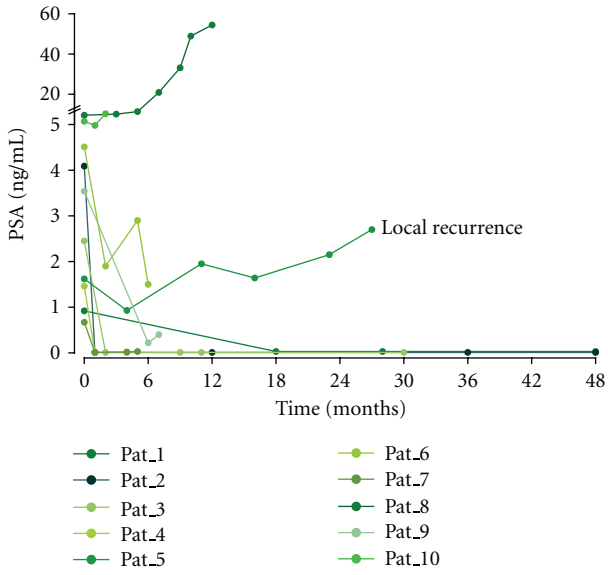

Figure 2: PSA development after secondary resection of LNM without adjuvant therapy.

patients with 3 LNMs. After 24 months 79% (one positive LN, Gleason-Score ≤7) or 29% (≥two positive LN, Gleason-Score ≥8) were free of biochemical relapse. Catalona et al. [10] reported that LN-positive patients without an adjuvant treatment developed no biochemical recurrence in 75% over six years and up to 58% over seven years. A population-based case-cohort study indicates a possible therapeutic benefit of PLND in node negative patients [11]. However, several studies demonstrated that in histologically negative LN tumor cells could be detected by real-time reverse transcriptase PCR [12, 13].

A limitation of secondary LN surgery in PCa is the limited sensitivity of the currently available imaging, especially in detection of small LNM. Contrary to conventional MRI and CT, the PET ([^{11}C]choline, [^{11}F]choline) offers key benefits in detecting LNM in the primary and recurrent diagnosis of PCa foci of sizes up to 5 mm [14, 15]. Nonetheless, the value of this method is limited because of the frequency of smaller metastases (<5 mm) [16, 17]. Other authors have also shown the method's inaccuracy in detecting lesions smaller than 1 cm [18–20], but CT and MRI are far more unreliable in these cases [21]. The lymphotropic nanoparticle-enhanced MRI can detect smaller LNM (>2 mm) [8] but has not been approved for routine diagnostics. In the future, the diffusion-weighted MRI could provide additional information on tumor pathophysiology compared to the standardized uptake values (SUV) in choline PET/CT. In a pilot study of Beer et al., [22] the apparent diffusion coefficient value in diffusion-weighted MRI and the SUV in PET showed a highly significant inverse correlation in LN diagnostics.

Whether choline PET/CT offers the basis of early treatment decisions in patients with PSA failure after radical prostatectomy is a subject of ongoing discussion. Picchio et al. suggest that the routine use of choline PET/CT cannot be recommended for PSA values <1 ng/mL [23]. However, patients with local recurrence after radical prostatectomy are best treated by salvage radiotherapy when the PSA serum level is <0.5 ng/mL. We could detect positive findings with a very low PSA value (≥0.67 ng/mL). Also Scattoni et al. [5] and others [24, 25] have shown positive results in patients with very low PSA levels (<1 ng/mL). In a study of Castellucci et al. it was possible to detect recurrent disease in 28% of patients with PSA <1.5 ng/mL by PET/CT [26]. In 21% of the patients distant unexpected metastases were detected by PET/CT. In those cases an unnecessary local radiotherapy can be avoided.

Our study shows a complete correlation between [^{11}C]choline PET/CT as well as [^{18}F]fluoroethylcholine PET/CT and histological findings in patients with single LNM (specificity 100%) and a specificity of 86% over all patients. With respect to the method, conclusions on sensitivity of choline PET/CT cannot be given.

5. Conclusions

Especially patients with minimal LNM seem to benefit from the secondary removal of LNM in prostate cancer. The here observed lasting, complete PSA remissions after secondary resection of single LNM appear to have a feasible therapeutic benefit without adjuvant therapy. For this purpose, the [^{11}C]choline or [^{18}F]fluoroethylcholine PET/CT is, despite its limitations, currently the most reliable routinely available diagnostic tool. Whether the secondary resection of LNM has an influence on the course of disease or could even be curative must be demonstrated in further studies in consideration of more patients and a long-term followup.

