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Salvage lymphadenectomy in patients with lymphogenic prostate cancer progression after radical treatment: results of a multicenter study

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Prostate cancer (PC) is one of the most challenging and pressing problems of modern oncourology because of high morbidity associated with the disease. The main methods of radical treatment of patients with localized and regional PC are radical prostatectomy and beam radiation therapy, external or brachytherapy. Nonetheless, the rate of biochemical progression of the disease after radical treatment remains high and averages 27–53 %. Of the utmost importance is determination of the tumor nidus which raises the marker level. Currently, in patients with distant metastases the only widely accepted treatment method is palliative hormonal therapy (HT). However, in majority of patients marker recurrence can be associated with so-called oligometastatic progression characterized by a minimal number of detectable metastases. Research shows that surgical treatment or beam radiation therapy in selected patients of this cohort allows to significantly increase the time until HT prescription, and in some cases to abandon it altogether. The article describes the results of surgical treatment of patients subjected to salvage lymphadenectomy for oligometastatic PC progression at three centers: P.A. Hertzen Moscow Oncology Research Institute, N.N. Petrov Research Institute of Oncology and Russian Research Center for Radiology and Surgical Technologies. In the multicenter study, short-term and long-term results of surgical treatment of 57 patients were evaluated. It was shown that in some patients, salvage lymphadenectomy can be an effective treatment option significantly lengthening the time until HT prescription, and in 23.4 % of patients it can lead to long-term (12 months) stabilization of the disease and 90 % decrease in prostate-specific antigen level compared to the initial pre-surgery level without any additional forms of therapy.

Key words: *prostate cancer, oligometastases, lymphogenic progression, salvage lymphadenectomy, short-term treatment results, long-term treatment results, multicenter study*

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Introduction

Prostate cancer (PC) is the 2nd most common malignant tumor among males in Russia, and it constitutes 14.3 % of all cancer cases in this population [1]. In men after 60 this number rises to 18.5 %. In 2014, 37,168 new cases of PC were registered in Russia, and the average age of men with newly onset PC was 64.4 years (in 2003, the average age was higher – 70.4 years). Adjusted incidence rate for PC in 2014 was 39.38 in 100,000 males. Considering the average annual growth rate of 7.11 %, morbidity increase from 2004 to 2014 was 116.68 %. Compared to 2004, in 2014 standardized mortality ratio for all malignant tumors dropped considerably for men (–12.3 %), but it increased for malignant prostate tumors (26.2 %). Thus, PC is a cause of death for 6.2 % men aged 60– 69, but in 70 and over age group this number amounts to 14.16 %, which places PC as the 2nd most common oncological cause of death after trachea, bronchi, and lung tumors [1]. Therefore, PC is one of the most challenging and pressing problems in oncology today.

Surgical or radiation treatment is considered the main therapy for patients with local or regional PC. Nonetheless, after radical treatment recurrence or progression of the disease are quite common. Thus, after surgical treatment biochemical relapse develops in 27–53 % of patients [2–5]. Clinical progression in the form of distant metastases occurs only in one third of biochemical relapse cases [6]. Treatment of these patient requires a personalized approach depending on the distribution of metastatic sites. Metastatic PC is a heterogenous disease which includes a subgroup of patients with minimal number of metastases (oligometastatic process), as well as a subgroup of patients with extensive metastatic lesions. Routine radiology methods used in clinical practice, such as skeletal scintigraphy,

ultrasound, magnetic resonance tomography, and computed tomography (CT), are not sensitive or specific enough to detect minimal tumor shifts accompanied by an insignificant increase in prostate-specific antigen (PSA) level. Thus, for skeletal scintigraphy the number of patients with 5 and less detectable lesions is only 41 %. Use of CT allows to detect 3 metastases with median PSA level ≥ 25 ng/ml in 73 % of patients [7, 8]. Positron emission tomography/computed tomography (PET/CT) is a relatively new radiology method which allows to verify small metastases with high accuracy even for low PSA levels. Choline-based radiopharmaceuticals labeled with positron-emitting radionuclides ^{11}C or ^{18}F are commonly used in diagnostics of PC relapse [9]. Lately, in the USA and some European countries, diagnostic methods involving Gallium isotope are being actively introduced in clinical practice, as well as PET with prostate-specific membrane antigen [10–13]. However, these methods aren't universally accessible because of their high cost. As of today, in Russia the only accessible methods of PET diagnostics are methods based on choline and ^{11}C-glucose.

