Advanced prostate cancer: place of surgery

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Introduction

The definition of advanced prostate cancer is confusing: T4, T3b and also T3a prostate cancer stages are considered by many as advanced diseases and the treatment advocated is often hormonal treatment in combination with radiotherapy. Furthermore, clinically node positive, pathologically node positive and metastatic disease, either asymptomatic or symptomatic all belong to the group of advanced prostate cancers as well as hormone sensitive and hormone refractory prostate cancer.

It is therefore not obvious how to distinguish early from advanced prostate cancer. To which category belongs a pT2-3 with negative surgical margins and PSA persistence, a pT2-3 with positive surgical margins, and a pT4? To which category belongs the radical prostatectomy patient with PSA (Prostate Specific Androgen) persistence, with early PSA rise, with late PSA recurrence or the patient who was treated with radiotherapy who never reached a PSA nadir below 1 ng/ml or who has PSA relapse after having reached an initial nadir?

It is therefore proposed to use the terminology of *early* prostate cancer for the T1T2 cases and to consider as *locally advanced* all tumors that are clinically extending outside the prostate capsule (T3-4) for which local treatment could still be an option.

Advanced prostate cancer is then the terminology to be used for the Tx N+M+ patients where cure cannot be obtained by local treatment.

Place of surgery in advanced prostate cancer

In advanced prostate cancer, the role of surgery is minimal and aims at symptomatic relief for problems that can occur in locally incurable patients suffering from e.g. lower urinary tract obstruction or incontinence. In these patients indeed a transurethral resection of the prostate can be proposed. Others can be helped by insertion of a suprapubic cystostomy or by upper urinary tract diversion by nephrostomy tubes or insertion of a double J ureteral stent. Surgery can also be necessary in patients that suffer debilitating radiocystitis or radiorectitis after radiotherapy and that might benefit from a salvage cystoprostatectomy or from urinary or fecal diversions.

Surgical castration as hormonal therapy for advanced prostate cancer is still the cheapest and equally effective treatment available. However, this surgical way of androgen deprivation is no longer popular in Western Europe and LHRH (Luteinizing Hormone Releasing Hormone) agonists have greatly taken over. Many urologists will still perform surgical castration when the patient becomes hormone refractory to guarantee continued androgen deprivation without the need of further expensive medication.

Place of surgery in locally advanced prostate cancer

Despite the stage migration since the introduction of PSA, about 10% of men detected with prostate cancer present with locally advanced disease. These patients have a substantial risk of tumor progression either by local recurrence after definitive treatment or by lymph node invasion or by distant metastases.

Locally advanced T3 prostate cancer is an aggressive disease for which watchful waiting is not an option in patients with sufficient life expectancy since local progression and systemic progression occur within a few years in about all patients. Local and systemic progression has been reported in 100% and 87% respectively within 36 months [1]. The reasonable results obtained by radiotherapy alone were significantly improved by adding hormonal treatment, and randomized trials have shown a clear advantage of this combination treatment as concerned to cancer specific and overall survival [2,3]. Since these publications, many clinicians have adopted a combination of radiotherapy and hormonotherapy as the golden standard for T3 prostate cancer. However, this combination treatment was never shown to be superior to surgery

alone or surgery in combination with either early or late radiotherapy or/and hormonotherapy. Therefore the role of radical prostatectomy in locally advanced prostate cancer remains to be further clarified.

The goal of the treatment of locally advanced prostate cancer is to cure a deadly disease, to prolong survival or the metastasis free survival and to improve the quality of life.

