MULTIMODAL THERAPY FOR PATIENTS WITH LOCALLY ADVANCED PROSTATE CANCER A RETROSPECTIVE STUDY ON PATIENTS TREATED AT CLINICAL COUNTY HOSPITAL OF SIBIU, BETWEEN 2012-2016

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Abstract: *Objective: To indentify management strategies in patients with locally advanced prostate cancer receiving multimodality therapy at Clinical County Hospital of Sibiu, from January 2012 through December 2016. Methods: the study included 179 patients with locally advanced prostate cancer who were treated by radical prostatectomy (RP), radiotherapy with adjuvant androgen deprivation therapy or neoadjuvant androgen deprivation therapy (ADT) followed by adjuvant ADT, or only hormone therapy. Trends in multimodality therapy were assessed over time to identify treatment patterns in locally advanced prostate cancer. Results: 116 (65%) patients were treated with radiotherapy, external beam radiotherapy (EBRT). 13 patients with better performance status, no IRM nodes enlargement had radical prostatectomy (RP). Neoadjuvant hormone therapy before radiotherapy was the treatment in 9 (5%) of these 179 patients; all of them, received adjuvant hormone therapy after RT. Of the 41 (23%) patients treated with primary hormone therapy alone, combined androgen blockade was the treatment in 22 (54%) and 19 (46%), had analogues LHRH alone or Bicalutamide alone. Conclusion: treatment for advanced non-metastatic prostate cancer is a multimodality approach. Radiotherapy with adjuvant ADT may be considered the standard therapy for these patients.*

INTRODUCTION

Clinical staging according to AJCC.(7) Locally advanced prostate cancer includes T3 and T4 disease (where tumour extends beyond the prostate capsule and may invade local structures) (table no. 1) and any tumour that has metastasised to local lymph nodes cN+ (table no. 2) without presence of metastasis, M0.(1)

Table no. 1. T3 and T4 - TNM prostate cancer (2)

T3 Tumour extends through the prostatic capsule *
T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b Tumour invades seminal vesicle(s)

*) Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

Table no. 2. Defining category N according TNM staging for prostate cancer (2)

N - Regional lymph nodes*
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis **

*) The pelvic nodes below the bifurcation of the common iliac arteries
**) Laterality does not affect the N-classification

D'Amico and colleagues described three prognostic groups in advanced non metastatic prostate cancer using additional parameters of Gleason score (denoting the degree of differentiation of cancer cells) and prostate-specific antigen (PSA) before starting the treatment. In selecting patients with with significant risk of extraprostatic invasion and undetectable micrometastases the TNM staging alone does not provide sufficient prognostic information.(3)

In 1966, Donald Gleason devised grades of 1 to 5, based on glandular architecture at low to medium power, that were shown to predict outcome in prostate cancer.(4) Gleason score is a sum of the two most prevalent histological patterns and its value lays between is 2 and 10 (primary and secondary patterns). Needle biopsy sets contain cores from different anatomically designated sites. It is recommended that the Gleason score be assigned separately for each anatomically designated site, since information is lost if only a global score is given. Primary pattern is defined by the most prevalent pattern, while the worst pattern is defined as secondary.(5) The ISUP 2014 prostate cancer grade range from 1 to 5 is presented in table no. 3.(6)

Table no. 3. International Society of Urological Pathology 2014 grade groups (6)

Gleason score	Grade group
2-6	1
7 (3 + 4)	2
7 (4 + 3)	3
8 (4 + 4) or (3+ 5) or (5 + 3)	4
9-10	5

The treatment for advanced nonmetastatic prostate cancer is a multimodality approach. European association of urology (EAU) guidelines recommend radical prostatectomy for selected patients with small low volume T3 tumour, organ-confined disease preoperatively and without clinically nodal involvement (cN0), PSA <20 ng/ml, Gleason score < 8 and life expectancy of > 10 years.(7) Radical prostatectomy (RP) means the removal of the entire prostate gland and ablation of both seminal vesicles, with negative margins (R0). The procedure is accompanied by bilateral pelvic lymph node dissection. For the patients with positive lymphnodes at histopathology after surgery (pN1), the hormonotherapy (adjuvant HT) started early after resection, increases the 10-year survival rate.(6)

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External beam radiation therapy has documented benefits for nonmetastatic advanced prostate cancer. The combination of radiotherapy and antiandrogen therapy (ADT) produces better overall survival and is clearly superior to antiandrogen therapy alone. Hormonotherapy may start 2 or 3 months before surgery (neoadjuvant ADT).

Long-term hormonotherapy (2 to 3 years) is preferred for advanced prostate cancer (6,8,9) to short term (6-months).(6) The appropriate hormonal treatment (monoterapy with antiandrogens, monotherapy with LHRH agonists or complete androgene blockade) was not defined.

MATERIALS AND METHODS

From January 2012 through December 2016, 179 patients with local advanced prostate cancer were treated with multimodal therapy at the Clinical County Emergency Hospital Sibiu. Data were obtained from the Oncology Department, County Cancer Registry and Statistic Department.

Patients with an incident diagnosis of cT3, cT4 or cN+ prostate cancer between 2012 and 2016 were included in the study. The treatments were defined as radical prostatectomy (RP), radiation therapy (RT) and hormonotherapy androgen deprivation (ADT), monotherapy or in combinations.

