The role of postoperative radiotherapy in prostate cancer patients

Małgorzata Zarzycka[1], Ewa Ziółkowska[1], Tomasz Wiśniewski[1], Wiesława Windorbska[2], Agnieszka Żyromska[2,3], Zbigniew Wolski[4]

[1]Department of Radiotherapy I, Oncology Centre – prof. Franciszek Łukaszczyk Memorial Hospital, Bydgoszcz, Poland
[2]Department of Teleradiotherapy, Oncology Centre – prof. Franciszek Łukaszczyk Memorial Hospital, Bydgoszcz, Poland
[3]Chair and Clinic of Oncology and Brachytherapy, Ludwik Rydygier *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland
[4]Chair and Department of General, Oncologic and Pediatric Urology, Ludwik Rydygier *Collegium Medicum* in Bydgoszcz, Nicolaus Copernicus University in Torun, Poland

Aim of the study: The aim of the study was to evaluate the effectiveness of postoperative radiotherapy in prostate cancer patients with unfavorable prognostic factors.

Material and methods: In the years 2002–2008, 121 consecutive prostate cancer patients underwent radical prostatectomy and postoperative radiotherapy. The median dose was 64 Gy (range: 60–72 Gy). Biochemical and clinical progression-free survival were estimated. Univariate and multivariate analyses were used to analyze clinicopathological variables associated with treatment failure.

Results: The median follow-up was 27 months. Three-year bPFS was 72%. On univariate analysis it was influenced by: extracapsular tumor extension (60% vs. 75%, $p = 0.0232$), seminal vesicles invasion (52% vs. 85%, $p = 0.00041$), Gleason score ≥ 7 (65% vs. 86%, $p = 0.044$) and the use of hormonal therapy (50% vs. 80%, $p = 0.0058$). On multivariate analysis bPFS was associated with: TNM stage (HR = 3.19), postoperative hormonal therapy (HR = 2.6), total irradiation dose (HR = 0.82) and the maximum pretreatment level of prostate-specific antigen (PSA) (HR = 0.95). Three-year cPFS was 84%. On univariate analysis it was influenced by: preoperative PSA level > 10 ng/ml (75% vs. 90%, $p = 0.04$), vascular-nerve bundles involvement (63% vs. 88%, $p = 0.0031$), adjacent organs infiltration (50% vs. 85%, $p = 0.018$) and the use of postoperative hormonal therapy (62% vs. 90%, $p = 0.02$). On multivariate analysis cPFS was associated with: TNM stage (HR = 2.68), postoperative hormonal therapy (HR = 3.61) and total irradiation dose (HR = 0.78).

Conclusions: Postoperative radiotherapy in patients with unfavorable prognostic factors provides good biochemical and local control. Total irradiation dose and postoperative hormonal therapy are important treatment factors influencing prognosis.

Key words: prostate carcinoma, radical prostatectomy, postoperative radiotherapy

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Introduction

Despite the increased level of diagnostic methods, a significant number of prostate carcinoma cases are still detected in advanced stages. Radical prostatectomy is a basic method of prostate carcinoma treatment [1–5]. Surgical treatment provides perfect control in cases of patients with cancer limited to the organ (stage T1–T2) [6]. However, in about 38-52% of patients treated with prostatectomy, unfavorable prognostic factors [7, 8], such as extracapsular extension (ECE), seminal vesicles invasion (pT3b stage) or positive surgical margins (SM+), are observed and are considered to influence local control [9–11]. The pathological T3 stage is connected with 67% risk of biochemical failure appearing in a period of 5 years observation after prostatectomy [12]. In 50% of cases clinical symptoms of local recurrence develop and in about 30% of cases distant metastases appear [13–15].

Positive surgical margins constitute a prognostically important factor [11, 16]. The percentage of patients with microscopically positive margins (R1) in stage T2 is 5–10%, but in stage T3 it increases to 10–40% [17]. The meaning of R1 status in T2 stage is widely discussed, while in T3 it is considered an independent factor of biochemical progression. In about 60% of cases defined as pT3-R1 PSA increases during 5 years, often with no clinical symptoms [11]. On the other hand, in 35–40% of asymptomatic patients with PSA increasing after radical prostatectomy, the recurrence appears in an area of postoperative anastomosis and is revealed by biopsy [18].

