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Review

Role of Surgery in Treatment of Locally Advanced Prostate Cancer

DOMENICO PREZIOSO, RAFFAELE GALASSO, MARIO DI MARTINO, GENNARO IAPICCA and FABRIZIO IACONO

Department of Urology "Federico II" University, Naples, Italy

Abstract. *The proportion of prostate cancer diagnosed at localized stages increased from 56.7% to 74.0% between 1973 and 1993 ("stage migration"). A corresponding increase in the number of radical prostatectomies performed each year was also noted. Nomograms are mathematical algorithms derived from statistical models that are used to predict outcomes for an individual patient, or for groups of patients. In fact, careful pre-operative patient and tumor selection before radical prostatectomy is mandatory. Locally advanced prostate cancer is defined as tumor that has extended clinically beyond the prostatic capsule, with invasion of the pericapsular tissue, apex, bladder neck or seminal vescicle, but without lymph node involvement or distant metastasis. It is estimated that 12-15% of prostate cancer are stage T3. Overstaging or understaging of this cancer is common. Correct staging of clinical T3 disease is even more difficult and both overstaging pT2 and understaging pT4 or pN+ are common. The goals of treatment for T3 tumors are to cure the disease, prolong survival or metastasis-free survival and improve the quality of life. The authors reviewed the most important studies, investigated radical prostatectomy as monotherapy for locally advanced prostate cancer and the integration of surgery with hormonal treatment. The EAU guidelines on prostate cancer state that radical prostatectomy in locally advanced disease is an option for selected patients with small T3, PSA <20 ng/ml, Gleason score <8 and a life expectancy >10 years. Ten to 15% of clinical T3 are overstaged as pT2. This may lead to the possibility of curing these patients with surgery as the monotherapy. The increased use of nomograms and increased knowledge of recognized prognostic factors could lead to the selection of a large number of patients, often with a long life expectancy, who could benefit from surgical treatment.*

Correspondence to: Prof. Domenico Prezioso, Department of Urology, "Federico II" University, Via Sergio Pansini, 5, 80131 Naples, Italy. e-mail: dprezioso@libero.it

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Epidemiological studies have shown that screening based on PSA has led to a decreased mortality in prostate cancer (1). Furthermore, the proportion of prostate cancer diagnosed at localized stages increased from 56.7% to 74.0% between 1973 and 1993 ("stage migration"). A corresponding increase in the number of radical prostatectomies performed each year was also noted (2).

For patients with localized disease, an assessment of the location, size, extent and histological features of the primary tumor provides prognostic and staging information and is essential for treatment planning. These cancers are best characterized by the clinical stage, Gleason grade and serum PSA level, which are the only features independently predictive of pathological stage and prognosis (3). Pathological stage is determined by histological examination of radical prostatectomy specimens, including the seminal vescicles and the pelvic lymph nodes.

Partin *et al.* developed an algorithm that combined the clinical T stage, Gleason grade in the biopsy specimens and pre-operative PSA levels to predict the pathological stage. This is then assigned as one of four groups: organ-confined, established capsular penetration, seminal vescicle invasion or lymph node metastasis (4). These staging tables offer probabilities for the categories and are widely used in clinical practice. Predicting the pathological stage is important in clinical decision-making and may help to determine the need for more intensive therapy, or for modifying this surgical technique to resect a neurovascular bundle. This is important, not only for the success of a given treatment, but for the assessment of the microscopic extent of the cancer.

Many risk stratification schemes have been published to predict the outcome after therapy (5), but, to date, the nomogram remains the most effective measure for the prediction of success or failure of a therapy (6). Kattan *et*

al. developed the first scale to predict the probability that a patient would remain free of recurrence for at least 5 years (7). Graefen and collegues (8) found, in their classification and regression tree (CART) analysis, that the number of Gleason grades 4 and 5 was the strongest predictor for disease recurrence after radical prostatectomy. More recently, the same group published a nomogram predicting site-specific organ confinement for the safe selection of nerve-sparing-procedures (9). The age of the patient and degree of co-existing diseases play further key roles in the estimation of life expectancy.

