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The efficacy of radical radiotherapy for patients with primarily diagnosed prostate cancer with metastases to regional lymph nodes

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Objectives. Retrospective analysis of 22 patients with high risk prostate cancer and clinical regional lymph node involvement treated with radical radiotherapy and ADT.

Material and methods. The mean pre-treatment PSA level was 69 ng/ml. Median age — 65 years. Lymph nodes involvement was determined by radiological imaging. Duration of ADT was 2–3 years. All patients underwent conventional radiotherapy. Dose to the prostate ranged from 75.6 to 78 Gy, to elective lymph nodes — 44 to 50 Gy, boost dose to involved lymph nodes — 60 to 75,6 Gy. Median follow-up was 40 months.

Results. The 3-year and prognosed 5-year bCR in studied group was 78% and 65%. The 3-years and 5-years prognosed OS was 88% and 73%. We observed 5 failures. No relapse in a nodal boost region was observed. No dose-effect relationship was observed for bCR nor OS. Only T stage proved prognostic for bCR.

Conclusions. The results showed good outcome for node positive prostate cancer patients treated with radical intent. No dose-effect relationship suggest that metastatic pelvic lymph nodes may not require such dose escalation as primary tumor.

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Key words: radiotherapy, prostate cancer, oncology

Introduction

Prostate cancer is the second most common cancer diagnosed among men in Poland. Every year over 14 000 new cases are diagnosed, which is due in part to the aging of the population. Thanks to screening, modern diagnostic and therapeutic methods, it is often detected at an early stage and despite an increase in morbidity, the mortality rate remains constant [1]. While patients with low-risk disease have a very good prognosis, patients with locally or locoregionally advanced prostate cancer pose a major challenge in contemporary urological oncology.

Among patients with prostate cancer, the group in which the optimal treatment is not clearly established, are patients with metastases in regional lymph nodes [2]. These patients are stratified as "regionally advanced" by NCCN [3]. In this case, hormonal therapy based on full androgen deprivation is a widely-recognized method of treatment [3–5]. However, if isolated, single or minor, regional node involvement have been determined, a radical treatment may be considered, although there is no straightforward evidence of the superiority of such method over palliative treatment. No randomized trial has undertaken this topic. Hormonal therapy is not radical approach, which is why different medical centers, depending on their own experience, include radiotherapy or surgery in the form of prostatectomy with lymphadenectomy [6]. Such treatment may seem justified even for oligometastatic disease [7], which is why it can be considered in the case of isolated lymph node metastases.

Material and methods

The subject of this study is to present the results of patients' treatment with conventionally fractionated radiotherapy along with hormonotherapy at the Maria Skłodowska-Curie Institute — Oncology Center, Branch in Gliwice in

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the years 2008–2014, in patients with prostate cancer with clinically diagnosed regional lymph node involvement eligible for radical treatment.

The study group included 22 consecutive patients with prostate cancer destined for primary radical radiotherapy with clinically diagnosed regional lymph node metastases (N+) who were treated in the years 2008–2014. Only patients treated with conventionally fractionated radiotherapy were included in the analysis. An alternative way of treatment for patients with N+ in our center, which has been implemented gradually since 2012, was a stereotactic boost with the use of the CyberKnife method after the completion of conventionally fractionated radiotherapy. Patients treated in this way were not included in the analysis.

The decision regarding radical radiotherapy in patients with metastatic diagnosis in regional lymph nodes was arbitrarily based on physical examination, patient's medical history and imaging studies with regard to expected survival.

To asses the primary disease, each patient had a PSA test, along with TRUS, abdominal and pelvic computer tomography, chest x-ray and bone scintigraphy. The presence of metastases in regional lymph nodes was assessed clinically, i.e. based on imaging studies of CT, MRI (17 cases) or PET-CT (5 cases). No surgical procedures (lymphangectomy) have been performed to confirm the presence of metastases. The AJCC 2002 classification system was used to assess the stage of TNM.

