The Role of Palliative Surgery in Castration-Resistant Prostate Cancer

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Keywords
Castration-resistant prostate cancer · Radical prostatectomy · Radical cystectomy · Continent vesicostomy · Subcutaneous pyelovesical bypass · Detour system · Ureteral reimplantation

Summary
Androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) analogues or antagonists represents the treatment of choice in men with metastatic prostate cancer (PCA). Depending on the serum concentration of the prostate-specific antigen (PSA) nadir, the survival might vary between 11 and 78 months. In castration-resistant PCA (CRPC), all new medical treatment options can induce complete and partial remissions in metastatic foci, but they have no profound effect on the prostate itself, as has been shown recently. About one-third of all patients without local treatment of the primary will develop significant complications of the lower and upper urinary tract due to local progression of the PCA. In men with CRPC and lower urinary tract symptoms, palliative transurethral resection of the prostate (TURP) can be performed with a 60–70% success rate. Infiltration of the pelvic floor, the bladder neck and trigone, and the external urethral sphincter can make palliative radical surgery necessary. Bladder neck closure with continent vesicostomy, radical cystoprostatectomy with an incontinent urinary diversion, and anterior and posterior exenteration are individual therapeutic options in men with a good performance status and a considerable life expectancy. Symptomatic involvement of the upper urinary tract can be managed by the placement of endoluminal stents or a percutaneous nephrostomy in men with poor performance. In men with a good response to ADT and a good performance status, reconstructive ureteral surgery might be considered and the options of ureteral reimplantation, ureter ileal replacement, and a subcutaneous pyelovesical bypass have to be discussed. The indication to perform one of the above-mentioned surgical approaches needs to be discussed in a multidisciplinary tumor board.

Introduction
Prostate cancer (PCA) is the most common malignant tumor and the reason for the third most frequent tumor-associated death in men [1]. Approximately 1 in 9 men will develop PCA during their lifetime. In 2008, about 899,000 cases with PCA have been diagnosed worldwide and about 50% of these men will develop metastatic disease within the 5–10 years of follow-up, and approximately 10–20% of those will develop castration-resistant PCA (CRPC) within 5 years of follow-up [2]. Androgen deprivation therapy (ADT) with luteinizing hormone-releasing hormone (LHRH) analogues/antagonists represents the guideline-recommended treatment of choice for PCA with skeletal metastases [1]. The M1 population, however, comprises a very heterogeneous group of patients with survival times varying between 11 and 75 months [3–6]. An updated, more precise classification of the Southwest Oncology Group (SWOG) 8894 trial has been published, which discriminates patients into 3 groups according to survival, with a median overall survival (OS) of 54, 30, and 21 months, respectively [4]. The prospective randomized SWOG 9346 trial compared the oncological efficacy of intermittent versus continuous ADT in a cohort of 1,078 M1 PCA patients [5]. After controlling for prognostic factors, the amount of prostate-specific antigen (PSA) decrease stratified patients into 3 risk groups that exhibit statistically significant differences in OS. The median survival was 13, 44, and 75 months in men with PSA serum levels of > 4, > 0.2, and < 0.2 ng/ml, respectively.
At the time of diagnosis, 84% of men with CRPC exhibit metastases and another 5% will develop metastatic disease within 2 years after the diagnosis [2]. Until recently, the median survival after diagnosis of CRPC was only 14 months. However, due to the development of new drugs and the various sequencing options of immunomodulatory, endocrine, and cytotoxic manipulations, median survival can achieve a time frame ranging from 20 to about 80 months in good responders [1]. Due to this considerably long life expectancy even in men with CRPC, we might be faced with a higher frequency of complications of the lower and upper urinary tract due to progression of the prostate itself, local recurrences, and/or pelvic or retroperitoneal lymph node metastases. More than one-third of all patients without local treatment of the primary will develop significant complications of the urinary tract due to local progression of the PCA [6, 7].

Complications might include subvesical obstruction, recurrent gross hematuria with or without clotting, upper urinary tract dilatation, rectourethral or rectovesical fistulae, and rectal obstruction. Besides the involvement of the urinary tract, the skeleton represents another organ system that is prone to complications, such as bone pain, pathologic fractures, or spinal cord compression/infiltration. In their final year of life, 46% of the patients with CRPC experienced PCA-related symptoms and 25% of the patients needed surgical interventions.