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Clinical Study

Surgical Castration in Hormone-Refractory Metastatic Prostate Cancer Patients Can Be an Alternative for Medical Castration

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Background. Most patients with metastatic prostate cancer are endocrinologically treated with LHRH agonist, but finally castration-refractory and hormone-refractory cancers occur. Serum testosterone levels get low to "the castration level" by LHRH agonists but may not get low enough against castration-refractory prostate cancer. *Methods*. As case series, twelve patients suffering from hormone-refractory prostate cancer continuously on LHRH agonist underwent surgical castration. Additionally, one hundred and thirty-nine prostate cancer patients on LHRH agonist or surgical castration were tested for serum total testosterone levels. *Results*. Surgical castration caused decrease in serum PSA in one out of 12 hormone-refractory prostate cancer patients with PSA reduction rate 74%. Serum total testosterone levels were below the sensitivity threshold (0.05 ng/mL) in 40 of 89 (44.9%) medically castrated patients and 33 of 50 (66.0%) surgically castrated patients ($P = .20$). *Conclusion*. Even hormone-refractory prostate cancer patients are candidates for surgical castration because of endocrinological, oncological, and economical reasons.

1. Background

Prostate cancer is the most prevalent cancer and the second ranked malignancy which causes death among males in the United States. In Japan as well, the prevalence and death rate of prostate cancer is recently increasing (http://ganjoh.ncc.go.jp/pro/statistics/gdb_trend.html?1). Organ confined and minimally invasive prostate cancer can be treated with local therapy such as radical prostatectomy, external beam radiation, and brachytherapy with excellent prognosis. Cryotherapy and high-intensity focused ultrasound for the treatment of localized prostate cancer are also under vigorous investigation with promising initial results. On the contrary, metastatic prostate cancer is usually treated primarily with androgen deprivation therapy with or without antiandrogens, leading to good to fair cancer control, but finally resulting in hormone-refractory cancer, cancer relapse, and cancer death. By definition, castration-refractory prostate cancer responds to secondary hormonal manipulations, including antiandrogen withdrawal, estrogens, and corticosteroids, while true hormone-refractory prostate cancer is resistant to all hormonal measures (Guidelines on prostate cancer, European Association of Urology 2010: http://www.uroweb.org/gls/pdf/Prostate%20Cancer%202010%20June%2017th.pdf).

Androgen deprivation therapy to benign prostatic hypertrophy was first reported by White in 1895 [1]. In 1941, Huggins and Hodges successfully applied androgen deprivation therapy to metastatic prostate cancer patients in the form of surgical castration [2]. In the early 1980s, LHRH agonists were introduced [3] in the endocrinological treatment of advanced prostate cancer, and the oncological outcomes of surgical castration by bilateral orchidectomy and medical castration by LHRH agonists are now generally regarded as the similar. Nevertheless, there are reports indicating that LHRH agonists fail to achieve castrate levels of testosterone [4–6]. According to a nonsystematic review of the literature,

castration level of less than 0.5 ng/mL was yielded in 95–98.8% by leuprolide, and that less than 0.2 ng/mL was in 87–92% by leuprolide and in 96% by goserelin [7]. Generally accepted definition of the cut-off point of castration level 0.5 ng/mL was determined by the lower detection limit of assay methods developed in the late 1960s and early 1970s [8] but not used anymore. Despite advances in methodology with more accurate lower limits of detection, the definition of testosterone levels after bilateral orchiectomy, that is, castration level, has not been updated so far. Moreover, there have been no controlled trials which show that the cancer-specific survival of the patients achieving testosterone level less than 0.2 ng/mL or less than 0.05 ng/mL were more favorable compared with those having testosterone level between 0.2 and 0.5 ng/mL.

Olapade-Olaopa et al. presented two cases of prostate cancer who were compliant but resistant to LHRH agonist therapy with normal testosterone levels, while they responded to following surgical castration resulting in low testosterone levels and clinical improvement as well as decrease in PSA [9]. Those cases showed cluster of Leydig cells in the excised atrophic testes. One reason why prostate cancer is resistant to LHRH agonists may be because they occasionally fail to castrate patients sufficiently by unknown reasons in the hypothalamo-pituitary-gonadal axis. Another possibility is that testosterone levels get low to "the castration level" by LHRH agonists but may not get low enough against castration-refractory prostate cancer, as an upregulation of androgen receptor in prostate cancer, and changes in the signal transduction pathways downstream of the receptor get to utilize even little amount of testosterone. Thus, surgical castration can completely eliminate remnant testosterone produced by the testes then may have a possibility in selected cases to control PSA and clinical symptoms of prostate cancer which has been already treated with LHRH agonists.

