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Locally Advanced Prostate Cancer at High Risk of Progression: A Treatment Strategy, A Review of Clinical Studies

M. S. Salomov

Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology of the Surkhandarya branch Uzbekistan Termez, st. Ibn Sina 38a

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Abstract: The clinician doctors should be decided the difficult task of determining the exact stage of prostate cancer. This concerns, first of all, stage T3 - or locally progressive, the presence of which indicates that the tumor is spreading beyond the capsule. Prostate cancer is the most common solid tumor in Europe, with an incidence rate of 214 cases per 1,000 men, which is higher than for lung and colorectal cancers [3]. In 2013, prostate cancer ranked 3rd in the structure of oncological diseases in men in Russia, 29,158 new cases of the disease were recorded, 9,535 patients died from prostate cancer. Over the past 5 years, the number of patients with PCa in our country has increased, in particular, in 2015 - 372, in 2016 - 443, in 2019 the number of patients reached 483 (an increase of 23%). There is also an increase in the incidence, which in 2015 amounted to 1.2 patients per 100 thousand of the population, in 2019 this figure was 1.5. (Tillyashaikhov M.N. et al., 2020). The optimal therapy for patients with clinically locally progressive prostate cancer has not been finally determined, and the tactics of treating these patients cause a lively discussion. Many controversial issues regarding the choice of a particular method remain unresolved.

Keywords: locally advanced prostate cancer, prostate cancer recurrence, hormone therapy, chemotherapy, radiation therapy.

Background. Recommendations for the treatment of patients at high risk for progression of non-metastatic prostate cancer have changed significantly over the past few years.

A high risk of non-metastatic PCa includes all cases with an initial prostate-specific antigen (PSA) level of more than 20 ng/ml, or a Gleason index value of more than 7, or stage T3 [5]. In the era of PSA diagnosis, locally advanced PCa accounted for about 10–20% of newly diagnosed PCa cases [7], while about 20% of localized PCa cases have a high risk of progression [8]. Expectant management, external beam radiation therapy (EBRT), radical prostatectomy (RP) with or without lymphadenectomy, androgen deprivation therapy, or any combination thereof, are used to treat non-metastatic PCa at high risk of progression.

Radical prostatectomy has become widespread due to the fact that it most closely matches the concept of an –ideal operation in relation to the treatment of patients with localized forms of prostate cancer: radicality, ablaticity, a high probability of maintaining preoperative quality of life, and the absence or low probability of any complications [9].

Methods of choice in the treatment of locally progressive prostate cancer are radical prostatectomy, external beam radiation therapy, hormonal therapy \ vigilant observation \. In many cases, a multimodal treatment principle is used. Radical prostatectomy can achieve high tumor-specific survival in clinical stage T3. Good patient selection is a prerequisite for this. In this case, it is possible to achieve tumor-specific survival for the pT3 stage, the same as for pT2 tumors.

The aim to combine the available information on the choice of treatment for patients in a group for examination with local recurrence. Study of the clinical significance of risk factors for local recurrence after complex treatment in patients diagnosed with locally advanced prostate cancer.

Material and methods. To determine the optimal method of treatment, an examination is necessary to exclude metastatic lesions [3, 5, 9–10]. For this, magnetic resonance imaging (MRI) and bone scintigraphy are recommended. New technological advances in metabolic imaging and nano-MRI can detect the spread of PCa at an early stage [11–13]. The determining factor in the choice of treatment is life expectancy, as well as concomitant diseases [14]. Poor prognostic factors for high-risk non-metastatic PCa that dictate treatment options include a high Gleason score, high initial PSA, extracapsular extension and/or positive surgical margin, seminal vesicle and lymph node invasion. ADT in combination with EBRT or RP with extended pelvic lymph node dissection is the treatment of choice in the treatment of non-metastatic PCa at high risk of progression in patients with a life expectancy of more than 5 years [5]. Although it should be noted that the influence of life expectancy on the choice of treatment method remains debatable at the moment [1].