Radiotherapy has been widely used after prostatectomy for years. Its aim is to sterilize the cancer cells in the prostate bed and thus to decrease the risk of local and biochemical recurrence. Apart from a number of retrospective studies, three randomized studies proved that implementation of postoperative radiotherapy in patients with high risk of recurrence has an influence on improving biochemical progression-free survival (bPFS) and clinical progression-free survival (cPFS) [19–24]. An improvement of overall survival after the use of adjuvant radiotherapy was proved in the SWOG study [22].

Material and methods

In the years 2002–2008, 121 consecutive prostate cancer patients underwent radical prostatectomy and postoperative radiotherapy. Radiotherapy was indicated by stage T3 (extracapsular extension or seminal vesicles invasion) and/or positive surgical margins. Patients with postoperative PSA level above 0.2 ng/ml were excluded. Imaging tests were not performed routinely before radiotherapy. After surgery hormonal therapy was given to 30 patients by urologists according to individual indications. Median patients' age at the

Table 1. Characteristics of patients

Feature	Value
Average patient's age	62.28 years (range: 45–81)
Median patients' age	62 years (range: 45–81)
Average preoperative PSA level (ng/ml)	13.77 (range: 0.28–102)
Median preoperative PSA level (ng/ml)	10 (range: 0.28–102)
Pathological TNM stage	
pT2c	2 (1.6%)
pT3a	69 (55.2%)
pT3b	48 (38.4%)
pT4	6 (5%)
pN0	112 (93%)
pN(+)	9 (7%)
Gleason score	
average	6.6
median	7
2–6	49 (40%)
7–9	72 (60%)
Extracapsular tumor extension	93 (77%)
Seminal vesicles invasion	51 (42%)
Vascular-nerve bundles infiltration	42 (35%)
Positive surgical margins	26 (21%)
Adjacent organs infiltration	6 (5%)
Hormonal therapy before surgery	12 (10%)
Hormonal therapy after surgery	30 (25%)
Average total irradiation dose (Gy)	64.45 (range: 56–72)
Median total irradiation dose (Gy)	64 (range: 56–72)
Median time between surgery and radiotherapy	1.8 months (range: 0.03–8.5)
Median follow-up	27.4 months (range: 3.5–108.3)

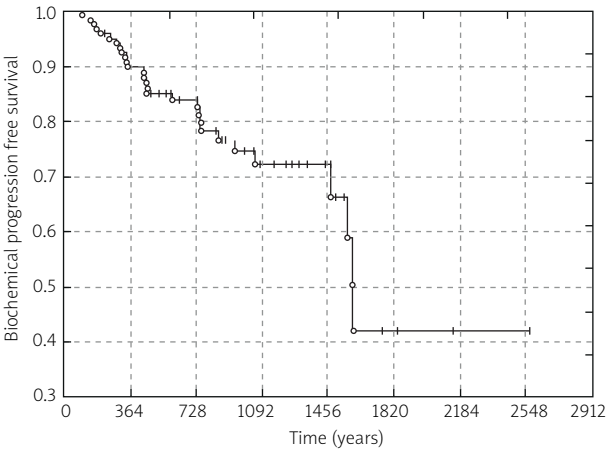

Fig. 1. Results of Kaplan-Meier analysis of biochemical progression-free survival (bPFS)

beginning of radiotherapy was 62 years (range: 45–81). Characteristics of patients are presented in Table 1.