Worldwide, a lot of knowledge on surgical treatment of oligometastatic PC progression after radical therapy was accumulated. The main indication for this type of treatment is lymphogenic progression of the disease, i.e. presence of metastases in lymph nodes (LNs). One of the earliest large trials was the work of P. Rigatti et al. They analyzed outcomes of surgical treatment of 72 patients with PC accompanied by biochemical relapse after radical prostatectomy (RP) and metastases in LNs identified by PET/CT with ^{11}C-choline [14]. Local recurrence and distant metastases were ruled out in all patients. Mean and median PSA levels were 3.7 and 1.5 ng/ml, respectively. All patients received salvage lymphadenectomy (SL), extent of which depended on lesion location per PET/CT (extended pelvic lymph node dissection (ePLND) was performed in 47 (65.3 %) patients, retroperitoneal LND – in 12 (16.7 %) patients, their combination – in 13 (18.0 %) patients). Mean and median numbers of distant LNs were 30.6 (4–87) and 29.0, respectively; mean and median numbers of metastases in LNs were 9.8 and 2.0, respectively. In 60 (83.3 %) of 72 patients LN metastases were histologically confirmed. In 41 (56.9 %) patients PSA level on the 40th day after the surgery was < 0.2 ng/ml. Immediate adjuvant hormonal therapy (HT) was recommended for 13 (31.7 %) patients, 28 patients were followed up. Biochemical relapse developed in 24 of 28 patients, and they too received HT. Therefore, only 4 patients didn't receive HT during the follow-up; 5-year biochemical relapse-free survival was 19 %. Five-year survival without clinical progression and tumor-specific survival (TSS) were 34 and 75 %, respectively. Analysis revealed factors unfavorably influencing survival: PSA level > 4.0 ng/ml before SL, absence of PSA level decrease to less than 0.2 ng/ml after the surgery, metastases in retroperitoneal LNs. Independent predictors of clinical progression were PSA level > 4 ng/ml, drug accumulation in retroperitoneal LNs according to PET/CT, and metastases in retroperitoneal LNs according to histological tests.

C.A. Jilg et al. evaluated results of surgical treatment of 52 patients who received primary therapy for PC [15]. Mean and median preoperative PSA levels were 3.9 and 1.1 ng/ml, respectively; mean and median numbers of distant LNs after salvage PLND were 23.3 and 17.0 respectively; mean and median numbers of LN metastases were 9.7 and 4.0, respectively. The criterion of complete biochemical response after PLND was PSA level decrease < 0.2 ng/ml. Complete PSA response was achieved in 24 (46 %) of 52 patients. In 27 (52 %) of 52 patients beam radiation therapy was used after salvage PLND. Radiation area included anatomical area with detected histologically confirmed metastases in LNs. Median follow-up time was 35.5 months. Among patients with PSA level decrease to less than 0.2 ng/ml (n = 24) after salvage PLND, 12-month relapse-free biochemical survival was 71.8 %. For the total group (n = 52) 5-year relapse-free survival was 26 %, 5-year TSS was 78 %.

D. Tilki et al. performed a retrospective analysis of surgical treatment outcomes for 58 PC patients, who underwent salvage PLND in 2005-2012 [16]. After primary treatment, all patients underwent PET/CT with ^{18}F-choline due to PSA level increase, and pathological accumulation of the contrast agent was observed in at least 1 LN. In 4 patients drug accumulation was also detected in prostatic fossa, in 2 patients besides LN changes solitary bone lesions (considered non-specific changes) were detected. All patients received ePLND and/or retroperitoneal LND in accordance with the presence of metastases in LNs in the corresponding area per PET/CT. ePLND alone was performed in 23 (39.7 %) patients, retroperitoneal LND only – in 3 (5.2 %) patients, ePLND and retroperitoneal LND – in 32 (55.2 %) patients. Mean number of excised distant LNs was 19 (1–88). In 45 (77.6 %) patients metastases in LNs were detected during routine histological study (mean number of metastases was 6). In 31 (86 %) of 36 patients with preoperative PSA level > 4.0 ng/ml metastases were confirmed histologically. Metastases in LNs after SL were detected only in 14 patients with preoperative PSA level < 4.0 ng/ml (mean number of metastases was 3). Thirty-nine (67.2 %) patients received adjuvant HT after SL. Treatment response was defined as PSA level decrease to less than 0.2 ng/ml on the 40th day after the surgery. Median follow-up duration was 39 months. PSA response was observed in 13 (22.4 %) patients. Only in 1 patient during the follow-up period no subsequent marker increase was observed. Clinical tumor progression was diagnosed in 25 (48.1 %) patients. Six (10.3 %) patients died of PC progression (all with metastases in other organs except LNs per PET/CT performed before the surgery). Five-year TSS was 71.1 %. Factors significantly increasing TSS were PSA level < 4 ng/ml,

absence of extralymphatic lesions per PET/CT, and metastases in 2 LNs or less.

