Indications for postoperative radiotherapy in patients with prostate cancer after surgery with positive surgical margins

Krzysztof Kamecki¹, Marta Biedka¹, Roman Makarewicz¹, Jerzy Siekiera¹

¹Clinical Department of Oncological Urology, The Franciszek Lukaszczyk Oncology Center, Bydgoszcz, Poland
²Chair and Clinic of Oncology and Brachytherapy, Ludwik Rydygier Collegium Medicum Bydgoszcz, Nicolaus Copernicus University, Torun, Poland
³Radiotherapy Department 1, Oncology Centre, Bydgoszcz, Poland

Introduction

Prostate cancer is the second most prevalent cancer among men in Poland. The etiopathogenesis of prostate cancer, like most other cancer types, is obscure. Among the risk factors there are age, race and genetics [1]. Over 95% of prostate cancers are adenocarcinomas, which arise most frequently in the peripheral zone of the prostate. The first metastases occur in pelvic lymph nodes and bone. The most important prognostic factors for prostate cancer include TNM stage, histopathological classification (Gleason score), PSA level, the status of the lymph nodes and evaluation of distant metastases [2].

Selection of an optimal treatment method for patients with prostate cancer depends on the stage of the disease as well as the patient’s life expectancy and general quality of life. In the case of organ-confined cancer radical treatment is possible. The main methods of radical treatment are radical prostatectomy and radiotherapy [1–3]. Both methods are used alone or in combination [4, 5]. The predictors of treatment efficacy, useful in observing patients undergoing radical prostatectomy, include post-operative PSA level, TNM stage, Gleason score and surgical margin status. Apart from the last factor, the others are related to tumor characteristics and are independent of the operator. Since in patients who have been correctly qualified for surgery a positive surgical margin is always an unexpected and undesirable factor, surgical margin status can be considered as a criterion for the quality of surgery. The percentage of positive margins is related to the surgeon’s experience (unintended injury of prostate capsule during treatment of the tumor not extending beyond the capsule), tumor characteristics (tumor infiltration beyond the capsule), anatomical features of the patient (patient’s obesity causing technical difficulties during the preparation of the prostate located deep in the pelvis minor), and the way of processing the material during histopathological evaluation (false positive margins) [2].

The presence of positive surgical margins can imply incomplete excision of malignant tissue and is an indication for adjuvant therapy. However, in contrast to non-radical surgical treatment of solid tumors in other organs, in the case of prostate cancer with positive surgical margins, there is no standard regime. According to some investigators, the presence of positive surgical margins does not necessarily mean a worse prognosis and is not in each case an indication for adjuvant treatment.

Aim of the study

The aim of this prospective study was to evaluate the incidence of positive margins in more than 100 consecutive patients with prostate cancer undergo-
Table 1. Study group characteristics

| Clinical stage | cT1 | cT2 | cT3 |
|---------------|-----|-----|-----|
| Number of patients who underwent radical prostatectomy | 51 | 44 | 19 |
| 44.7% of the group | 38.6% of the group | 16.7% of the group |
| Gleason score on prostate biopsy | 2–8 mean 5.98 | 5–9 mean 6.06 | 5–8 mean 6.37 |
| Preoperative PSA level in the blood [ng/ml] | 3.09–53.00 mean 9.87 | 3.44–28.30 mean 9.32 | 1.06–60.00 mean 20.99 |
| Patient age [years] | 44–71 mean 61.27 | 51–78 mean 62.75 | 51–70 mean 59.58 |

Table 2. Study group Gleason score

| Gleason score | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---------------|---|---|---|---|---|---|---|---|---|
| Number of patients | 0 | 0 | 1 | 18 | 66 | 17 | 9 | 3 | 0 |

Material and methods

The study included 114 patients aged 44–78 years (mean 61.5 years) who underwent surgery for prostate cancer in stage cT1–3NO/M0 (according to the TNM staging system) in the years 2010–2011 in the Clinical Department of Oncological Urology in the Center of Oncology in Bydgoszcz. Descriptive data of the tested group of patients are presented in Tables 1 and 2. Each patient was treated in accordance with the standard procedures for prostate cancer and each patient was informed about the research and signed informed consent on participation.