Results. The evidence for preference for radiotherapy with ADT is based on several randomized clinical trials (Table 1). The combination of ESWL with ADT compared with ESWL without ADT statistically significantly reduced the risk of biochemical recurrence, clinical progression, local recurrence, and distant metastases by 24%, 19%, 36%, and 28%, respectively, with no increase in overall adverse events (relative risk (RR) 0.92; 95% confidence interval (CI) 0.87–1.11), genitourinary toxicity (RR 0.66; 95% CI 0.36–1.22), gastrointestinal toxicity (RR 0.69; 95% CI 0.46–1.03) and mortality from cardiovascular complications (0.87 RR; 95% CI 0.70–1.09) [23]. In general, the combination of ADT with standard doses of EBRT improves overall and cancer-specific survival rates without a significant increase in toxicity [24–27]. It should be noted that all these studies were carried out in the era of suboptimal doses of EBRT, with the highest total dose of 66 Gy, while in modern conditions the recommended total dose is 76–78 Gy [4, 21]. Currently, there is no evidence not to use ADT in combination with EBRT in the treatment of patients with non-metastatic PCa at high risk of progression. In patients with non-metastatic PCa at high risk of progression, the combination of long-term adjuvant ADT and radiotherapy showed a statistically significant increase in overall survival compared with short-term ADT. It should be noted that the use of short-term ADT in combination with EBRT did not show any effectiveness in patients with a low risk of progression, while there was an increase in cancer-specific and overall survival in patients at an intermediate risk of progression.

Table 1

The advantages of addition neo\adjuvant ADT to beam therapy						
Research	Duration of neo\adjuvant ADT	Number of patients	Classification of PCa	Dose of beam therapy	Median observation	5 years survival
RTOG 8531	till progression	56	cT1-2N1M0 or cT3-4N0-1 M0 or pT3 after radical prostatectomy	40-42 Gr and 20-22 Gr on the place of the prostate	3 years	65%
EORTC22342	Goserilin 3 years Siproteron acetat 1 month	41	T1-2 stage 3 M0 or T3-4 N0-1 M0	50 Gr+20 Gr to prostate	4.1 years	72%
TROG9321	3-6 month	46	T2b-4N0M0	66 Gr to prostate and place to	2.8 years	no data

				prostatectomy		
RTOG8610	2 month	53	T2-4N0Mx	44-46Gr to small pelvis and 21-22 Gr to prostate	4.9 years	46%

Radical prostatectomy with extended lymphadenectomy

Opposite opinions are expressed regarding the possibilities of recognizing intra- and pericapsular tumor invasion. The presence of different points of view and debatable questions about the advisability of neoadjuvant hormone therapy before radical prostatectomy prompted us to conduct a clinical assessment of our own observations, which will be discussed below. Retrospective data show good oncological outcomes, with 10-year cancer-specific survival in men at high risk of non-metastatic PCa ranging from 60% to 92% [16,17]. These studies showed a pattern between cancer-specific survival and the number of initial adverse factors (PSA above 20 ng/mL, Gleason index above 8, clinical stage T3 and above, invasion into the seminal vesicles).

Long-term results of the EORTC 22342 randomized study of postoperative radiotherapy after RP showed an increase in biochemical disease-free survival in the group of patients younger than 70 years with a positive surgical margin. At the same time, in patients older than 70 years, postoperative adjuvant EBRT caused an increase in the frequency of genitourinary complications. An improvement in biochemical disease-free survival was also demonstrated in the ARO 96-02 study, which evaluated early ESW after RP at pT3 stage and with a positive surgical margin, compared with observation (56% vs 35%; $p < 0.001$) [15,18].

In cases of positive lymph nodes (pN+) in stage T3b, a carefully performed radical prostatectomy with mandatory lymphadenectomy is effective. This benefit is unambiguously evidenced by the data presented. L. Cheng et al (2001) [12] reported a relatively good cancer-specific 10-year survival rate of up to 74% after radical prostatectomy in the pN+ stage. The risk of progression was proportional to the size of the lymph nodes. With minimal lymph node involvement, cancer-specific mortality increased only slightly compared with patients without lymph node involvement. Survival was 94%

Multimodal approach

Several strategies are currently available to prevent recurrence and improve outcomes in patients with locally advanced prostate cancer after RP with neoadjuvant and adjuvant therapy [10,16]. Most experts believe that in locally advanced prostate cancer, multimodal treatment has the greatest advantages, in which surgical intervention occupies only part of the protocol [7,13,15]. early adjuvant and late salvage EBRT or hormonal therapy are also included in the treatment regimen in patients with locally advanced prostate cancer [18]. The Mayo Clinic suggests considering rPE as the first step in a multimodal approach to managing patients with cT3 prostate cancer. Yes, J.F. Ward and J.M. Slezak's a large retrospective study followed by a 15-year follow-up showed that 78% of patients with pT3 disease received adjuvant and salvage therapy (hormonal therapy, EBRT, or both) after RP. The authors classified rPE as an important part of the multimodal approach in locally advanced prostate cancer [12].