Clinically Localized Prostate Cancer - Surgical Therapy: Oncological Outcome

Because clinically localized prostate cancer is a slow growing cancer, an estimated patient life expectancy of at least 10 years should be given before choosing radical prostatectomy. Radical prostatectomy should, therefore, be questioned for patients over 70 years old and should not be performed in the over 75-year age group. However, the progression rate depends on many more parameters like the Gleason score and surgical margins status. The surgical technique employed might influence the long-term results after radical prostatectomy. For surgery to be successful, the cancer must be removed completely. However, the influence of a positive surgical margin on PSA recurrence remains unclear. Hull and collegues (3) found a two or four times higher probability of recurrence per year when the cancer extended to the resection margin. Quinn and collegues (10) found similar results, but, in a sub-analysis of patients with pT2 cancer or seminal vescicle invasion, the margin status was prognostic and an independent predictor of outcome.

Babaian and collegues (11) quantified the length of the tumor at the surgical margin and found that a >3 mm cancer at the resection site had a significant adverse effect compared to positive margins ≤3 mm. Taking into consideration the clinical stage, serum PSA level and biopsy Gleason score, patients can be classified into four risk groups: low-risk (cT1a-T2a or Gleason score 2-6 or PSA<10 ng/ml); intermediate-risk (cT2b-T2c or Gleason score 7 or PSA 10-20 ng/ml); high-risk (cT3a-T2b or Gleason score 8-10 or PSA>20 ng/ml); very high-risk (cT3c-T4 or any T, N1, M1 or any T, any N, M1). While the extremes are accurate, the two intermediate groups are heterogeneous.

The gold-standard treatment for clinically localized disease is radical prostatectomy. The goals of surgery are to excise the cancer completely, to preserve normal urinary control and to restore erectile function to the greatest extent possible. Achieving these goals requires careful surgical planning. Extension of the cancer through the capsule is common and occurs in 20% to 50% of all surgical specimens (pT3b) (12-14). Several recent series have shown that the actuarial non-progression rates after radical prostatectomy are about 70% to 80% of patients at 5 years, 50% to 75% at 10 years and 68% to 73% at 15 years. These patients had no evidence of cancer and had had no treatment for cancer except for radical prostatectomy (15-17).

In multivariate analysis, the only independent clinical prognostic factors were stage, grade and PSA level, with stage having the weakest association (3). The single most powerful prognostic factor was the pathological stage of the cancer (3, 18). If the cancer is confined to the prostate, 85% to 93% of patients will remain free of recurrence at 10 years. Nevertheless, prognosis also depends on grade and surgical margins status, and is best estimated from a nomogram that considers all these features, along with the pre-operative PSA level (19).

A detectable and rising post-operative PSA level (usual threshold 0.2 ng/ml) is considered to be a biochemical recurrence, being reported in 25% to 40% of cases after 10 years (20). Some contemporary series have reported more favorable results (3). Not all patients with PSA failure need immediate intervention. Pound and collegues (20) showed that the median time from the occurrence of detectable metastases after biochemical recurrence was 8 years, and the median time from the manifestation of metastases to death from prostate cancer was 5 years. If histopathological parameters and PSA kinetics support local rather than systemic recurrence (histopathological stage pT3a or positive surgical margin, Gleason score not greater than 7, PSA velocity up to 0.75 ng/ml per year, PSA doubling-time greater than 12 months), prostate bed irradiation may be an option (21). In the case of positive lymph nodes, radical prostatectomy is controversial. Surgery alone does not appear to be curative, with a high risk of progression.

Locally Advanced Prostate Cancer

Locally advanced prostate cancer is defined as a tumor that has extended clinically beyond the prostatic capsule, with invasion of the pericapsular tissue, apex, bladder neck or seminal vescicle, but without lymph node involvement or distant metastasis (22). It is estimated that 12% to 15% of prostate cancers are stage T3 (23, 24). Overstaging or understaging of early prostatic cancer are common. The correct staging of clinical T3 disease is even more difficult, and both overstaging pT2 and understaging pT4 or pN+ are common (25, 26). The overstaging of T3 prostate cancer occurs in about 13% to 27% of cases, meaning that these patients, who have organ-confined disease, can be cured with complete removal of the gland.

The goals for treatment of T3 tumors are to cure the disease, prolong survival or metastasis-free survival and improve the quality of life. In locally advanced prostate cancer, watchful waiting has been proposed. Allison and

collegues reported local and systemic progression rates with watchful waiting in cT3 patients of 100% and 87% within 36 months (27). However, watchful waiting can be considered if the patient has a short life expectancy (<5 years), or if he is asymptomatic with a low Gleason score.