Radical retropubic prostatectomy involved removing the prostate with the tumor, the seminal vesicles and iliac and obturator lymph nodes. Following the outcome of the histopathological examination, patients were directed to adjuvant therapy (radiotherapy and/or hormone therapy) in the case of the presence of at least one of the risk factors for recurrence: stage pT3 carcinoma of the prostate, the presence of lymph node metastases (pN1), or incomplete excision of malignant tissue.

Teleradiotherapy involved radiation of the prostate bed including a margin of healthy tissue (total dose of 60–74 Gy in 2 Gy daily fractions). For patients with confirmed lymph node metastases, in the first phase radiation was directed to the pelvic area, including the area of obturator lymph nodes, presacral lymph nodes, external, internal and common iliac lymph nodes to 45–46 Gy dose, and the next step was increasing the dose to the prostate bed to 60–74 Gy. The first follow-up visit took place 4–6 weeks after surgery, and subsequent visits took place at 3-month intervals. Follow-up ranges from 4 to 18 months after surgery.

Results

The study was conducted in a group of 114 patients aged 44–78 years (mean 61.5 years) who underwent radical surgical treatment of adenocarcinoma of the prostate. Gleason score was evaluated based on biopsy before treatment initiation. On baseline testing mean PSA level in the blood was 11.74 ng/ml (1.06–60 ng/ml). On follow-up PSA testing 3 months after surgical treatment, median PSA level was 0.226 ng/ml (0.002–8.7 ng/ml). Mean follow-up was 12 months (range 6 to 18). During this period, a biochemical relapse after radical treatment (PSA > 0.2 ng/ml) occurred in 16.36% of the patients (patients with pN1 were excluded, as the resection was recognized as incomplete). All recurrences occurred within 6 months after surgery. PSA concentration in the blood of patients with biochemical relapse after surgery was above 0.2 ng/ml, with a growing trend. Biochemical progression also occurred in all patients with lymph node metastases.

The presence of positive surgical margins was found in 45 (39.47%) patients, and in 20 (17.54%) margins were assessed as close (1–2 mm). Among the patients with positive surgical margins about 22% had biochemical recurrence.

Among patients with negative surgical margins 13% of pT2c and 12.5% of pT3a had biochemical recurrence. Given the histopathological evaluation and Gleason score, recurrence concerned 15.47% of patients with Gleason score < 7, 14.28% of Gleason score = 7, and 27.27% of Gleason score > 7. Five (4.39%) patients had lymph node metastases. Since the surgical treatment in these patients could not be recognized as radical, this group of patients was excluded from the statistics relating to the incidence of positive margins and biochemical recurrence. Data on the early postoperative results of patients are shown in Table 3.

Discussion

The aim of radical surgery is removal of the prostate along with the malignant tumor, seminal vesicles and lymph nodes in such a way that surgical margins are negative and urinary continence and potency maximally preserved. The only objective criterion of how radical the prostatectomy was is the lack of positive surgical margins in the histopathological evaluation.

The presence of positive surgical margins always raises the question of whether the surgeon performed the operation correctly and whether the presence of positive mar-
gins will affect the outcome of the disease and its treatment [6]. Unfortunately, despite the improvement of surgical techniques positive margins after surgery occur in an average of 28% of patients with organ-confined (pT2) prostate cancer as a result of preparation of the prostate in the wrong anatomical plane [7, 8], and in up to 46.5% of patients with non-organ confined (pT3) prostate cancer [9]. Patients with positive surgical margins, along with patients diagnosed with tumor extending beyond the prostate (pT3a) or invading seminal vesicles (pT3b), are at an increased risk of recurrence and progression, reaching up to 30–50% over 10 years. The risk is 2–4 times higher in patients without positive operating margins [10].

According to large multicenter statistical analyses, the percentage of patients with increased risk factors for prostate cancer recurrence after surgery is up to 50% [11]. These data are of potential concern to urologists performing radical prostatectomy, but it should also be pointed out that not all patients with positive surgical margins will have cancer recurrence. At least two conclusions can be drawn from this observation: the presence of a positive surgical margin does not always mean leaving the cancerous tissue behind in the site of surgery, and a positive surgical margin is not the only factor affecting the prognosis.