Here we show the changes in serum testosterone levels and PSA of hormone-refractory prostate cancer patients who had been treated with LHRH agonists and were surgically castrated. Additionally, we have assessed serum testosterone levels of prostate cancer patients continuously on androgen deprivation treatments, LHRH agonist, and surgical castration, irrespective of their oncological status.

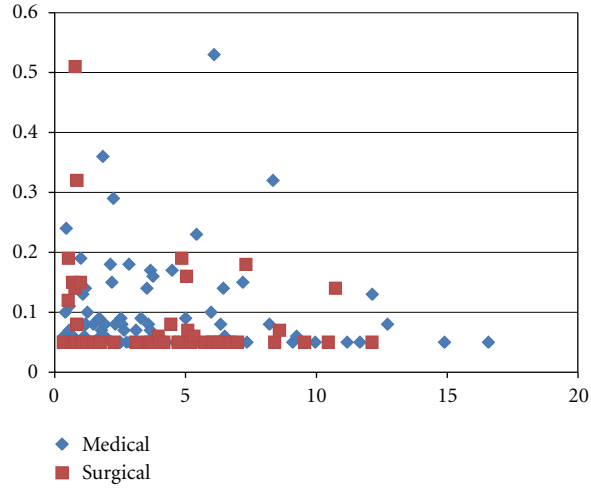

Figure 1: Serum testosterone levels in prostate cancer patients continuously on LHRH agonist or surgical castration. Medical: LHRH agonist, Surgical: surgical castration, vertical line: serum testosterone level (ng/mL), horizontal line: time after induction of LHRH agonist/surgical castration (years).

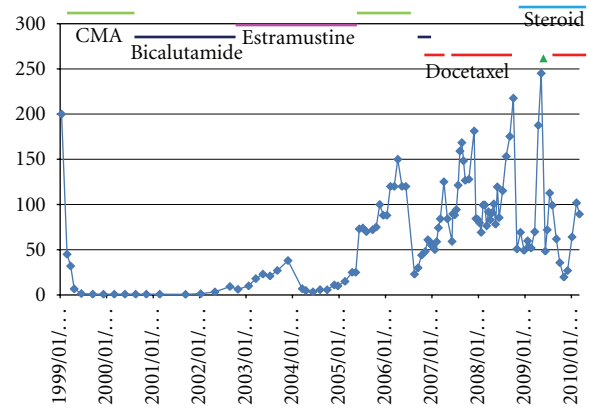

Figure 2: PSA course of a hormone-refractory prostate cancer patient whose PSA declined due to surgical castration. △: surgical castration, CMA: chlormadinone acetate, vertical line: PSA (ng/mL), horizontal line: date. Before surgical castration, dose of docetaxel every other week was 35 mg/m^2 per course.

2. Methods

Twelve patients suffering from hormone-refractory prostate cancer with multiple bone metastasis underwent surgical castration under spinal or total anesthesia without leaving testicular capsule between October, 2008 and August, 2010. There were no complications associated with surgery. They all were continuously on LHRH agonist, either leuprolide or goserelin, until the time of surgery. All patients had been given at least one antiandrogen (bicalutamide for all, flutamide for 8, chlormadinone acetate for 1), 9 given estramustine, and 10 given corticosteroid during some periods. Seven cases had been previously treated with docetaxel before surgical castration. Their clinical characteristics are listed in Table 1. Serum PSA in all patients and total testosterone in 8 patients were evaluated in pairs before and more than one month after surgical castration. Excised testes in every patient were histologically evaluated especially for the existence of remnant Leydig cells using Hematoxylin-Eosin staining by a board-qualifying pathologist.

One hundred and thirty-nine prostate cancer patients on LHRH agonist ($n = 89$) or surgical castration ($n = 50$) at least for three months and patients who had never experienced ($n = 31$) or who had quitted androgen deprivation therapy ($n = 10$) were tested for their serum total testosterone levels between August and October 2010, regardless of their oncological status. In this study, serum total testosterone was measured by the ECLIA assay (Electrochemiluminescence Immunoassay), and the sensitivity threshold of total testosterone measurement was 0.05 ng/mL.