Recently, radiotherapy has been the most frequently used treatment option for T3 tumor. Perez and collegues described a 5-year disease-free survival rate after radiotherapy as monotherapy of about 50% to 70% (28). Arcangeli *et al.* reported an overall survival at 5 and 10 years of 66% and 42.5%, with a cancer-specific survival at 5 and 10 years of 72.5% and 57.4% (29). However, increasing evidence suggests that radiotherapy does not provide long-term control of prostate cancer (30). Lawton *et al.*, in RTOG trial 85-31 with 977 patients, and Bolla *et al.*, in an EORTC phase III trial with 415 patients, showed a clear advantage of combination therapy in cancer-specific and overall survivals, but the optimal duration of therapy was uncertain (31, 32).

Role of surgery. Today, surgical treatment is still controversial because tumor extension outside the prostate and the limited ability of surgeons to excise a wide margin of healthy tissue might prevent radical resection of the tumor. This leads to positive margins of resection and tumor recurrence (33). The EAU guidelines on prostate cancer have mentioned that radical prostatectomy in locally advanced disease is an option for selected patients with small T3, PSA <20 ng/ml, Gleason score <8 and a life expectancy >10 years (34). The surgical approach necessitates extensive resection. Several studies of progression and survival after radical prostatectomy for locally advanced prostate cancer have been published, but many patients were treated with neoadjuvant or adjuvant therapy (35).

Radical prostatectomy as monotherapy. Since Walsh and collegues described the surgical anatomy of the prostate with the definite possibility of preserving the neuro-vascular structures, the surgical approach has been confirmed as the standard treatment for locally confined and locally advanced prostate cancer (36).

In 1994, van den Ouden and collegues (37) published interesting results of progression and survival with long follow-up of surgery as monotherapy in T3 prostate cancer. Later, other authors reported their experience with radical prostatectomy in cT3 tumors (38). In 1998, van den Ouden's group (39) analyzed 83 patients who had had radical prostatectomy as monotherapy for locally advanced prostate cancer, and found that surgery alone could produce acceptable results. The 5-year and 10-year overall survival rates were 75% and 60%, while the cancer-specific survival rates were 85% and 72%. The clinical progressions (defined as local recurrence and/or distant metastasis) were 41% and 69%. The local recurrence (defined as histologically-proven evidence of tumor cells at the bladder-urethral anastomosis) were 18% and 44%, and the distant metastases (defined as the presence of new hot-spots on bone scan, ultrasonography, chest X-ray or CT) were 31% and 50%, respectively. Biochemical progression (defined as the first occurrence of two consecutive PSA values greater than 0.1 ng/ml) at 5 years was 71%. Comparing these results with those in the literature, in which adjuvant therapy was often used, it is evident that adjuvant therapy does not prolong survival. In this study, the patients were divided in two sub-groups, T3G1-2 and T3G3, and the results were compared to those of 190 patients with locally confined disease. Progression and survival in patients with a T3G1-2 tumor were not significantly different from patients with a locally confined tumor. However, patients with poorly-differentiated tumors (T3G3) had early progression and needed adjuvant treatment. It was interesting that, on pathological evaluation, the prostatic tumor was organ-confined (pT2) in 15 patients (18%), pT3 in 64 (77%) and pT4 in four (5%). Lymph node metastases were present in ten patients (12%). Patients with minimal lymph node metastases (one metastasis less than 5 mm) showed benefit from radical prostatectomy (40), but the remaining patients received adjuvant therapy (39).

Gerber and collegues suggested that surgery as monotherapy has a role in T3 disease with low to intermediate grade tumors (38). Van Poppel's team showed that radical prostatectomy can provide a cure for well-selected cT3 disease, in particular if the serum PSA is below 10 ng/ml (41). Recently, in 2004, Martinez de la Riva *et al.* reported an overall survival and a cancer-specific survival of 97.6% and 100%, respectively, at a mean follow-up of 68.7 months, with radical prostatectomy as monotherapy for clinical T3 disease (42).

Several investigators have suggested that surgical resection could be a valid option for patients with a life expectancy of less than 10 years. The appropriate candidates for surgery are men in reasonably good health, aged 73 years or younger, with organ-confined disease. In a Mayo Clinic study, 191 patients who were <55 years old and 51 elderly patients aged >75 years old underwent radical prostatectomy. Compared with the younger group, the elderly patients had a higher stage, about 70% of them had no perioperative complications and none of them died within 5 years of the operation. The major criticism of these trials is that the older patients were well-selected, healthy men (43). Unfortunately, in many old patients, radical surgery does not appear to improve survival (44, 45).