All patients underwent radiotherapy with the use of a linear accelerator equipped with a multileaf collimator and generating photons of 15 MV energy. The median time between prostatectomy and the beginning of radiotherapy was 1.8 months (range: 0.031–8.5). The prostate and seminal vesicles postoperative bed was the irradiation target (CTV – clinical target volume) drawn by the radiation oncologist on the CT scans performed for treatment planning. Planning target volume (PTV) was created by adding a 10 mm margin to the CTV. The median dose given to the PTV was 64 Gy (range: 60–72 Gy). During the period of radiotherapy the patients were examined once a week. The first post-treatment examination was conducted a month after the treatment. Further examinations were conducted every three months for the next three years and then every six months. PSA levels were checked during each control visit. Imaging examinations were performed in the case of patients suspected of clinical or biochemical recurrence. Biochemical recurrence was defined by PSA increase over 0.2 ng/ml (second result exceeding this limit). Clinical recurrence was differentiated into local or distant. In case of suspected local recurrence magnetic resonance imaging (MRI) of the pelvis was conducted together with biopsy of detected changes and/or biopsy of urethra-bladder anastomosis. Distant spread of the disease was diagnosed by image tests (bone scan, X-rays, computed tomography (CT), ultrasonography of lymph nodes). Bone metastases were proven by 18F-FDG positron emission tomography (PET) in two patients, because bone scans in these cases were not diagnostic. The biochemical progression-free time was defined as from the day of surgery to the date of the second result exceeding the limit of 0.2 ng/ml. The clinical progression-free time was defined as from the day of surgery to the date of the image or histopathological test confirming the recurrence. Primary endpoints were biochemical progression-free survival (bPFS) and clinical progression-free survival (cPFS) and were estimated using the Kaplan-Meier method. As a secondary endpoint the influence of the following clinicopathological variables on recurrence was evaluated: patient's age, maximum preoperative PSA level, pathological grade according to the Gleason scale, vascular-nerve bundles infiltration, extracapsular tumor extension, seminal vesicles invasion, positive surgical margins, total dose of irradiation and the use of hormonal therapy. For this purpose univariate (log-rank test) and multivariate analyses (Cox's regression) were used. *P* value of 0.05 was defined as statistically significant. The statistical analysis was proceeded with the use of Statistica program ver. 9.0.

Results

The median follow-up was 27 months (range: 3.5–108.3). Three-year bPFS was 72% (Fig. 1).

The univariate analysis proved that bPFS was influenced by the following factors: extracapsular tumor extension (60% vs. 75%, $p = 0.0232$) (Fig. 2A), seminal vesicles invasion (52% vs. 85%, $p = 0.00041$) (Fig. 2B), Gleason score ≥ 7 (65% vs. 86%, $p = 0.044$) (Fig. 2C) and the use of hormonal therapy (50% vs. 80%, $p = 0.0058$) (Fig. 2D). Such factors as maximum preoperative PSA level, positive surgical margins, adjacent organs infiltration and irradiation dose did not significantly influence bPFS. Table 2 presents bPFS depending on the risk factors included in the univariate analysis.

According to the multivariate analysis, the following factors influenced bPFS: pTNM stage (HR = 3.19, $p = 0.007$), adjuvant hormonal therapy (HR = 2.6, $p = 0.02$), total irradiation