Historically, clinical T3 prostate cancer was for many years considered to be an advanced disease for which local treatment was not useful and the reason why only hormonal treatment was offered. However since the good results obtained with radical prostatectomy for T2 prostate cancer (that are often pT3) there has been a limited number of reports from authors who published their experience with radical prostatectomy in clinical T3 prostate cancer patients [4–9]. Emerging from these reports, the European Association of Urology has prepared the guidelines for treatment of prostate cancer. Following these guidelines a radical prostatectomy is recommended for locally advanced prostate cancer for selected patients with a unilateral rather limited T3, a PSA lower than 20 ng/ml, a Gleason score less than 8 and a life expectancy of at least 10 years [10]. Indeed radical prostatectomy for locally confined prostate cancer remains the treatment of choice with the highest local cure rate and therefore surgery continues to play the key role in this stage of the disease. Less effective local treatment by radiotherapy, either conformal 3D external beam radiotherapy or high or low dose brachytherapy (with Iridium or Iodine/Palladium), are an option in patients above a certain age where in the case of recurrent disease, hormonotherapy will still give the patient the chance to reach his normal life expectancy allowing him to die from other causes. It is remarkable that the role of surgery in locally advanced prostate cancer is still a matter of debate although, even in monotherapy, radical prostatectomy can achieve reasonable cure rates.

A major advantage of a primary surgical approach is that this allows a correct pathological staging and to identify those patients with a locally confined prostate cancer (pT2) that can then be avoided the morbidity of an adjuvant treatment with its known toxicity. It also allows to identify those patients who have a high risk of recurrence and can benefit from adjuvant treatment strategies either by radiotherapy (for margin positive disease or seminal vesicle invasion) or by hormonal treatment in case of PSA persistence or of significant lymph node invasion.

Series of radical prostatectomy in monotherapy have shown overall survival rates at 5 and 10 years of 75% and 60% [7]. In a multi-institutional study it was confirmed that radical prostatectomy is the best treatment for clinical T3 when the tumor is not poorly differentiated [6]. Moreover when the serum PSA is lower than 10 ng/ml radical prostatectomy is the treatment of choice [8]. A recent paper on radical prostatectomy in monotherapy reports a 100% 5 year disease free survival. Although a follow up for 5 year prostate cancer is still short, it confirms that radical prostatectomy alone can cure a significant number of clinical T3 prostate cancers [9].

It is obvious that the surgical approach for locally advanced prostate cancer supposes a special expertise of the extensive resection. Indeed the surgery must achieve a more radical extirpation than in the T1-T2 prostate cancers with an extended lymphadenectomy, a safe apical dissection, a wide resection of the neurovascular bundle, at least at the ipsilateral side, a complete resection of the seminal vesicles and in many cases a resection of the bladder neck.

The extended lymphadenectomy in locally advanced prostate cancer is not similar to the limited lymphadenectomy that is performed in earlier stages. Effectively, the lymphatic drainage goes to the external iliac artery, the internal iliac artery and to the paravesical and sacral nodes at the level of the promontorium below the aortic bifurcation [11]. Recent publications have shown that patients with a high risk prostate cancer benefit from such an extensive resection that encompasses all lymphatic tissue between the external iliac vein, the femoral canal, the bifurcation of the common iliac artery, the lateral wall of the bladder and the obturator fossa [12,13].

Even with limited nodal invasion (pN1), 20% of patients remain PSA free at 13 years confirming the role and usefulness of the extended lymphadenectomy [14].

A proper apical dissection necessitates dissection of the puboprostatic ligaments. Preservation of the puboprostatic ligaments increases the risk of a positive margin at the level of the apex or the anterior commissure. The dorsal vein complex is controlled in a conventional way taking good care to section Santorini' s plexus as caudally as possible, far away from the prostate. The dissection of the apex is done with an extensive resection of the neurovascular bundle that is divided lateral to the urethral stump. This then allows to largely excise all tissue anterior to the anterior surface of the rectum. Eventually the contralateral neurovascular bundle might be preserved in younger patients with an important sexual activity under condition that the systematic biopsies on that side were negative and that there is no clinical,

ultrasonographical or magnetic resonance suspicion of tumor present on that side. In older patients preservation of one of the neurovascular bundles does not allow them to regain erectile potency and neurovascular bundle sparing is therefore not useful [15].

In all cases the seminal vesicles need to be completely resected. The resection of the seminal vesicles is important since it was demonstrated that even with invasion of the seminal vesicle, 35% of patients remain PSA free at 13 years under condition that the surgical margins were negative. In patients with tumors at the prostate base it is safe to completely resect the bladder neck and to perform a classical racket closure and reconstruction.