Ohori et al. confirm this, demonstrating that surgical margin status is an independent prognostic factor only for pT3a patients, unlike pT2 and pT3b patients. They point out that prostate-confined tumors, especially the early-stage disease (pT2a–pT2b), have a very good prognosis regardless of the state of the surgical margin, whereas advanced tumors, infiltrating the seminal vesicles (pT3b) or with lymph node metastases, have poor prognosis irrespective of surgical margin status [12].

The incidence of positive surgical margins in patients undergoing surgical treatment is directly related to preoperative PSA level > 10 ng/ml, tumor extending beyond the prostate (pT3), Gleason score, the volume of tumor in the prostate, the presence of vascular invasion into the nerve bundles and emboli made of cancer cells in the lymph vessels, applying techniques saving neurovascular bundles, smaller prostate volume, and increasing BMI [10, 13–15]. Pelvic MRI performed prior to surgery in patients with suspected infiltration outside the prostatic capsule confirmed neither protective significance of positive margins nor increase in their incidence. Causes of positive surgical margins are presented in Table 4.

Much of today’s research confirms not only a greater likelihood of recurrence in patients with pT2 and iatrogenic damage to the prostate capsule than in patients without this damage, but also similar to or greater than pT3 patients but with negative surgical margins [16]. It is worth noting that even 28% of post-operative histopathological examination shows

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**Table 3. Postoperative study group characteristics**

| Clinical stage prior to surgery | Number of patients who underwent prostatectomy | cT1 | cT2 | cT3 | Total |
|--------------------------------|-----------------------------------------------|-----|-----|-----|-------|
| Number of patients who underwent prostatectomy | pT2a | 52 | 6.14% | 4 | 3.51% | 64 | 56.14% | 14 | 12.28% | 19 | 21.05% | 1 | 0.88% | 114 | 100% |
| Number of pN1 patients | 0 | 0 | 0 | 0 | 4 | 1 | 5 |
| Number of pN1 patients with positive surgical margins | 0 | 0 | 0 | 0 | 4 | 1 | 5 |
| Number of patients with negative surgical excluding pN1 patients | 7 | 4 | 46 | 9 | 3 | 0 | 69 |
| Number of patients with positive surgical excluding pN1 patients | 0 | 0 | 18 | 5 | 17 | 0 | 40 |
| Number of patients with close margins | 0 | 1 | 15 | 2 | 2 | 0 | 20 |
| Number of patients with biochemical recurrence, excluding pN1 patients | 1 | 0 | 9 | 2 | 6 | 0 | 18 |
| Including number of patients with positive margins | 0 | 0 | 3 | 1 | 6 | 0 | 10 |
| Including number of patients with close margins | 0 | 0 | 2 | 0 | 0 | 0 | 2 |
| Including number of patients with negative margins | 1 | 0 | 6 | 1 | 0 | 0 | 8 |
| Postoperative RT alone – number of patients | 0 | 0 | 7 | 9 | 16 | 0 | 32 |
| Including patients pN1 | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Including patients with positive margins | 0 | 0 | 4 | 4 | 13 | 0 | 21 |
| Including patients with close margins | 0 | 0 | 0 | 1 | 1 | 0 | 2 |
| Postoperative RT combined with HT – number of patients | 0 | 0 | 3 | 0 | 9 | 0 | 12 |
| Including pN1 patients | 0 | 0 | 0 | 0 | 3 | 0 | 3 |
| Postoperative HT alone | 1 | 0 | 1 | 0 | 0 | 1 | 3 |
| Including pN1 patients | 0 | 0 | 0 | 0 | 0 | 1 | 1 |
the presence of prostate cancer in the lobe in which the preoperative biopsy failed to detect the tumor. The surgical technique for neurovascular bundle preservation on the side of the lobe which in the biopsy evaluation did not contain tumor results in the presence of a positive surgical margin in 4% of surgeries, compared to 8% of cases in which cancer was found in the lateral lobe before prostatectomy [10].

Biochemical recurrence after radical prostatectomy in pT2 patients with positive margins is observed almost twice as frequently as in patients without positive surgical margins; it also occurs earlier and proceeds more rapidly in patients with a higher Gleason score [4, 16]. In long-term observation it was found that the risk of biochemical recurrence was similar in pT2 patients with positive surgical margins and pT3 patients without positive surgical margins approximately 9 years after prostatectomy [6, 13]. Therefore, a modification of the TNM staging system has been postulated, suggesting the inclusion of patients with organ-confined prostate cancer and positive surgical margins to group pT3 [17]. The risk of recurrence is not related to the location or size of positive surgical margins [13]. In pT3 patients, in turn, infiltration beyond the prostate is such a strong risk factor for recurrence that the presence of positive surgical margins in the postoperative specimen no longer has clinical significance [13].