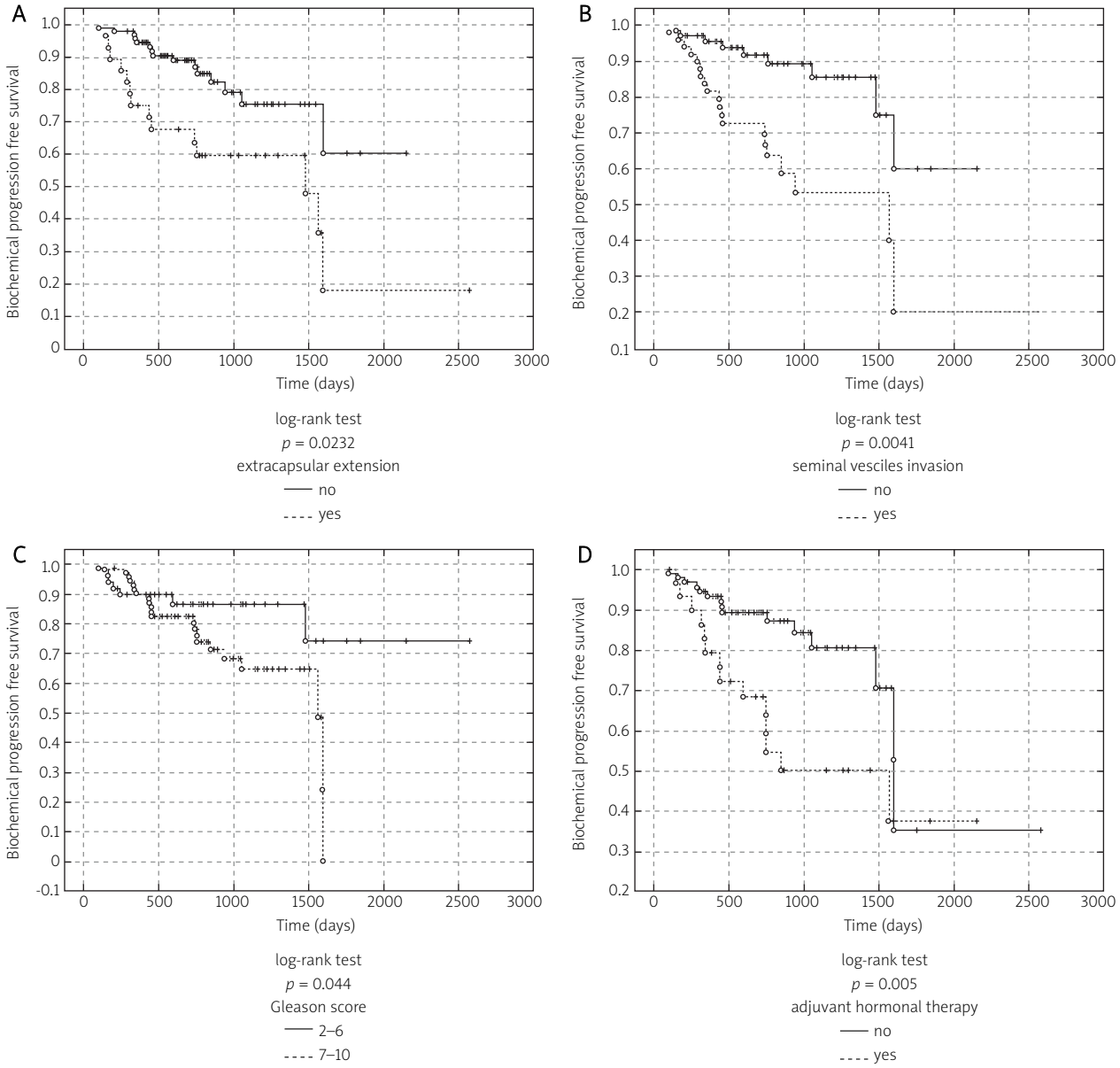

Fig. 2. Results of Kaplan-Meier analysis of bPFS depending on: **A)** the presence or absence of extracapsular extension; **B)** the presence or absence of seminal vesicles invasion; **C)** Gleason score; **D)** the use or lack of adjuvant hormonal therapy

dose used in the postoperative treatment (HR = 0.82, p = = 0.02) and the maximum pretreatment level of PSA (HR = = 0.95, p = 0.05) (Table 3).

When in the multivariate analysis we included histopathological data only, the most significant parameter influencing the risk of biochemical progression was the invasion of seminal vesicles (HR = 2.86, p = 0.02) (Table 4).

Biochemical recurrence was noted in 29 (24%) out of all analyzed cases and appeared 3–52 months (median: 15 months) after the day of surgery. Among them in 18 (62%) cases clinical recurrence was diagnosed. In 13 patients biochemical progression preceded clinical recurrence, on average by 5 months. In the remaining 5 patients biochemical and clinical progression appeared at the same time. In 3 cases the clinical recurrence involved the tumor bed and in the other 15 cases distant metastases appeared, mainly to the bones (11 cases) and in individual cases to the lung, brain, liver and supraclavicular lymph nodes.

Three-year clinical progression-free survival (cPFS) was 84% (Fig. 3).

The univariate analysis proved that cPFS was influenced by the following factors: preoperative PSA level > 10 ng/ml (75% vs. 90%, p = 0.04) (Fig. 4A), vascular-nerve bundles involvement (63% vs. 88%, p = 0.0031) (Fig. 4B), adjacent organs infiltration (50% vs. 85%, p = 0.018) (Fig. 4C) and the use of postoperative hormonal therapy (62% vs. 90%, p = 0.02) (Table 2, Fig. 4D).