Neoadjuvant therapy. Neoadjuvant hormonal therapy (NHT) prior to surgery is not a new concept. In the past, it has been suggested that it may improve the rate of negative margins.

However, it is a highly controversial topic and its benefit in term of disease-free survival has not yet been established.

In 1999, Iselin *et al.*, reported data on a group of patients with organ- or specimen-confined prostate cancer who had died with, or of, cancer at 15 years (46). The median cancer-specific survival in patients with positive margins was 12.7 years. The rate of biochemical PSA failure in patients with organ-confined, specimen-confined and margin-positive disease at 5 years was 8%, 35% and 65%, respectively. These findings underscored the prognostic importance of negative surgical margins. The aim of NHT is to decrease the rate of positive surgical margins and, perhaps, to improve patient outcome after radical surgery.

The outcome of NHT in cT2 prostate cancer showed the reduction of positive margins, while there are no clear data of efficacy in stage cT3. There are at least seven randomized studies that investigated 3 months of NHT in patients with localized disease (cT1-2). These studies showed that the rate of positive margins was reduced by about 50% in those treated with NHT. Many of these patients had not reached an undetectable PSA level before radical prostatectomy. The biochemical disease-free outcome at 3 years was similar in those had or had not received NHT. There could be several reasons why the studies of 3-month NHT did not result in differences in PSA recurrence. First, the concept that androgen ablation may eliminate a sufficient number of cells may be flawed. Second, these trials were designed only to detect the effects on surgical margins, not on PSA recurrence. Finally, follow-up may also have been insufficient since the number of PSA recurrence events in these studies was small. The duration of NHT may not have been long enough to have had a significant effect (47-54).

A prospective randomized study of 547 men comparing 3 *vs.* 8 months of NHT has been completed by the Canadian Uro Oncology Group to determine whether longer hormone therapy influences the surgical outcome in cT2 disease (55). After 8 months of therapy, the positive margin rate decreased another 50% relative to the 3-month arm, from 23% to 12%, using leuprolide (7.6 mg *i.m.*, monthly) and flutamide (250 mg orally, three times daily).

A subsequent analysis of the PSA recurrence outcomes in this study at 3 years showed that there was no statistically significant difference in outcome between the two treatment groups if all patients were considered *in toto* (56). Sub-analysis of patients stratified by risk group showed that the intermediate-risk patients (PSA between 10-20, pT2b) seemed to benefit the most from a longer course of NHT.

There have been over 20 trials investigating 3-month NHT prior to radical prostatectomy for cT3 disease. Downsizing of the prostate and a decrease in tumor volume were observed, but pathological downstaging was uncommon. A similar rate of positive margins were seen, with or without NHT. Also, the rate of seminal vescicle (57, 58) and lymph node metastasis (59) were the same in the hormone-treated and untreated groups. Moreover, Goldenberg and collegues identified a higher rate of seminal vescicle invasion in the neoadjuvant group (cyproterone acetate) than in the radical prostatectomy alone group (27.7% *vs.* 14.3%, $p=0.035$: S) (58). An important caveat is that conventional histological staining is compromised after NHT. Also, it has been stated that the staining conditions for NHT overstimate organ confinement (45% *vs.* 27.3%) and understimate capsular penetration (45% *vs.* 68%) and positive surgical margins (13% *vs.* 22%) (60).

The Southwest Oncology Group (SWOG) study 9109 investigated 4 months of NHT in cT3-4 prostate cancer (61). Sixty-two patients received 4 months of combined androgen blockade (goserelin plus flutamide) and were followed-up for a median of 6.1 years. Organ-confined disease was found in 62% of patients and only 30% had positive margins. The 5-year progression-free survival was 70% and overall survival 90%. These results suggest that a more extended course of NHT may be of benefit to patients with locally advanced disease.