Table 1

Case No.	Age at orchiectomy	Prebiopsy PSA	Biopsy GS	LHRH agonist administered	Duration of LHRH agonist	PSA		Testosterone		Overall survival
						pre-	post-	pre-	post-	
1	75	69	8	goserelin	3.9	4.9	2.9	0.10	0.05>	14.9
2	80	488	9	leuprolide	2.5	3.3	2.1	0.12	0.05>	10.6
3	90	10.7	9	goserelin	13.8	29.6	14.9	0.14	0.05>	17.5<
4	76	4.7	8	goserelin	7.0	9.6	16.6	0.11	0.05>	13.7<
5	67	315	8	leuprolide	1.6	924	553	0.07	0.51	9.6
6	77	1463	9	leuprolide	2.1	696	914	0.05>	0.05>	10.1
7	78	2.8	7	leuprolide	1.0	12	4.2	0.05>	0.05>	9.7<
8	78	107	8	goserelin	1.7	0.26	0.12	0.05>	0.05>	3.3<
9*	77	200	7	goserelin	10.3	187	48	0.07	NA	10.1
10	80	426	9	goserelin	0.9	34.1	53.7	NA	0.22	14.8
11	69	334	8	leuprolide	3.2	7.0	0.8	NA	NA	26.1<
12	45	191	6	leuprolide	1.3	138	146	NA	NA	4.4

Units of PSA: ng/mL, GS: Gleason score, duration of LHRH agonist: years, units of serum testosterone: ng/mL, overall survival: survival after surgical castration (months), pre-: before surgical castration, post-: after surgical castration,
*: a case where decrease in PSA was supposed to be due to surgical castration.

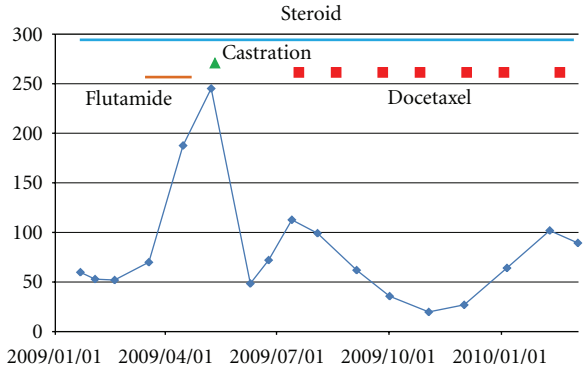

Figure 3: PSA course after 2009/1/1 of the patient described in Figure 2 is enlarged. After surgical castration, docetaxel (70 mg/m^2 per course every three weeks) was administered together with zoledronic acid (4 mg/body).

3. Results

PSA declined following surgical castration in 8 cases of hormone-refractory prostate cancer patients on LHRH agonist (Table 1), but only in one case PSA reduction was supposed to be due to surgical castration itself (Figures 2 and 3) on the condition that cases where there exist probable influences of other treatments as docetaxel were excluded. As shown in Table 1, surgical castration made detectable serum testosterone in 4 cases undetectable, while in one case detectable serum testosterone remained detectable (even increased). In 3 cases, serum testosterone had been already undetectable with LHRH agonist. The postorchiectomy rate of cases with serum total testosterone less than 0.05 ng/mL was 87.5% compared with 37.5% before orchiectomy (P = .039 by the chi-square test). In the case which showed 74% PSA reduction due to surgical castration, presurgical serum testosterone was 0.07 ng/mL, but post-surgical one was unfortunately unavailable.

Leydig cells were not identified in excised testes of hormone-refractory prostate cancer patients by the ordinary examination of histological specimens.

In patients on LHRH agonist or surgical castration at least for three months, the ordinary castration levels of serum testosterone (<0.5 ng/mL and <0.2 ng/mL) were achieved in 98.9% and 93.3%, respectively, by medical castration and in 98.0% and 96.0% by surgical castration with the median follow-up period 2.9 years. Serum total testosterone levels were below the sensitivity threshold (0.05 ng/mL) in 40 of 89 (44.9%) medically castrated patients and 33 of 50 (66.0%) surgically castrated patients as shown in Figure 1 (not statistically significant by the chi-square test; P = .20). Median serum testosterone levels in patients (age: 56–78 yrs) without experience of androgen deprivation therapy was 4.02 ng/mL (1.61–25.24). Serum testosterone levels in patients (age: 65–77 yrs) who had quitted androgen deprivation therapy was 0.07–5.50 ng/mL (median: 1.49) with time after cessation of androgen deprivation therapy 0.2–5.1 years.