According to the multivariate analysis, cPFS was influenced by such factors as TNM stage (HR = 2.68, p = 0.005), postoperative hormonal therapy (HR = 3.61, p = 0.02) and total irradiation dose used in the postoperative treatment (HR = 0.78, p = 0.03) (Table 3).

Table 2. Dependence of bPFS and cPFS on progression risk factors – univariate analysis results

	N	3-year cPFS	*P* value	3-year bPFS	*P* value
Gleason score					
≤ 6	49	86%	NS	86%	0.044
≥ 7	72	82%	(p = 0.09)	65%	
Preoperative PSA level (ng/ml)					
≤ 10	64	90%	0.04	81%	NS
> 10	57	75%		64%	
Patient's age (years)					
≤ 62	61	75%	NS	75%	NS
> 62	60	81%		81%	
Extracapsular extension					
Yes	93	72%	NS	75%	0.0232
No	28	88%		60%	
Seminal vesicles invasion					
Yes	51	75%	NS	52%	0.00041
No	70	91%	(p = 0.06)	85%	
Vascular-nerve bundles infiltration					
Yes	42	88%	0.031	63%	NS
No	79	63%		63%	
Positive surgical margins					
Yes	27	91%	NS	86%	NS
No	94	82%		70%	
Adjacent organs infiltration					
Yes	6	50%	0.018	50%	NS
No	115	85%		72%	
Adjuvant hormonal therapy					
Yes	30	62%	0.02	50%	0.0058
No	91	90%		80%	
Total irradiation dose					
≤ 64 Gy	80	82%	NS	70%	NS
> 64 Gy	31	86%		75%	

Table 3. Dependence of bPFS and cPFS on progression risk factors – multivariate analysis results (Cox regression)

	cPFS		bPFS	
	hazard ratio	*P* value	hazard ratio	*P* value
Patient's age	0.93	0.08	0.9	0.17
pTNM stage	2.68	0.005	3.1	0.00018
Gleason score	1.46	0.11	1.2	0.01
Neoadjuvant hormonal therapy	0.49	0.42	1.3	0.60
Adjuvant hormonal therapy	3.61	0.02	2.6	0.02
Maximum preoperative PSA level	0.95	0.13	0.95	0.05
Total radiation dose	0.78	0.03	0.82	0.02

Table 4. Influence of histopathological parameters on bPFS – results of multivariate analysis

	Hazard ratio	*P* value
Extracapsular extension	0.59	0.22
Seminal vesicles invasion	2.86	0.02
Vascular-nerve bundles infiltration	0.67	0.40
Positive surgical margin	0.72	0.57
Adjacent organs infiltration	2.75	0.11
Positive lymph nodes	0.96	0.96

Discussion

Postoperative, adjuvant radiotherapy of patients after prostatectomy has been controversial for years. Some authors have claimed that in patients with unfavorable prognostic factors it should be performed immediately after surgery [14, 26, 27, 30], while others have advised to wait until the PSA is increased or until biopsy confirms local recurrence [31, 32]. However, external beam irradiation has been widely used as a postoperative method of treatment. Approximately in about 30–50% of patients with a tumor clinically limited to the prostate, evaluation of postoperative mate-

rial shows infiltration of the prostate capsule. Standard indications for postoperative irradiation include pT3 stage (extracapsular extension, seminal vesicles invasion), positive surgical margins and a detectable level of PSA after three weeks following surgery. The last indication is justified by the fact that 50% of patients with enduring PSA have a positive result of biopsy of urethra-bladder anastomosis.

A number of nonrandomized retrospective studies have been conducted in order to evaluate the role of postoperative radiotherapy. Their results proved that in the case of patients treated with postoperative radiotherapy it is possible to achieve even 95–100% local control [14, 33–36] and a dose of 60 Gy significantly influences asymptomatic survival [37–42].