A. Winter et al. evaluated results of SL in 13 PC patients with metastases in LNs after primary treatment [17]. Median PSA level before the surgery was 1.64 ng/ml. SL was performed in the area of pathological contrast agent accumulation per PET/CT performed before the surgery. In 11 of 13 patients metastases in LNs were confirmed histologically. In 13 of 16 LNs interpreted during PET/CT as metastases, presence of tumor cells was confirmed histologically. PSA response, i.e. PSA level decrease < 0.2 ng/ml without HT, was observed in 10 of 11 patients after the surgery. Total remission during the follow-up was achieved in 3 patients without adjuvant HT after SL (median follow-up duration was 72 months).

N. Suardi et al. combined experiences of 5 medical centers and analyzed treatment outcomes of 162 patients with recurrent PC after primary radical therapy and metastases in LNs per PET/CT with ^{11}C-choline [18, 19]. Mean and median preoperative PSA levels were 3.6 and 1.9 ng/ml, respectively. Mean follow-up duration until biochemical recurrence was 29.2 months. Mean and median numbers of excised LNs were 25 and 20, respectively. Patients were distributed by volume of lymph node dissection as follows: PLND was performed in 76 (46.9 %) patients, retroperitoneal LND – in 2 patients (1.2 %), both PLND and retroperitoneal LND – in 84 (51.9 %) patients. Metastases in LNs were histologically confirmed in 132 (81.4 %) patients. Mean and median number of diagnosed metastases in LNs were 6.1 and 2.0, respectively. Complete biochemical response was observed in 66 (40.7 %) patients after salvage PLND in 40 months of the follow-up. In this patient group 3- and 5-year biochemical relapse-free survivals were 59 and 40 % respectively. After 5-year follow-up, 11 patients experienced no biochemical relapse without HT. According to Cox multivariate regression analysis, only the number of metastases (≤ 2) in LNs and complete biochemical response (PSA level decrease < 0.2 ng/ml) after SL were independent favorable prognostic factors.

Therefore, in near future the standards for treatment of PC patients with solitary metastases after primary treatment may be reconsidered. SL can be used efficiently in carefully selected patients with lymphogenic PC progression after radical treatment. The article describes experience of performing SL in these patients in 3 Russian medical research centers.

Study objective – To evaluate SL outcomes in PC patients with disease progression after radical therapy.

Materials and Methods

The study was conducted at 3 medical centers: P.A. Hertzen Moscow Oncology Research Institute, N.N. Petrov Research Institute of Oncology, and Russian Research Center for Radiology and Surgical Technologies. Total number of patients included in the study was 57. The patients had PC with biochemical progression after radical treatment and confirmed solitary metastases in LNs per PET/CT with ^{11}C-choline: 22 (38.6 %) patients received treatment at P.A. Hertzen Moscow Oncology Research Institute, 24 (42.1 %) patients – at Russian Research Center for Radiology and Surgical Technologies and 11 (19.3 %) – at в N.N. Petrov Research Institute of Oncology. Oligometastatic lymphogenic disease progression was confirmed in all patients by PET/CT with ^{11}C-choline: metastatic LNs were detected in the absence of metastases in other locations and local disease recurrence. In 44 (77.2 %) patients metastases in LNs were detected after previous surgical treatment, in 7 (12.3 %) patients – after external beam radiation therapy, in 4 (7.0 %) patients – after brachytherapy. After focal therapies (high intensity focused ultrasound (HIFU) or cryoablation), lymphogenic PC progression without local recurrence according to PET/CT was observed in 2 (3.5 %) patients (Fig. 1). Baseline patient data is presented in Table 1. Mean patient age at the time of SL was 63.2 ± 6.9 years (54–74 years), mean PSA level before