Some authors have demonstrated that postoperative radiotherapy mainly benefits patients with pT2 and positive surgical margins, not pT3 patients [13]. However, the use of adjuvant radiation therapy in patients with positive margins and biochemical progression is widely recognized as standard of care, regardless of the stage of the tumor.

The recognition of positive surgical margins as an independent prognostic factor for recurrence of cancer is still controversial and results in a lack of established standard procedure in patients with localized prostate cancer and positive margins after surgery [13].

Table 4. Causes of positive surgical margins after radical prostatectomy

| Causes of positive surgical margins after radical prostatectomy |
|---------------------------------------------------------------|
| 1. iatrogenic, surgical damage to the prostate, which reaches the tumor in patients with organ-confined cancer (pT2) |
| 2. Surgical incision through infiltration that extends beyond the confines of the prostate gland (pT3) |
| 3. Incorrect qualification of patients for surgical techniques aimed at preserving neurovascular bundles |
| 4. The use of techniques of bladder neck preservation with a view to improving urinary incontinence [4] |
| 5. Artifact resulting from improper handling of specimen during prostatectomy or during preparation of specimen for histopathological evaluation |

Published reports informing that only about 30% of patients in this group have a biochemical recurrence and 20% experience local recurrence can be hypothetically explained with the effect of electrocautery during surgery, vascular damage in the site of positive margin or the effect of the inflammatory response associated with healing [8].

Higher risk of recurrence in patients with pT2 and positive surgical margins correlates with increasing Gleason grade. According to some authors, this allows one to extract a group with a low risk of recurrence, which includes patients with a preoperative PSA level < 10 ng/ml and Gleason score 2–6. Patients from this risk group may be put under observation, where PSA > 0.4 ng/ml would be considered as the criterion for recurrence and exceeding that level would be an indication for radiotherapy. Such a procedure aims at limiting the indications for postoperative radiotherapy, which carries the risk of complications and significantly increases the cost of treatment. The proposal to recognize the recurrence criterion PSA > 0.4 ng/ml is due to a number of observational studies in which it was found that PSA levels below this value in patients with positive margins who will not have recurrence tend to be stable and not likely to progress. Observation and using adjuvant radiotherapy after exceeding the threshold PSA = 0.4 ng/ml best identifies patients who actually have a recurrence of cancer and allows one to avoid the risk of complications and cost of radiation therapy for patients who have positive surgical margins but never experience recurrence [18, 19]. Even more remarkably, the latter group includes patients who underwent surgery aimed at preserving potency and good urinary continence, which would be largely wasted on the use of radiotherapy. The trend towards reducing the toxicity of adjuvant treatment and its use only in patients with the highest risk of recurrence may help to modify the current procedure so that not only the patients with positive surgical margins and pT2 stage, but also selected patients with pT3a prostate cancer would be referred for observation. According to current guidelines, all patients in stage pT3a are referred for radiotherapy. The criteria for deferral of adjuvant therapy in patients with positive margins and/or infiltration beyond the prostate gland but without invasion of seminal vesicles and lymph nodes are shown in Table 5 [20].

It is quite a popular view that a positive surgical margin means leaving a small number of non-vascularised cancer cells and the resulting possible recurrence can be quickly and reliably identified on the basis of increase in PSA. However, the decision to postpone the adjuvant treatment of patients

Table 5. Predictors of high-risk prostate cancer recurrence after surgery with positive surgical margins and extracapsular invasion pT3a

| Predictors of high-risk prostate cancer recurrence after surgery with positive surgical margins and extracapsular invasion pT3a |
|---------------------------------------------------------------|
| Patient age > 60 years |
| Preoperative PSA level > 10 ng/ml |
| Gleason score 4 + 3, 8–10 |
| Two or more positive surgical margins |
| Surgical specimen weight after prostatectomy < 30 g |

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with positive surgical margins and extracapsular invasion pT3a is difficult, especially as some research points to better prognosis of patients with prostate cancer in stage pT3a and positive margins involving prolonging the biochemical recurrence-free period by 60%, resulting from immediate radiation therapy after surgery [8, 21].