Regional lymph nodes were defined as pelvic lymph nodes up to common iliac lymph nodes (N1–N3). Nodes above the aortic bifurcation were considered as distant metastases. Patients diagnosed with oligometastatic disease (M+) treated radically were not included in the study. No patient from the study group was diagnosed with distant metastases before radiotherapy.

The median age was 65 (+/- SD 8 years) and ranged from 42 to 81 years. The PSA level in the blood before treatment ranged from 7.1 to 247.5 ng/ml (with an average value of 69 ng/ml).

All patients were subject to neoadjuvant hormonal therapy before radiotherapy. The duration of neoadjuvant hormonal therapy ranged from 2 to 18 months and averaged 7 months. In 18 patients, total androgen deprivation was used, in 2 patients — LH-RH analogue alone, and in the next two patients — antiandrogen. All patients, except two, had continued hormonal therapy after radiotherapy for a period of 2–3 years, and in the event of a recurrence, hormonal therapy was introduced permanently. Clinical characteristics of the study group are presented in Table I. Highly differentiated prostate cancer without a Gleason score was reported in 2 patients who were classified as Gleason 3+3.

Table I. Clinical characteristics of the study group

Factor	Number of patients
T tumor characteristics	
T1c	4
T2a	2
T2b	2
T2c	5
T3a	4
T3b	3
T4	2
Gleason score	
3 + 3	6
3 + 4	4
4 + 3	4
4 + 4	4
4 + 5	2
5 + 4	1
5 + 5	1
Number of nodes involved	
1	10
2	6
3	6

Radiotherapy

Patients were immobilized in thermoplastic masks, lying on the back, with a comfortably filled urinary bladder (1.5–2 h after micturition).

CT was used for radiotherapy treatment planning and, in justified cases, PET-CT or additionally MRI. Treatment planning was conducted in the ARIA system, with scans reconstructed every 3 mm. Contouring of the target volumes was performed according to the following principles: CTV-prostate, CTV-N+ involved lymph nodes, CTV-N elective pelvic lymph nodes, from common iliac lymph nodes to the obturator foramens. The PTV was defined by adding 6–10 mm around the CTV. The radiation dose was specified in the isocenter. Conventional fractionation was used. The total dose in the prostate gland was 76 Gy, while in the involved lymph nodes it ranged from 60 to 76 Gy. All patients at the first stage of radiotherapy had elective irradiation of pelvic lymph nodes to a total dose of 44–5 0 Gy. Patients were irradiated using 6 or 20 MV photon beam with linear accelerator (19 patients) or tomotherapy (3 patients). 3D conformal techniques — 2 patients, or dynamic techniques (IMRT, RapidArc, tomotherapy) — 20 patients, were performed.

IGRT in 2D-2D KV system was used in all patients treated with the accelerator. Verification was performed to the bones in 6 patients and to the gold marker implanted in the prostate in 13 patients. In the case of three patients treated with tomotherapy, a verification with tomography was performed. Radiotherapy parameters are presented in Table II.

The evaluation of acute and late radiation morbidity was carried out by using the RTOG/EORTC scale. In addition, the local effect of treatment was assessed by using actuarial

Table II. Radiotherapy parameters

IGRT verification method	
Bones	6
Prostate marker	13
RT technique	
3DCRT	2
IMRT/RapidArc/tomotherapy	20
Total dose pelvic lymph nodes	
44 Gy	19
45 Gy	1
50 Gy	2
Total dose, lymph nodes involved (N+)	
60 Gy	5
64–66 Gy	11
70–72 Gy	5
75.6 Gy	1
Total dose prostate	
75.6 Gy	2
76 Gy	18
78 Gy	2

survival curves for local, regional and nodal control (N+). The Kaplan-Meier method was used for this purpose. As regards nodal control (N+), a complete remission, partial remission or stable disease were assumed to be a beneficial effect (i.e. nodal control).

For the global assessment of treatment efficacy, an analysis of actuarial biochemical control and overall survival (OS) was used. Following the definition provided by Phoenix, a 2 ng/ml value above the PSA nadir was assumed to be a local failure. The evaluation of the impact of selected prognostic factors of treatment efficacy was conducted with the use of Cox proportional hazards model or logit regression. The value of $p < 0.05$ was considered statistically significant.