4. Discussion

Levels of serum total testosterone in prostate cancer patients on medical and surgical castration were grossly comparable in this study. Surprisingly, serum testosterone above the sensitivity threshold was observed even in patients who had undergone surgical bilateral orchiectomy more than five years before. The source of testosterone is basically unknown in such cases. Extratesticular synthesis of androstenedione and testosterone was reported to be below 0.2%, but detected in liver, kidney, and the gastroduodenal tract in rats [10]. There is possibility that testosterone production is upregulated in those organs other than testis in patients

who were surgically castrated and show serum testosterone measurement above the sensitivity threshold. In the clinical setting, the androgen synthesis in the adrenal gland consisting of 10% of circulating androgen is more important for the growth of prostate cancer than extratesticular, extra-adrenal androgen synthesis. Thus, drugs inhibiting adrenal function such as ketoconazole and corticosteroids are in the clinical use.

Surgical castration in patients who have been on medical castration may possibly be more effective in controlling prostate cancer when castration level caused surgically can be occasionally more profound than that caused medically. Actually in this study, one of twelve hormone-refractory prostate cancer patients with multiple bone metastasis, who were on LHRH agonist, showed 74% reduction of PSA following surgical castration. There may be a question if this case was really hormone refractory or otherwise castration refractory, because hormone-refractory prostate cancer is not controlled anymore by hormonal manipulations by definition. However, it seems reasonable to classify the case into hormone refractory as it failed to control cancer with antiandrogens, estramustine, and corticosteroid. Complete eradication of testosterone by surgical castration may occasionally be effective even to "hormone-refractory" prostate cancer. There is a little possibility that flutamide, which was administered for forty days just before surgical castration without any effects, accelerated PSA increase, and cessation of it returned PSA to the preadministration level as shown in Figure 3. But considering that there was no preceding administration of flutamide and shortness of the duration of flutamide prescription, it was not very probable that there existed mutations in androgen receptor which would drive cancer growth as flutamide binds to the receptor as an agonistic ligand.

In reality, changes in serum testosterone levels of those patients undergoing surgical castration were inconstant, as some showed decrease with surgical castration while others not. In some of the latter cases, serum testosterone levels were already low enough (<0.05 ng/mL) with LHRH agonist, then additional decrease in testosterone might have not been demonstrable due to the sensitivity of measurement. The lower threshold of total testosterone measurement is as low as 0.02 ng/mL owing to the recent development of more sensitive assays [11]. If more sensitive total testosterone assays than that with the lower threshold 0.05 ng/mL are used, we may detect changes in serum total testosterone following surgical castration more precisely. Otherwise extratesticular testosterone production might have occurred as stated before in a case with considerable remaining serum testosterone level following surgery.

Standard androgen deprivation by medical castration does not consistently suppress tumoral androgen activity and androgen-dependent gene expression in the prostate microenvironment, leading to adaptive cellular changes allowing prostate cancer cell survival in a low-androgen environment [12]. This may support a medical rationale for indicating surgical castration for prostate cancer patients resistant to LHRH agonist. Interestingly, there is recently a paradoxical observation that the growth of some "androgen sensitive" human prostate cancer cells expressing androgen receptor can be inhibited by supraphysiologic levels of androgens [13]. Considering that, there may be cases where the administration of androgen can paradoxically suppress prostate cancer which has been treated with androgen deprivation therapy and finally converted to "hormone-refractory" cancer.

Administrating LHRH agonists every one or three month is costly compared with surgical castration which is not expensive and requires a hospital stay shorter than a week. In Japan, surgical fee for bilateral orchiectomy for the endocrine treatment of prostate cancer is just 27,700 yen, while 1-month depots of goserelin and leuprolide cost 43,856 and 46,776 yen, respectively, and 3-month depots of those cost 76,883 and 87,548 yen, respectively. In the time of economical recession as Japan is suffering from, it may be reasonable to think of giving surgical castration instead of medical castration to patients with castration-sensitive and castration-refractory prostate cancer who would hardly quit androgen deprivation therapy in the course of their illness. Japan is supposed to be surpassed by China in the Gross Domestic Product (GDP) by the end of 2010.

5. Conclusion

In conclusion, even hormone-refractory prostate cancer patients can be candidates for surgical castration because of endocrinological, oncological, and economical reasons.

Conflict of Interests

There are no competing interests.

Author's Contributions

M. Zaitsu conceived of the study, participated in its design and coordination, and carried out acquisition of data. M. Yamanoi participated in acquisition of data. K. Mikami participated in acquisition of data. Y. Takeshima participated in acquisition of data. N. Okamoto participated in acquisition of data. S. Imao participated in acquisition of data. A. Tonooka performed the pathological diagnosis of excised testes. T. Takeuchi participated in the design and coordination of the study, carried out analysis and interpretation of data, and drafted the manuscript. All authors read and approved the final manuscript.

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