In addition to the clinical studies, it has been shown recently that systemic treatment will not result in complete eradication of intraprostatic vital and lethal cancer cell clones that might give rise to local progression and systemic metastases. Tzelepi et al. [8] analyzed the outcome of a well-selected cohort of high-risk PCA patients with lymph node metastases who were treated with docetaxel chemotherapy and 1 year of ADT before they underwent radical prostatectomy (RP) and pelvic lymphadenectomy. Despite the extensive pretreatment, all RP specimens contained vital cancer cells with biologically lethal properties, as assessed by immunohistochemistry of various biomarkers implicated in disease progression and therapy resistance. These data at least raise the suspicion that persisting intraprostatic cancer foci may be involved in local progression and the development of systemic metastases [9–13].

Apparently, all new medical treatment options can induce complete and partial remissions in metastatic foci but they have no profound effect on the prostate itself. Therefore, it seems to be necessary to develop palliative surgical strategies in order to relieve patients from symptoms and thereby to improve quality of life.

The current review article focuses on surgical options in the management of patients with CRPC and symptomatic involvement of the upper or lower urinary tract.

### Lower Urinary Tract

The frequency of symptomatic lower urinary tract involvement in CRPC depends on the treatment of the primary, as has been shown by various groups [6, 9–12]. RP significantly reduced the incidence of local complications compared to that of patients who did not undergo local surgical therapy (20% vs. 54.3%, p = 0.001) or who did undergo external-beam radiation therapy (EBRT) (20% vs. 46.7%, p = 0.007 [6]). The risk of local complications was not significantly reduced in patients who underwent EBRT as compared to those with no local treatment (46.7% vs. 54.6%). Bladder outlet obstruction developed in 4.4%, 35.6%, and 42.8% of patients who underwent RP, EBRT, or no local treatment, respectively. Similar results were reported by Steinberg et al. [9] who described a risk of local progression requiring surgical intervention in 3%, 43%, and 46% of men with CRPC who underwent RP, EBRT, or no local treatment. Various other groups described significantly increased local control rates in men with PCA who underwent RP and ADT as compared to those who were only subjected to ADT alone [10–12].

Symptomatic local recurrences after RP might develop at the anastomotic site, at the resection site of the vas deferens, or at remnants of the seminal vesicles left behind despite RP.

### Palliative Transurethral Resection of the Prostate

Palliative transurethral resection of the prostate (TURP) represents the surgical treatment of choice in men with subvesical obstruction and/or recurrent gross hematuria due to locally recurrent CRPC with or without bladder neck infiltration who are not candidates for a radical surgical approach such as salvage RP (SRP) [14–16]. It is still discussed controversially if palliative TURP might lead to an accelerated frequency of systemic metastases due to the intraoperative tumor cell shedding, which could result in an increased PCA mortality rate during follow-up.

Various groups have described a therapeutic success rate of 70–90% in terms of desobstructing the bladder outlet and prevention of recurrent bleeding and bladder clotting [14–16]. About 10% of the patients will need surgical reinterventions due to local recurrences during follow-up. Another 10–15% will remain on a transurethral or suprapubic catheter due to recurrent subvesical obstruction or surgery-related incontinence. If performed properly, palliative TURP is not associated with a higher frequency of surgery-related complications as compared to standard TURP for the management of benign prostatic hyperplasia (BPH).

In our own series of 83 patients with CRPC who underwent palliative TURP, the mean resection weight was 13 (5–39) g and 15% developed postoperative complications with the need of reinterventions: acute urinary retention in 2, bladder clotting in 3, permanent suprapubic catheter in 3, re-TURP in 3, and urinary incontinence in 2 patients. The perioperative mortality was 0%, and after a mean follow-up of 3.6 years, 32.5% had died due to PCA.