Results

The median follow-up period was 40 months. It was found that the 3-year and the estimated 5-year rates of local control were 86% and 86%, locoregional control was 77% and 77%,

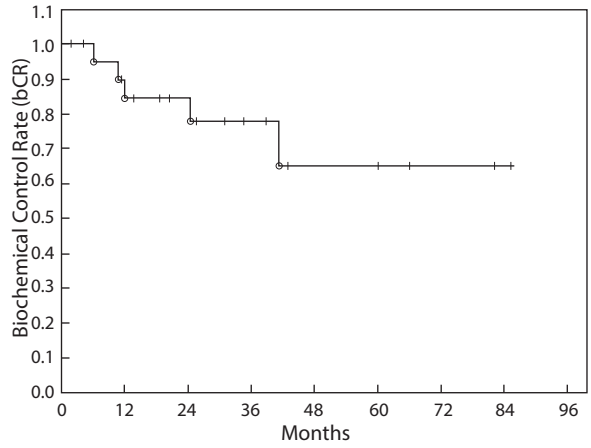

Figure 1. Biochemical control rate in the study group

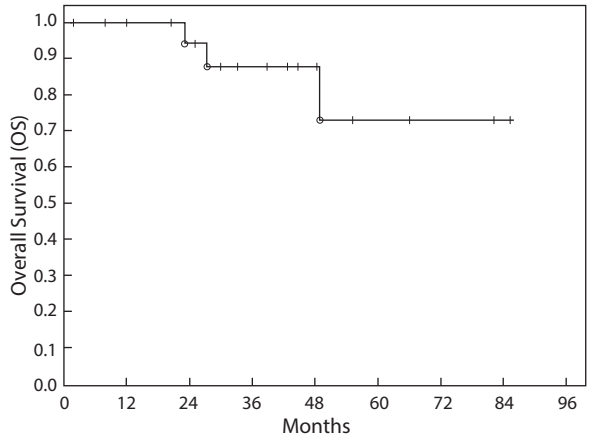

Figure 2. Overall survival in the study group

distant metastases free survival were 76% and 76%. Due to the retrospective nature of the study and the fact that the majority of routine follow-up visits after treatment was based primarily on PSA evaluation, no early radiological assessment after treatment was performed in 50% of patients, which is why there was no possibility of conducting a reliable analysis of the early local response to radiotherapy. After radiotherapy, a 3-year and estimated 5-year biochemical control in the study group amounted to 78% and 65% respectively. The 3- and 5-year overall survival (OS) amounted to 88% and 73%. 5 treatment failures are presented in Table III.

Table III. A list of 5 patients with failure after treatment

No	T-stage	Gleason	Highest pre-RT PSA	Type of failure	Neoadj HT duration	Adjuvant HT duration	Number of nodes N+	Total dose N+
1	T2c	4 + 4	57.5	Biochemical recurrence	12	26	1	60
2	T4	3 + 4	31	Nodal dissemination(outside the boost N+ area)	9	31	1	70
3	T3a	3 + 3	58.2	Bone metastases	3	na	2	66
4	T2c	4 + 4	35.4	Nodal dissemination (outside the boost N+ area) + bone mets	3	28	1	66
5	T4	5 + 5	81.4	Nodal dissemination (outside the boost N+ area) + bone mets	6	12	3	66

Among patients with relapse, no progression in the irradiated, primarily involved lymph nodes (N+) was observed. Among the analyzed factors: age, Gleason score, T-stage, number of involved lymph nodes, highest PSA level before oncological treatment, duration of neoadjuvant HT, duration of adjuvant HT — only the T-stage was associated with biochemical control (Fig. 3).

No dose-effect relationship for biochemical reccurence was observed (p = 0.81, Fig. 4).The total radiation dose in the involved lymph nodes also did not affect the overall survival (p = 0.76). Other analyzed parameters of radiotherapy also did not increased the risk of biochemical failure. Due to the small number of events (deaths), no detailed analysis for overall survival was conducted.