In recent years there have been significant advances in the technology of radiation, thus allowing for more efficient use of the radiation dose, while reducing side effects. In the SWOG 8794 study conducted among 431 patients with pN0 after surgery, diagnosed with extraprostatic infiltration, positive margins or seminal vesicle invasion, observation or adjuvant radiotherapy was applied at a dose of 60–64 Gy. It has been shown to improve the overall 15-year survival by 10% from 37% to 47%, and distant metastasis-free survival also improved from 38% to 46%. The study also assessed biochemical recurrence, finding that it occurred in a smaller group of patients (55% vs. 77%), whereas local failure decreased from 22% to 8%. In addition, research on a group of 217 patients evaluated the quality of life and showed a higher percentage of dysfunction of the bladder in patients who received radiation therapy, but this difference disappeared after a period of 2 years after termination of treatment. The authors did not demonstrate differences in sexual dysfunction between the group undergoing observation and the group with adjuvant radiotherapy [22].

The authors of the EORTC 22911 study evaluated a group of 1005 patients with pN0 with infiltration beyond the capsule of the prostate, positive margins or seminal vesicle invasion. Half the group underwent observation and the remainder were treated with radiotherapy at a dose of 60 Gy. The groups showed no difference in the overall 5-year survival, but the authors observed a higher rate of biochemical progression-free survival (74% vs. 53%) and of clinical progression-free survival (85% vs. 77%). Local failure was lower in the irradiated group, accounting for 5% vs. 15%. The researchers have demonstrated the predictive and prognostic value of the benefit of radiotherapy in patients with positive margins [23].

Although the incidence of positive surgical margins in histopathological assessment can be treated as a criterion for the evaluation of urological performance, there are no universally accepted standards for detection of positive margins. The method of preparation of specimens for histopathological evaluation may have as great an impact on the incidence of positive margins as the experience of the operator. In the case of an experienced surgeon, the incidence of positive margins, assessed by different pathological laboratories, can vary by 20% [19]. Differences are due to different standards of histopathological specimen preparation, experience of the histopathologist, workload and time spent on assessment. So far there has been no success in creating a classification of positive surgical margins and surgical experience suggests that the distinction between broad and focal positive margins will have different meaning for the prognosis of the patient. With this in mind it should also be taken into account that the decision about observation vs. adjuvant treatment, and the detection or non-detection of positive surgical margins, may not be based on fully reliable data.

Summary

The prognosis in patients after surgical treatment of prostate cancer based only on surgical margins will distinctly demonstrate that the presence of positive margins always implies worse prognosis. This is due to the fact that positive surgical margins are present primarily in patients with locally advanced disease and a high Gleason score, whereas no positive margins occur mostly in patients with organ-confined disease in which the prognosis is significantly better. Many studies have demonstrated that surgical margin status affects biochemical recurrence, but only large scale studies of patients after radical prostatectomy, assessing the results of treatment in a sufficiently long follow-up period, show the impact of surgical margins on prostate cancer mortality. In a study of a group of more than 65,000 patients it was demonstrated that the presence of positive surgical margins increases the risk of death from prostate cancer by 2.6 times [24]. In multivariate analyses, it has been proven that surgical margin status is an independent predictor of death from prostate cancer. This points to the necessity of improving the surgical technique to achieve the best oncological results.

In recent years, centers with vast experience in performing radical prostatectomy have reported a decreasing percentage of operations with positive surgical margins and have set the standard below 10% [21, 25]. This is probably a consequence of three factors: changes in surgical technique, surgeon experience and increased detection of early-stage prostate cancer. Since in pT2 patients with positive margins and undetectable PSA after surgery postoperative radiotherapy has been shown to double biochemical recurrence-free survival with minimal local toxicity, referring patients with positive surgical margins for adjuvant radiotherapy should be considered a standard [21].

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Address for correspondence
Marta Biedka MD, PhD
Clinic of Oncology and Brachytherapy
Ludwik Rydygier Collegium Medicum
Romanowskiej 2
85-796 Bydgoszcz, Poland
e-mail: martabiedka@tlen.pl

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