### Palliative Radical Prostatectomy

In case of an infiltration of the pelvic floor or the external urethral sphincter, a wide distal resection of the prostate is mandatory, which would result in urinary stress incontinence with sig-
Table 1. Indications for radical palliative surgery of the lower urinary tract

ECOG performance status 0–1
Charlson comorbidity score ≤ 10
American Society of Anesthesiologists (ASA) status ≤ 2
Life expectancy > 1 year
No infiltration of the pelvic floor (MRI obligatory)
Recurring macrohematuria with necessity of repetitive blood transfusion
Recurring bladder tamponade
Refractory pain in the small pelvis

nificant impairment of the quality of life. In order to combine both adequate resection of CRPC and maintenance of continence, we adapted the surgical technique of continent vesicostomy with the use of either the appendix or a small ileal segment [17]. To achieve a good functional outcome postoperatively, the bladder capacity should be at least 300 ml and no involvement of the upper urinary tract should be present. Following RP, the bladder neck is closed by a 2-layer running suture. If present, the appendix is isolated with its mesenterial blood supply and the tip of the appendix is resected [18]. The bladder is opened and a wide submucosal tunnel is created, through which the appendicular tip is advanced into the bladder and fixed by single sutures. The oral part of the appendix is implanted in the lower-right abdominal quarter or it is connected with the umbilicus to serve as catheterizable stoma. In case of a previously performed appendectomy, the Montie procedure is used to create an efferent stoma: 1 or multiple ileal segments of 5–10 cm in length are resected and opened antimesenterically [19]. The opposite edges of the ileal segment are sutured together over a 14F catheter to create a long efferent nipple, which is implanted in the bladder as described above. Our own experience comprises 31 patients. The mean surgical time was 125 (100–195) min and we did not observe significant intra- or perioperative Clavien grade 3–5 complications. The mean follow-up is 37 (10–78) months, and only 2 cases developed a stenosis at the level of the fascia of the rectus abdominal muscle. The remainder did not develop complications and is continent. This procedure can also be used to treat recurrent bladder neck strictures after RP [17, 20].

Palliative Radical (Cysto-)Prostatectomy

In some patients, local progression of CRPC can result in bladder neck infiltration or infiltration of the dorsal bladder with or without involvement of the ureters. In some cases, significant pelvic pain might result from local extension into the small pelvis. In order to avoid placement of suprapubic tubes, endoluminal stents, or percutaneous nephrostomy (PCN) tubes, radical (cysto-)prostatectomy and urinary diversion might be indicated in well-selected patients [21–23] (table 1). Selection criteria include: (1) Eastern Cooperative Oncology Group (ECOG) performance status 0–1, (2) a still well-circumscribed mass on preoperative magnetic resonance imaging (MRI) studies that makes a complete resection feasible, (3) absence of bulky lymph node disease interfering with a careful ureterolysis, which is mandatory to achieve a well-vascularized ureteroileal anastomosis, (4) absence of significant comorbidities as indicated by a Charlson comorbidity score ≤ 9, and (5) rectosigmoidoscopy and transrectal ultrasound to rule out infiltration of the rectum. In case of documented infiltration, the patient must be informed about the need of rectal resection and the placement of a permanent colostomy.

If the selection criteria are respected, palliative radical cancer surgery can be performed with a low rate of complications and good palliative results. However, the surgery itself is a challenging procedure and it should only be performed by very experienced hands to avoid any harm to the patient (fig. 1a–d). Due to our extensive experience in SRP for radiotherapy failures of PCA and in postchemotherapy retroperitoneal lymphadenectomy, we feel very comfortable with performing extensive radical cancer surgery in those patients [24, 25]. Palliative radical cystoprostatectomy has so far been performed in 40 patients, and no significant Clavien grade 3–5 complications were observed whereas 5 (12.5%) patients developed complications such as lymphoceles, intrapelvic abscess, and paralytic ileus, so that the complication rate of the palliative procedure resembles the experiences with radical cystectomy in bladder cancer [21]. The mean surgical time was 260 (150–430) min and the mean blood loss was 560 (400–1000) ml. The mean time of hospitalization was 14 (10–23) days. The mean survival time of our patient cohort was 20.4 (1–28) months and, most importantly, the mean symptom-free survival was 15.3 (1–25) months, covering 75% of the total survival time. These data are in line with the results of other groups [22, 23].

Symptomatic rectal infiltration makes an anterior and posterior pelvic exenteration necessary. The necessity for a permanent colostomy and an ileal conduit resulting in 2 external drainage systems has to be discussed preoperatively with the patient and his family.

With regard to urinary diversion, we prefer an ileal conduit or even a simple ureterocutaneostomy in selected cases over a continent urinary diversion, since surgery usually is faster, complication rates are lower, postoperative recovery is quicker, and a large proportion of patients already demonstrates an involvement of the upper urinary tract with impairment of the renal function. If ureterocutaneostomy is performed, we prefer a surgical technique allowing 1 external drainage system for both ureters [26, 27]. The left ureter is pulled to the right side retrosigmoidally, and both ureters are spatulated, allowing a side-to-side anastomosis of the ventral and the dorsal aspect of the right and left ureter. The tube-like common ureter is pulled through the stoma and fixed to the skin by evertting sutures similar to an ileal conduit. The outcomes of the patients are equivalent to those of other groups [22, 23].