One patient required a one week break in irradiation due to acute grade II radiation morbidity; other patients completed treatment without delay. Acute grade II morbidity was observed in 18% of patients — from rectum and among 22% patients — from urinary tract. No acute grade III reactions were observed. Late grade II urinary tract morbidity occurred in one patient, and the one from the rectum in two patients.

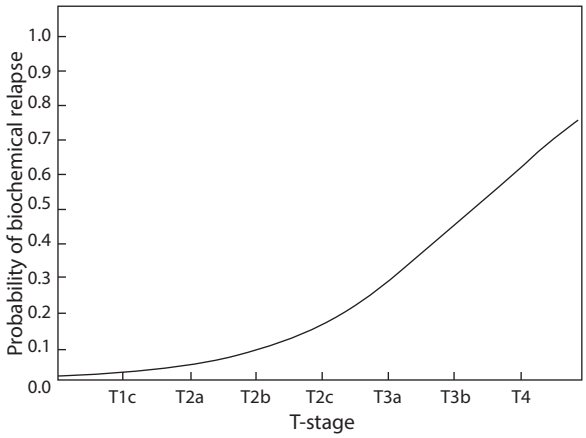

Figure 3. The probability of biochemical relapse as a function of T-stage

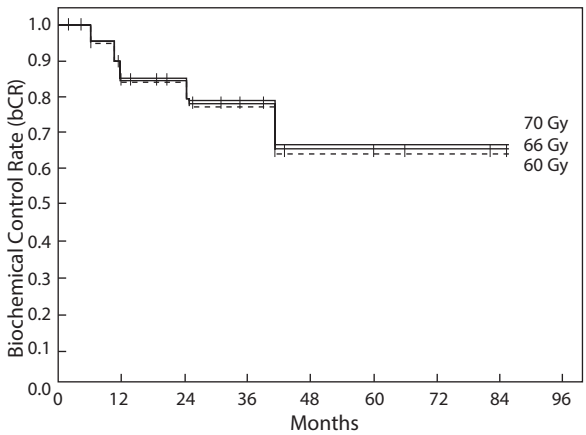

Figure 4. The biochemical control rate (bCR) as a function of Total dose to involved (N+) nodes

Discussion

In the 1990s, the RTOG 85-31 study demonstrated a 10-year overall survival of 49% in patients treated with radiotherapy combined with ADT vs 39% in patients receiving only RT. Disease-specific mortality was 16% vs 22% for the RT arm, and local failure for the combined arm was 23% vs 38% for RT arm [4]. It was one of several groundbreaking studies indicating the relevance of combined treatment, i.e. the addition of hormonal therapy to radical radiotherapy. The same study confirmed the need for hormonal therapy in patients with pathologically confirmed metastases in lymph nodes, who received adjuvant radiotherapy — differences in 5-year and 9-year progression-free survival were 54% and 10% for the above treatment vs 33% and 4% for patients treated only with RT. Such considerations in a reverse situation may lead to a question whether hormonal therapy alone in patients with locally advanced prostate cancer also requires the addition of radiotherapy? It turns out that the answer is "yes". Radiotherapy-induced activation of immune system as well as abscopal effect and the need for treating cancer's primary tumor are widely studied subjects. One randomized study concerning this subject demonstrated an improvement in 10-year survival from 49% to 55% after radiotherapy. What is more, the benefit in the reduction of biochemical recurrences was spectacular — approx. 30% vs 65%. It is worth mentioning fact is that those patients received RT doses below 70 Gy on prostate, which is well below modern standards [8]. This may lead to a conclusion that radiotherapy has supra-additive affect with ADT. However, for patients with regional advancement (N+), such generalization of results may not be justified and fully credible. Nonetheless, there are some retrospective reports which also indicate the benefit of combination treatment in these subgroups of patients [9–11].