The use of postoperative radiotherapy after radical prostatectomy in the pT3 stage significantly limits local recur-

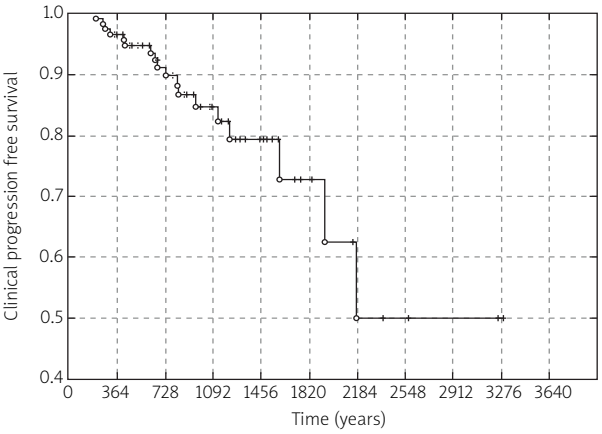

Fig. 3. Results of Kaplan-Meier analysis of clinical progression-free survival (cPFS)

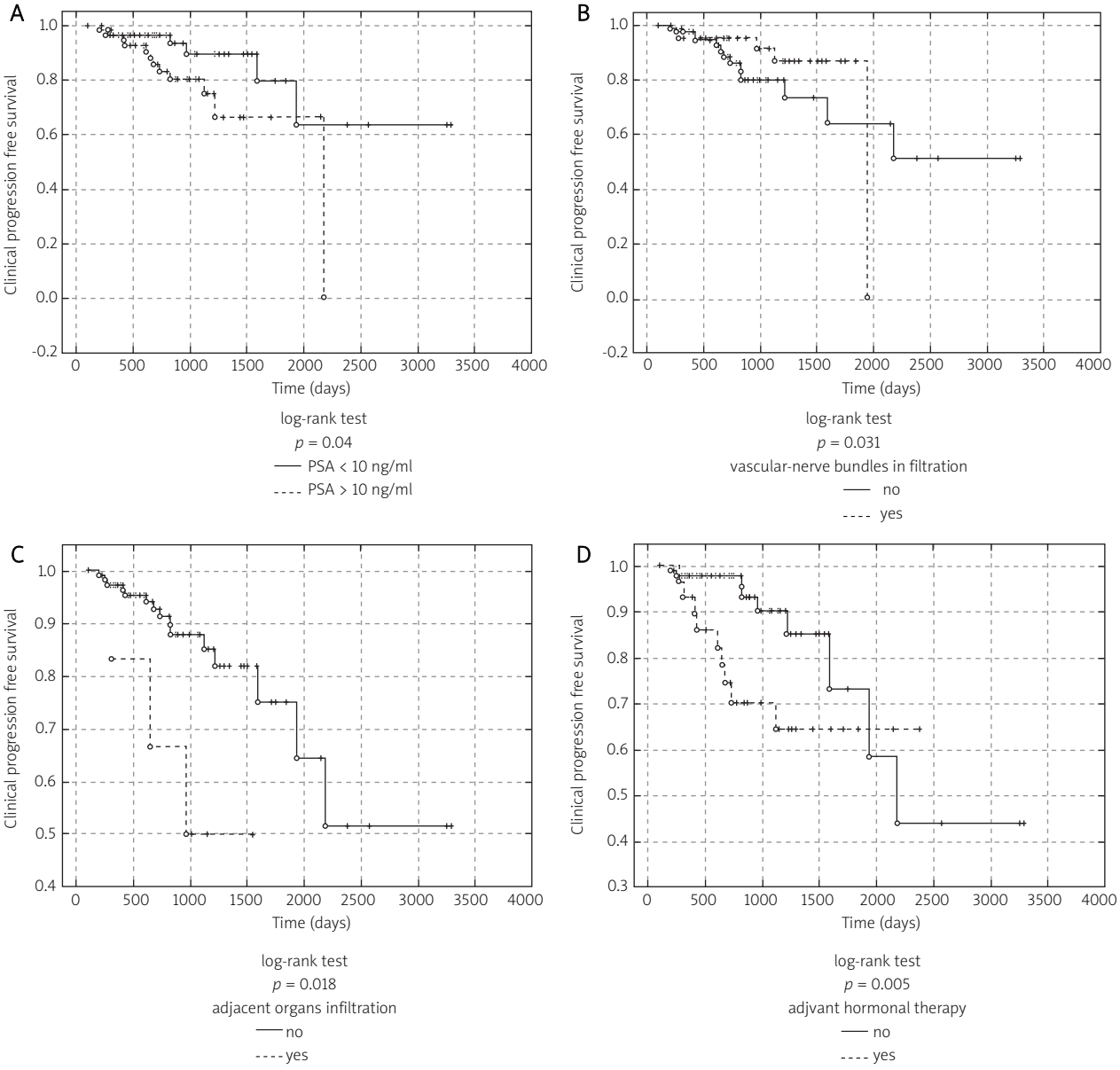

Fig. 4. Results of Kaplan-Meier analysis of cPFS depending on: **A)** preoperative PSA level; **B)** the presence or absence of vascular-nerve bundles infiltration; **C)** the presence or absence of adjacent organs infiltration; **D)** the use or lack of postoperative hormonal therapy

rence. During 10-year observation of a group of 46 patients Anshers *et al.* noted over 30% reduction of local recurrences, which was a result of using postoperative radiotherapy (40% vs. 8%). Also the percentage of 10-year asymptomatic survival in patients treated with postoperative radiation was significantly higher (55% vs. 37%). However, no increase of overall survival was confirmed [14, 43].

Schild *et al*. and Nudell *et al.* made a retrospective evaluation of immediate postoperative radiotherapy in patients with PSA increasing after surgery. Postoperative radiotherapy (in case of positive surgical margin or pT3) enabled 57–80% 5-year disease-free survival [30, 37, 44].

Valicenti *et al.* estimated the influence of irradiation dose on risk of recurrence in a group of 86 patients. Radiotherapy using doses of 55–70.2 Gy (average: 64.8 Gy) was applied within 3-6 months after prostatectomy. Among 52 patients with PSA undetectable before radiotherapy, better control appeared in cases of patients given 61.5 Gy or more than in a group with lower doses (91% vs. 57%) [26, 39].

Petrovich *et al.* published results of a study conducted on 432 patients with stage T3N0 cancer. Sixty-nine percent of the patients did not experience recurrence during 5-year follow-up. In the multivariate analysis Gleason score and pTNM stage were independent factors influencing asymptomatic survival. Results of T3bN0 patients with Gleason score of 7–10 were significantly worse. In this group probability of recurrence was 5.3 times higher than for patients with T3a and Gleason score 2–6 (4). Caraffini *et al.