In summary, palliative radical surgery is a challenging but feasible local treatment option in well-selected patients, if performed by experienced hands. Definitively, palliative radical (cysto-)prostatectomy should be considered more often in the management of men with locally progressing, symptomatic CRPC (table 1).
Ureteral Obstruction

About 5−15% of men with CRPC experience symptomatic or asymptomatic ureteral obstruction. Prior to any endourological, percutaneous, or surgical procedure, treatment must be individualized and risk stratification is of paramount importance [28−32]. A profound decision-making analysis is especially important in patients with an asymptomatic dilatation of the upper urinary tract and a well-functioning contralateral kidney. The potential life expectancy, comorbidities, and the wishes of the patient and his family have to be taken into consideration. Especially in the clinical scenario of minimally invasive procedures such as the placement of DJ stents or PCN tubes, the decision needs to be made carefully since placement of the devices is usually performed easily but stent infection, encrustation, and blockages are common problems that are difficult to manage and which significantly interfere with the patient’s quality of life [30]. New compression-resistant metallic stents seem promising for patients with malignant disease who require long-term urinary drainage [28, 29]. However, even with metallic and self-expandable ureteric stents, the main complications remain in about 25−30% of patients: stent migrations, urinary tract infections, and blockage of stents.

Endourological or percutaneous procedures (DJ, PCN) are indicated in men with symptomatic obstruction, impaired renal function, and a short life expectancy contraindicating reconstructive surgical procedures. If there is any choice, DJ stents should be preferred due to the internal drainage, the significantly longer changing intervals as compared to PCN (4−6 months vs. 6 weeks), and the lesser interference with daily life activities. In case the classical transurethral retrograde implantation is not possible due to a significant obstruction of the ureter, antegrade placement after percutaneous puncture of the lower renal calyceal system might be more successful.

PCN is safe and effective in relieving ureteral obstruction and reasonable survival can be achieved even in patients with renal failure [30−32]. About 75% of the patients who present with severe renal failure will experience an adequate return of renal function [31, 32]. The 1- and 2-year survival rates depend strongly on the
Table 2. Indications for palliative surgery of the upper urinary tract

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<td>ECOG performance status 0–1</td>
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<tr>
<td>Charlson comorbidity score ≤ 10</td>
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<tr>
<td>American Society of Anesthesiologists (ASA) status ≤ 2</td>
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<tr>
<td>Life expectancy &gt; 1 year</td>
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<tr>
<td>Symptomatic obstruction</td>
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<tr>
<td>Significant restriction of the kidney function</td>
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<tr>
<td>Bladder capacity &gt; 300 ml</td>
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<td>No subvesical obstruction</td>
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presence of hormone-sensitive PCA or CRPC. In men with androgen-sensitive PCA, the 1- and 2-year survival rates are 73% and 47%, whereas the numbers decrease to 48% and 19% in men with CRPC [31, 32]. The median survival time of the total cohort of patients with PCA and obstruction of the upper urinary tract is expected to be around 2 years so that PCA diversions are strongly recommended in those patients. However, one has to consider that PCNs are associated with a total complication rate of approximately 65%, including the development of arteriovenous fistulae and gross hematuria requiring additional interventions such as transfusion of red blood cells and superselective embolization [30–32].

When conservative measures have failed, the performance status of the patient is good, and his life expectancy is considerably long, supravesical reconstruction and diversion may be an option and the following treatment options need to be discussed and considered: ureteroneocystotomy, ureteral ileal replacement, and placement of a percutaneous pyelovesical bypass (Detour® system).