Neoadjuvant therapy

It is widely known that the goal of neoadjuvant hormone therapy is to reduce tumor volume, reduce the likelihood positive resection margins and reduced risk of both local and distant recurrence metastases in patients with prostate cancer with intermediate and high risk [9]. however, neoadjuvant hormone therapy is not usually recommended in prostate cancer in the clinical stage cT3 and its role with such a tumor process remains controversial. some experts believe that the described treatment regimen increases the complexity of the surgical intervention [6]. Many studies have shown the effect of short courses (6 weeks–4 months) of neoadjuvant hormone therapy (including maximum androgen blockade) to rPE. Foreign studies report a decrease risk of postoperative positive margins and

biochemical recurrence. However, no effect of this approach was recorded on overall or cancer-specific survival [12,14].

Systemic therapy for patients with non-metastatic prostate cancer at high risk of progression

A systematic review of 10 randomized trials comparing neo/adjuvant ADT before RP, on the one hand, and RP as monotherapy, on the other hand, showed similar overall and cancer-specific survival, but noted that ADT significantly reduced the risk of positive surgical margin (RR 0.49; 95% CI 0.42–0.56; $p < 0.00001$) and lymph node involvement (RR 0.49; 95% CI 0.42–0.56; $p < 0.02$) [18].

According to the EAU guidelines, adjuvant ADT is the standard of care in patients with lymph node involvement, and there is no evidence of benefit of adding ADT to RP in patients with seminal vesicle invasion [4]. In a retrospective study of patients with pT2-4pN1 undergoing RP with extended pelvic lymph node dissection, adjuvant ADT with radiotherapy showed better results compared with ADT alone. Further randomized clinical trials are needed to confirm these data [14].

In patients with a life expectancy of less than 5 years, neither RP nor ADT is used. The combination of EBRT and ADT is recommended for the treatment of patients with a Gleason score of 8 or higher in combination with clinical stage T3 and a PSA level above 20 ng/mL. If, for one reason or another, ESWL is not possible in such patients, ADT alone can be offered as an alternative [5].

Several phase III trials are investigating the effects of neoadjuvant and adjuvant chemotherapy in PCa, with or without hormonal therapy. It will take a long time to evaluate the results of treatment of such patients, although it is known that only a few of these studies have resulted in planned sets. The use of neoadjuvant chemotherapy has been evaluated in high-risk PCa. The combination of hormonal therapy and chemotherapy with docetaxel, apparently, leads to a decrease in the prevalence of the tumor process with satisfactory indicators of overall toxicity. There have been several phase III trials evaluating the benefit of chemotherapy over surgery for ADT, but the results of these trials have not yet been published [18].

A phase III randomized trial (CALGB 90203) is currently underway to evaluate neoadjuvant chemotherapy and ADT before RP versus direct RP in patients at high risk for localized and locally advanced PCa (stage T1-3aN0M0). A total of 750 patients were treated in the study; in the main group, patients underwent multimodal treatment, which included 6 cycles of neoadjuvant chemotherapy with taxanes against the background of ADT followed by radical prostatectomy; in the control group, only RP was performed. The primary endpoint of the study will be progression-free survival at 5 years [4,5,8].

GETUG 12 is a phase III French randomized trial comparing four cycles of neoadjuvant docetaxel and estramustine before topical therapy plus ADT for 3 years versus topical therapy plus 3 years of ADT. A total of 413 patients with high-risk locally advanced or localized PCa were randomized to this protocol, the majority (87%) of whom received external beam radiation therapy.

The data from this study significantly demonstrated a significant improvement in progression-free survival in the combination group compared with ADT alone (RR 0.75; 95% CI 0.55–1.01; $p = 0.06$). It also showed a benefit in PSA response, which was significantly higher in patients treated with chemotherapy than in patients treated with ADT alone. Analysis of adverse events showed that the combination of docetaxel with estramustine has an acceptable toxicity profile [1,7,15].

The phase III study RTOG 0521 was designed to evaluate the efficacy of adjuvant chemotherapy with docetaxel in combination with ADT and external beam radiation therapy. This study included high-risk PCa patients receiving ADT for 2 years in combination with radiotherapy with or without adjuvant docetaxel chemotherapy for 6 cycles. The primary endpoint was overall survival. Data from the RTOG 0521 study were presented at ASCO 2015. Thus, 5-year progression-free survival was 66% for ADT + EBRT and 73% for ADT + EBRT + chemotherapy ($p = 0.05$; RR 0.76; 95% CI: 0.57–1.00), 4-year overall survival in the chemotherapy group was 93% versus 89%, respectively. Toxicity was acceptable [17].

Conclusion

Treatment options for patients at high risk for non-metastatic PCa should always be discussed within a multidisciplinary team of physicians. Conversation with the patient, identification of clinical and pathological signs of the disease plays an important role in choosing a treatment strategy. Clinicians should be aware that ADT alone is not an appropriate treatment option for patients at high risk for non-metastatic PCa. At the same time, a thorough examination of patients is necessary in order to exclude distant metastases and adequately assess the somatic status of the patient.

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