* reported results of a nonrandomized study conducted on 97 patients among whom 41 underwent adjuvant radiotherapy and 56 underwent salvage radiotherapy after PSA increase. Five-year disease-free survival in the whole group was 53% and in the group with postoperative radiotherapy it was 76% [35]. Similar results were obtained by other researchers: Syndikus *et al.* (93%) [38], Zietman *et al*. (73%) [40], Choo *et al.* (88%) [41] and Vargas *et al.* (52%) [42].

Three randomized studies (EORTC 22911, SWOG 8794, ARO) proved benefits from postoperative radiotherapy in case of unfavorable prognostic factors. Postoperative radiotherapy improved asymptomatic survival (free of clinical or biochemical evidence of disease), decreased the risk of clinical recurrence [19–24] and influenced overall survival [23].

The Bolla *et al.* EORTC 22911 study compared the results of postoperative radiotherapy in a group of 502 patients with the results of prostatectomy alone in a group of 503 patients. Postoperative radiotherapy was performed in case of unfavorable prognostic factors, such as extracapsular extension, positive surgical margins and/or seminal vesicles invasion. During 5-year follow-up bPFS was better in the group of patients who underwent radiotherapy (74% vs. 52.6%). Clinical PFS was also better in the irradiated group (85% vs. 75%). Frequency of recurrence during the 5-year follow-up was significantly lower in the group with adjuvant radiotherapy (5.4% vs. 15.4%). An influence on overall survival was not proved. Toxicity of the treatment was not high and caused treatment discontinuation in 3.1% of cases. In a control group radiotherapy was used in case of PSA increase (61.3%) or locoregional progression (34.4%). The main objections against the study concern the use of conventional radiation, suboptimal total irradiation doses, including patients with constant increase of PSA (10.7%), and variation in treatment of recurrences [19, 20].