Ureteroneocystotomy

Uni- or bilateral ureteral reimplantation might be discussed as an alternative to endoluminal stents or PCN in patients with a distal obstruction of the ureter due to PCA infiltration of the trigone and the ureteral orifices. In some patients, distal ureteral resection and reimplantation might also be considered if the obstructive ureopathy is due to lymph node metastases occluding the ureter in the small pelvis. Patients should exhibit an ECOG performance status 0–1 and a life expectancy of at least 1 year (table 2). They also should have a normal bladder capacity of about 300–400 ml, no evidence of subvesical obstruction, and normal micturition characteristics. Ureteral reimplantation is performed as described for benign ureteral stricture disease, except that we do not prefer the Psoas Hitch technique in order to prevent secondary obstruction due to future lymph node involvement in the area of the external and/or common iliac artery. In the clinical scenario of palliative surgery, we favor an implantation technique usually used in renal transplantation procedures where the ureter is implanted at the bladder dome. Postoperatively, a transurethral catheter is left in place for 5 days and the endoluminal stent is left in place for about 2 weeks. The frequency of infra- and perioperative complications is in the range of 5%, usually comprising minor Clavien grade 2–3 complications. If the above-mentioned surgical technique of ureteral implantation is respected, the long-term outcome is good, with more than 90% of the ureteral implants remaining patent without recurrent obstruction. If the classical Psoas Hitch technique is used, 20–40% of the patients develop local complications during a mean survival time of about 2 years.

Subcutaneous Pyelovesical Bypass (Detour® System)

The subcutaneous pyelovesical bypass has been introduced recently as a minimally invasive surgical procedure to treat malignant ureteral obstruction in patients with considerable but still limited life expectancy. This new device can be applied for bypassing any ureteral obstruction located between the renal pelvis and the urinary tract, independent of its extent and cause [33–35].

The average follow-up of the reported patient cohorts is in the range of 2 years (range 1–92 months). The quality of life was significantly improved, as indicated by the analysis of European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaires. Intraoperative complications are minimal and should be expected to occur in about 10% of patients. Postoperative urinary tract infections and wound complications were encountered in about 15% of the patients. In the long term, about 10% of the patients might develop infections of the Detour system, which might be cured by intravenous application of antibiotics or by explantation of the system in the presence of severe complications. Limited patient numbers and lack of long-term data represent the only drawbacks of this technology.

The Detour system consists of 2 parts: the inner silicone stent with a diameter of 24F and the outer Goretex coat. Placement of the Detour system has to be performed under general anesthesia with the patient in the supine position. Prerequisites are basically identical to those for patients who are candidates for ureteral reimplantation (table 2). In brief, to place the cranial tip of the device, the lower calyx of the dilated collecting system is punctured under ultrasound guidance. The puncture canal is dilated to 27F under fluoroscopy, allowing the placement of an Amplatz shaft, which enables the placement of the cranial tip of the Detour system in the renal pelvis (fig. 2a). To allow an easy implantation at the bladder side, a small, vertical, lower-abdominal minilaparotomy of about 4 cm is performed, the spatium Retzii is explored and the bladder is opened between 2 stay sutures. Using a specific tunneling instrument, a subcutaneous tunnel is created bluntly between the flank incision and the urinary bladder so that the prosthesis can be advanced through the hollow tunneling instrument (fig. 2b). The silicone tip is inserted into the bladder and the Goretex tip is fixed to the bladder wall with 4–6 single sutures (fig. 2c, d). 5 days postoperatively, patency of both the bladder and the Detour system is proven via cystography and an excretory urography (fig. 2e).

Summary and Conclusion

Palliative surgery of the lower and the upper urinary tract will become more important in the future due to the availability of new medical treatment options such as abiraterone acetate, enzalutamide, cabazitaxel and radium-223, which significantly prolong sur-
vival. For unknown reasons, medical treatment induces objective remissions in metastatic deposits. However, it exerts only minor responses of the prostate if still in place. Palliative surgery to the prostate includes TURP, RP, or radical cystoprostatectomy with urinary diversion and even anterior and posterior exenteration in well-selected patients. If performed properly, patients will survive 75% of their remaining lifetime without symptoms due to local progression of the prostate. Symptomatic involvement of the upper urinary tract might necessitate the placement of endoluminal DJ stents or PCN in men with poor performance status and short life expectancy. In men with an ECOG performance status of 0–1, reconstructive surgery including ureteral reimplantation, ureter ileal replacement, or placement of a subcutaneous pyelovesical bypass represents a feasible treatment option. The indication to perform one of the above-mentioned surgical approaches needs to be discussed in a multidisciplinary tumor board. Both the urologist and the medical oncologist need to be well informed about the surgical palliative treatment options in men with CRPC.

**Disclosure Statement**

The authors declare no conflicts of interest.
References