Patients demographic characteristics included patient age, residence in urban and rural areas are presented in table 4. 141 (79%) patients were ≥ 60 years. A number of 116 patients (65%) had a Gleason score ≥ 7. PSA at diagnosis was higher than 20 ng/ml for 130 (73%) patients with locally advanced prostate cancer (table no. 4).

Table no. 4. Patients' characteristics

Total	**179**
Age at diagnosis	**N(%)**
50-59	38 (21%)
60-69	99 (55%)
70-79	28 (16%)
>80	14 (8%)
Urban-Rural residence	
Urban	101 (56%)
Rural	78 (44%)
Gleason score	
< 7	63 (35%)
≥7	116 (65%)
PSA at diagnosis	
>20 ng/ml	130 (73%)
<20 ng/ml	49 (27%)

RESULTS

179 patients with advanced nonmetastatic prostate cancer were treated with radiation therapy with neoadjuvant 9 (5%) or adjuvant ADT 116 (65%) and ADT alone 41 (23%) patients. Only 9 (5%) patients received neoadjuvant ADT for 3 month usually, followed by RT over the last 2 years (2015-2016) of the entire study period according to the locally advanced prostate cancer treatment guidelines. 13 (7%) patients had radical prostatectomy and 8 (4%) of them received adjuvant ADT after radical surgery (table no. 5). Patients treated with RP tended to be younger, absence of clinical node involvement, Gleason <7, lower PSA levels, under 20 ng/ml.

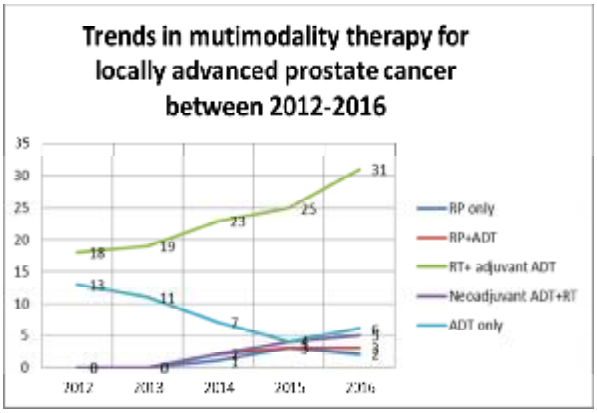
The categories cT and cN were assessed on MRI. Due to the difficult accessibility to MRI (expensive method, private – public MRI partnership that limited pretherapeutic staging) cT1, cT2 tended to be often pT3 or pT4 and cN0 more likely pN1. Pathological risk factors such as positive surgical margins and seminal vesicle involvement, differences between clinical and pathological staging challenge the individual treatment decisions.

Table no. 5. Treatment received between 2012-2016

Treatment	**N (%)**
RP only	5 (3%)
RP+ADT	8 (4%)
RT+ adjuvant ADT	116 (65%)
Neoadjuvant ADT+RT	9 (5%)
ADT only	41 (23%)

Treatment of advanced non-metastatic prostate cancer varies widely. Treatment patterns shifted during the study period (figure no. 1). From 179 patients with locally advanced prostate cancer, 41 received ADT only (older with comorbidities or patient preference). Regarding to ADT treatment alone, 22 (54%) patients received combined androgen blockade and 19 (46%), had analogues LHRH alone or Bicalutamide alone.

Figure no. 1. **Multimodality therapy for advanced prostate cancer between 2012-2016**



After 2013, decreases the use of ADT as monotherapy and increases the use of combined RT and ADT therapy. 2014-2016 registered the first patients receiving neoadjuvant ADT (9; 5%). The number of patients who received radical prostatectomy increased in the same period.

DISCUSSIONS

Treatment of locally advanced prostate cancer is not well defined and remains under discussion.

Multimodality advanced non-metastatic prostate cancer therapy is still changing due to the increase experience in radical prostate surgery, increasing access to MRI and a better communication between medical multidisciplinary radical protatectomyteam: urologist, medical oncologist, radiotherapy physician and anatomo- pathologist.

Use of combined RT and ADT and use of ADT alone fluctuated throughout the study period, but remains the standard approach for advanced non-metastatic prostate cancer, radical prostatectomy addressing a selected group of patients.

The slightly increased use of multimodality therapy since 2014 is encouraging, but further work is needed to increase combination therapy in appropriate patients and to identify predictors of different treatment protocols.

CONCLUSIONS

1. For selected patients 13 (7%) (cT3, absence of clinical node involvement, Gleason <7, lower PSA levels), radical prostatectomy is the appropriate option alone o without adjuvant ADT.
2. Radiation therapy with neoadjuvant ADT, followed by adjuvant hormnotherapy received 9 (5%) patients.
3. 116 (65%) patients were treated with radiation therapy (EBRT) combined with adjuvant ADT at the onset of RT.
4. Radiotherapy remains the standard for locally advanced

prostate cancer.

5. Hormonotherapy alone treated 41 (23%) patients especially elderly, patients with comorbidities, or patients' preference).
6. 22 (54%) patients with only ADT received combined androgen blockade and 19 (46%), had analogues LHRH alone or Bicalutamide alone.
7. The appropriate hormonal treatment (monotherapy with antiandrogens, monotherapy with LHRH agonists or complete androgen blockade) was not defined.

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