In meta-analysis, Chun Chieh Lin et al. compared 636 cN+ patients treated with hormonal therapy alone and those treated with hormonal therapy in combination with radiotherapy – an approx. 50% benefit in overall survival in favor of the ADT + RT group was demonstrated [9]. Tward et al. by analyzing 1.100 N+ patients, received a 10-year CSS of 62.7% for patients treated with radiotherapy, vs 50.3% for patients without RT [10]. Similarly, Rusthoven et al. by analyzing 796 cN+ patients showed a 10-year PCCS of 67% for patients treated with radiotherapy, vs 53% for patients who received only hormonal therapy [11]. Since all these studies are retrospective, the results should be interpreted with some caution. In the light of these studies, the results concerning our institute's patients (5-year bNED-65%) are comparable. It should be noted, however, that no information on the applied radiation doses and additional boost in involved lymph nodes is provided in the cited studies. This leads us to the conclusion that radiotherapy combined with hormonal therapy is a treatment method which allows

for achieving a satisfactory percentage of overall and cancer-specific survivals in patients with prostate cancer cN+.

Surgery is also worth mentioning as another valuable treatment method [5] — Steuber in a group of 158 patients showed a 10-year progression-free survival of 61% for the group treated with prostatectomy combined with ADT vs 31% for the group receiving only ADT. Adding surgery to multidisciplinary treatment also allows us to obtain pathological verification of clinically suspicious lymph nodes. Adjuvant radiotherapy may also play a role as a complementary treatment to prostatectomy and adjuvant hormonal therapy. Abdollah et al. analyzed a group of 1.107 patients after prostatectomy with pN1 involvement. Among them, 35% received adjuvant radiotherapy, which increased the cancer-dependent survival rate to 87%, in comparison to 82% in patients receiving only hormonal therapy [12]. Similarly, Briganti [13] by analyzing 703 postoperative patients with pN+ advancement, received a significantly higher 5- and 10-year survival in the group treated with radiotherapy and hormonal therapy, compared to the group treated only with adjuvant hormonal therapy (5-year 95% vs 88%, 10-year 86% vs 70%). These results were better for both minor and massive nodal involvement.

It is worth noting that we found no correlation between increasing total radiation dose to the involved lymph nodes and the efficacy of treatment among our patients. However, a small number of assessed cases, the retrospective nature of the work and the fact that only clinical evaluation of the involved lymph nodes (N+) without histopathological verification was performed, does not allow a fully reliable assessment of the dose-effect relationship and encourages further exploration of this topic. However, it should be emphasized that for instance in colorectal cancer there are suggestions concerning a different radiation sensitivity of the metastases than of the primary tumor, where metastatic lymph nodes are characterized by higher radiation sensitivity [14]. This might be potentially also true for prostate cancer. Of course, as long as the volume of these lymph nodes, and hence the number of clonogenic cells, does not exceed a certain level. This may explain the absence of the dose-effect relationship in the 60–75 Gy range, which was presented in this study, especially as there are empirical reports in the literature which confirm such observation for other cancers, such as cervical cancer [15, 16]. In those studies, total doses of ≥ 54–55 Gy were effective in eradication of nodal metastases.

If, however, there is a dose-effect relationship in that dose range, an escalation not only of the physical dose, but also its intensity and the use of radiation ablative effects (e.g. through hypofractionated stereotactic boost) may have a higher value. However, these considerations are of speculative nature and are not addressed in this paper. The fact is that the effectiveness of the response of metastatic nodes (N+) among our patients was high, and the distant spread and progression to non-boosted lymph nodes was the reason for failure of treatment. From the point of view of radiotherapy planning and the equipment capabilities of various radiotherapy centers, a radiation dose escalation in a standard-fractionated manner instead of a stereotactic boost appears to be a quite attractive method. Our study, as well as other reports, also indicate that this is a well-tolerated treatment [17].

Conclusions

Radical radiotherapy with a boost to the metastatic lymph nodes combined with ADT is an effective treatment. The lack of correlation between the dose in the involved lymph nodes and the effect of treatment may indicate a higher sensitivity of metastases to radiation in comparison to the primary tumor. The retrospective character of this analysis supports the need for randomized clinical trials of these issues.

Conflict of interests: none declared

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