The second randomized study, SWOG 8794, was performed in a group of 473 patients with extracapsular extension, positive margins and/or seminal vesicles infiltration. Patients who underwent radiotherapy were given a dose of 60–64 Gy. The follow-up was 9.7 years. Biochemical PFS (PSA < 0.4 ng/ml) was much longer in the irradiated group (72% vs. 42%). Distant metastasis-free survival was also better in the group with postoperative radiotherapy ($p = 0.023$) [22]. In patients with extracapsular extension, radiotherapy significantly improved bPFS (57% vs. 22%) and decreased local recurrence risk (8% vs. 22%). Side effects of radiotherapy were insignificant and did not affect patients' quality of life. In the control group 32% of patients underwent salvage radiotherapy [21–23, 46].

The third randomized study was performed by the German group ARO 96-02/AUO AP 09/95. The analysis included 385 patients from 22 centers in stage pT3 or with positive margins. One hundred thirty-two patients underwent postoperative radiotherapy and were given 60 Gy in 30 fractions. Patients diagnosed with postoperative PSA increase were classified as showing disease progression and thus given a higher average dose of 66.6 Gy. The follow-up was 40 months. In the irradiated group an improvement of bPFS was noted (72% vs. 54%). An influence of radiotherapy on overall survival was not proved. Frequency of recurrence was 16% vs. 7% in favor of patients who underwent radiotherapy. The tolerance of irradiation was good [24].

The quoted randomized studies provided evidence that postoperative radiotherapy improves bPFS with an acceptable level of side effects. It is, however, probable that 50% of patients will be irradiated unnecessarily. On the other hand, waiting for clinical recurrence in case of biochemical progression can cause spread of the disease.

Our study is a retrospective observation and presents results of treatment of 121 patients who underwent radical prostatectomy and postoperative radiotherapy. During 27 months of follow-up the biochemical progression-free survival for the analyzed group was 72%. These results are difficult to compare with others due to the high diversity of the group, which included patients with stage T3 or T4 disease and positive nodes, and due to the relatively short time of observation. In the univariate analysis it was proved that the following factors negatively influenced 3-year bPFS: extracapsular tumor extension, seminal vesicles invasion, Gleason ≥ 7 and no use of hormonal therapy. Maximum preoperative PSA level, infiltration of vascular-nerve bundles, positive surgical margins, infiltration of adjacent organs and dose of irradiation did not significantly influence bPFS. In the multivariate analysis such factors as advanced TNM stage, no use of postoperative hormonal therapy, lower total irradiation dose and higher maximum pretreatment PSA level were associated with worse bPFS. During the follow-up 29 patients (24%) experienced biochemical recurrence that appeared 3–52 months (median: 15 months) after the day of surgery. Among them in 18 cases (14.8%) clinical recurrence was diagnosed. In 13 cases biochemical progression preceded clinical recurrence (on average by 5 months). In the remaining 5 cases biochemical and clinical progression appeared

at the same time. Such a high percentage of recurrence may result from allowing in the analysis patients with stage T4 disease. In the univariate analysis it was proved that such factors as preoperative PSA > 10 ng/ml, vascular-nerve bundles and adjacent organs infiltration as well as no use of postoperative hormonal therapy negatively influenced 3-year cPFS.

In the light of randomized studies postoperative radiotherapy is a treatment option that should be considered in patients with unfavorable prognostic factors because of its significant local effectiveness and relatively low toxicity, which we confirmed in our observation. Early commencement of radiotherapy can bring better treatment results. Thus good cooperation between urologists and radiation oncologists is required, which was proved by a number of retrospective and prospective studies [14, 19–24, 35, 38, 42, 47].

Radiotherapy is nowadays a widely accepted method of treating prostate cancer patients. Technological progress and constant improvement of irradiating methods have significantly increased oncological effectiveness of this method in recent years. Also increased safety of irradiation and decreased risk of post-irradiation complications constitute significant benefits in treating patients after radical prostatectomy. Although the influence of radiotherapy on patients' quality of life requires further research, acceptance of the method is growing and growing.

The authors declare no conflict of interest.

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Address for correspondence

Ewa Ziółkowska MD, PhD
Department of Radiotherapy I
Oncology Centre – prof. Franciszek Łukaszczyk Memorial Hospital
I. Romanowskiej 2
85-796 Bydgoszcz
e-mail: ziolkowskae@co.bydgoszcz.pl

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