NHT produces an androgen ablation, so it is associated with morbidity, even after short-term use (62). The adverse events reported are hot flashes, gynecomastia, nipple tenderness, gastrointestinal diseases, dyspnea and venous trombosis, depending on the treatment given. Additionally, NHT is characterized by high costs related to the treatment duration, additional visits and PSA measurements. However, it was reported that NHT decreases the cost of other aspects of treatment, including operating time, hospitalization, blood loss or morbidity (63). However, these effects, in particular the reduction of bleeding and of operating time, were not confirmed in prospective randomized trials (59, 64). Although the prostate size was decreased by NHT, there was no difference in operative difficulty and the rate of intra- and post-operative complications between radical prostatectomy alone and NHT (66, 67).

In conclusion, neoadjuvant therapy decreased the rate of positive margins in cT2 tumors, but no study has shown an improved PSA-free or disease-free survival advantage with a follow-up of up to 4 years. Therefore, its use remains under investigation. Also, there is no evidence for a real benefit of NHT prior to surgery with respect to PSA progression in both cT1-2 and cT3 disease. A positive effect on the disease-specific and overall survival still requires further investigation. The duration and administration of NHT has not yet been elucidated, so long-term follow-up of the randomized trials is required.

Adjuvant therapy in pathological clinically advanced disease. For many years the administration of adjuvant hormonal therapy after radical prostatectomy has been shown to be

beneficial in the control of T3 disease. Several studies have suggested adjuvant therapy in poor-prognosis pT3 disease (25, 35, 68). While most patients with localized disease are cured by definitive therapy (radiotherapy and surgical therapy), about 1/3 of patients eventually recur. Most patients initially have biochemical failure and, in this situation, the disease is present as local or metastatic foci too small to be detected by conventional techniques. The goal of adjuvant therapy is to target these microscopic foci of disease. The earliest studies examining the use of adjuvant hormone therapy after prostatectomy were performed by the VACURG (Veterans' Administration Co-operative Group) (69). This study (compared with placebo) suggested that early hormone therapy might be of benefit *vs.* placebo followed by treatment with hormones when there is evidence of disease progression.

Recently, Messing *et al.* performed a randomized trial assessing the effects of adjuvant hormone therapy following radical prostatectomy in advanced disease (70). This phase III ECOG study treated 98 randomized patients with either androgen suppression or hormone therapy (goserelin or orchiectomy) after signs of progression. Overall survival was improved in the first group (85.1% *vs.* 64.7%; $p=0.02$) with a median follow-up of 7.1 years. Prostatic cancer-specific mortality was markedly reduced (6.3 % *vs.* 34 %; $p<0.01$) by immediate therapy.

The patients in the adjuvant group had decreased rates of disease recurrence (14.9% *vs.* 89.4%; $p<0.001$) compared with those receiving delayed therapy. Choo and collegues showed that early adjuvant radiotherapy (RT) after surgery was beneficial in cT3 tumors (71). Post-operative RT gave a lower risk of local relapse when compared to surgery alone. A recent EORTC trial showed a statistically significant benefit for post-operative RT in high-risk patients after surgery in terms of time-to-progression and cancer-specific survival (72).

Conclusion

In clinically localized prostate cancer, the surgical approach has often been discouraged, although the results of radical prostatectomy in monotherapy for well-selected patients have been encouraging. Improvement in staging, a better selection of patients and expert surgery with extensive resection mean that radical prostatectomy is a valuable adjuvant treatment option. One of the key points before radical prostatectomy is to evaluate pre-operatively the risk of possible histological T3 in order to determine the local extent of the tumor, the involvement of the seminal vescicle, lymph nodes and/or other distant sites.

Pathological findings from biopsy cores, PSA levels and clinical staging by digital rectal examination are useful to evaluate the pathological stage. Nomograms combining this data are statistically predictive, but their individual use for therapeutic decision-making is uncertain. Imaging data (TRUS, CT scan, PET scan, USPIO, immunoscintigraphy, endorectal MRI for assessment of local extension, lymph node status and distant metastasis) (73) are missing. These diagnostic tools could be useful to enhance the pathological staging, however, to date (74-77), there is no highly sensitive and specific widespread imaging test for local staging of prostate cancer.

In conclusion, it should be considered that 10% to 15% of clinical T3 are overstaged and found to be pT2 (64), leading to the possibility of curing these patients with surgery as monotherapy. Moreover, the increased use of nomograms and increased of knowledge of recognized prognostic factors can select a large number of patients, often with a long life expectancy, who could benefit from surgical treatment. Adjuvant therapy with either radiation or hormones can still be applied, depending on the definitive pathology of the resected specimen.

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