Obviously certain locally advanced tumors will not be cured by surgery alone but are then still amenable for combinations with either hormone treatment or radiotherapy. Neoadjuvant hormonal treatment before radical prostatectomy was well studied in T2 but less well in T3 prostate cancer. Like in the T2 cases, the number of positive margins can be significantly reduced also in T3 cancers, but the neoadjuvant hormonal treatment could not improve the percentages of cure without biochemical or clinical failure nor prolong survival when compared to surgery alone [16–18]. Therefore, although there is a clear benefit of a combination of hormones with radiotherapy, a neoadjuvant hormonal treatment before surgery has been abandoned. This does not mean that no single patients could benefit from this approach [19].

Adjuvant treatment can be proposed to patients who after radical prostatectomy show to have adverse pathology eg. positive surgical margins, extra capsular extension, invasion of the seminal vesicles, invasion of the lymph nodes and poorly differentiated tumors. Radiotherapy can be proposed when there is suspicion of residual tumor after surgery. Postoperative radiation treatment results, as expected, in a decrease of local recurrences but a recent EORTC (European Organisation for Research and Treatment of Cancer) study has shown that there is a significant improvement statistically in the time of progression and in cancer specific survival [20]. The highest benefit is for patients with positive surgical margins but also for those with seminal vesicle invasion. There is less (but still some) benefit for patients with extracapsular extension without margin or nodal involvement.

With these results it becomes obvious that the ultimate results of surgery in combination with early radiotherapy will continue to improve and that the indications for surgery in T3 will further expand.

When PSA failure occurs after having been undetectable for a certain time radiotherapy has been proposed for this so called PSA recurrence. This salvage radiotherapy for isolated PSA recurrence after radical prostatectomy can offer the patient a second chance for cure [21].

Also, hormonal treatment can be started after radical prostatectomy. It has been clinical practice to give early hormone treatment to patients with nodal invasion where it was shown to be highly efficient in non-poorly differentiated tumors to postpone disease progression [4,5]. One might believe that early hormone therapy after surgery in patients with lymph node invasion or with PSA persistence despite negative margins could increase time to progression; but its impact on survival has still not been studied in randomized clinical research.

Classically postoperative hormonal treatment has also been given to patients with seminal vesicle invasion. Since the recent EORTC (European Organisation for Research and Treatment of Cancer) results it seems that those patients with seminal vesicle involvement without other adverse pathological features can benefit from adjuvant radiotherapy so that hormonal therapy can be postponed till an eventual late PSA recurrence.

Discussion

For locally confined prostate cancer radical prostatectomy remains the best local treatment available. For locally advanced stages, surveillance is not indicated since it is an aggressive disease that must be eradicated with the best available treatment. While radiotherapy is probably the only possible approach for T3 prostate cancer with poor differentiation and high PSA, a comparison between radical prostatectomy and radiotherapy in earlier T3 prostate cancer from historically series, is impossible because of the unavoidable selection bias in the 2 treatment strategies.

Certain patients with a clinically locally advanced disease will be cured by surgery by the simple fact that they actually are pT2 or because they have a rather limited extracapsular extension of the disease. Some locally advanced prostate cancers will not be cured by surgery alone. Neoadjuvant hormonal treatment can decrease the number of positive surgical margins but cannot delay the time to recurrence and does not improve survival. Other adjuvant treatment strategies however can be beneficial. Patients with more advanced extracapsular disease that end up with positive margins or with seminal vesicle invasion benefit from adjuvant radiation treatment. Postoperative PSA persistence is amenable to early

hormonal manipulation and late biochemical failures can, depending on PSA doubling time, be due to a local recurrence amenable for radiotherapy or rather suggestive for systemic progression amenable for hormonal treatment.

Locally advanced prostate cancer remains an excellent target for clinical trials combining surgery with adjuvant and/or neoadjuvant measures. Maybe early instauration of chemotherapy in high risk cancers will bring new insight into how this patient group can be optimally treated. A joint effort and a multidisciplinary approach of this disease with intense collaboration between urologists, radiation oncologists and medical oncologists must result in the improvement of the quantity and the quality of the survival of these patients.

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