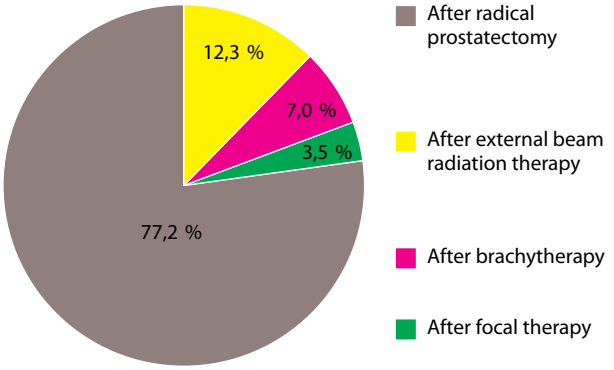

Fig. 1. *Distribution of patients by initial therapy*

Table 1. *Baseline data on patients before initial therapy (n = 57)*

Measure	Value
Average PSA level, ng/ml	22,1 ± 18,3 (5,6–114,0)
cT category, *n* (%): T1c–T2c T3a–T4	 20 (35,1) 37 (64,9)
Total Gleason score based on biopsy data, *n* (%): ≤ 6 7 (3 + 4) 7 (4 + 3) 8–10	 25 (43,9) 13 (22,8) 9 (15,8) 10 (17,5)

Note. *Here and in Tables 2, 3 and in Fig. 2, 9, 11, 12: PSA – prostate-specific antigen.*

Table 2. *Data on a subgroup of patients with lymphogenic progression of the disease after RP and before SL (n = 44)*

Measure	Value
Average PSA level, ng/ml	6,6 ± 5,8 (0,6–16,4)
Average time between RP and SL, months	22,5 ± 29,9 (9–142)
pT category, *n* (%): pT2c pT3a–T4	 13 (29,5) 31 (70,5)
Total Gleason score after surgery, *n* (%): 6 7 (3 + 4) 7 (4 + 3) 8–10	 4 (9,1) 11 (25,0) 13 (29,5) 16 (36,4)
pN category, *n* (%): pN0 pN+	 38 (86,4) 6 (13,6)

Note. *Here and in Table 3: RP – radical prostatectomy; SL – salvage lymphadenectomy.*

SL was 6.6 ± 5.8 (0.6–16.4) ng/ml, median PSA level was 2.5 ng/ml. Mean time between initial therapy and SL was 23.6 ± 26.4 (9–142) months.

Subset analysis of the patients who underwent surgery at the 3 centers did not reveal any statistically significant differences concerning the main prognostic clinical factors before primary treatment (initial PSA level, tumor differentiation based on the Gleason score calculated using biopsy data, clinical stage before initial therapy), $p > 0.05$. Percent of positive biopsy samples as a prognostic factor was evaluated only in 22 patients who received surgical treatment at P.A. Hertzen Moscow Oncology Research Institute and it amounted to 73.6 ± 30.3 % (20–100 %).

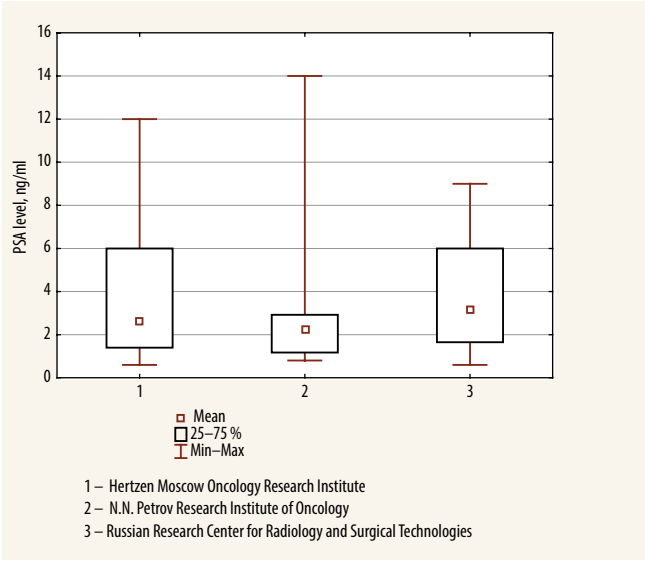

Fig. 2. *Median PSA level before salvage lymphadenectomy in patients at the 3 centers*

Data on the patient subgroup with lymphogenic progression after RP before SL is presented in Table 2.

Among the patients who underwent SL at the 3 centers no statistically significant differences in PSA levels before the surgery were observed (Fig. 2).

At the 3 centers, no statistically significant differences in morphological stage, tumor differentiation in removed prostates, and number of detected metastases were found in patient subgroup with lymphogenic progression after previous RP ($p > 0.05$).

Presence of metastases in LNs accompanied by absence of local metastasis or metastases in other organs was confirmed in all patients by PET/CT with choline (Fig. 3).

Median number of metastatic LNs before SL observed by PET/CT was 3 (from 1 to 7 metastases were diagnosed). The study only included patients with affected LNs located in the lesser pelvic cavity under aortic bifurcation. At the 3

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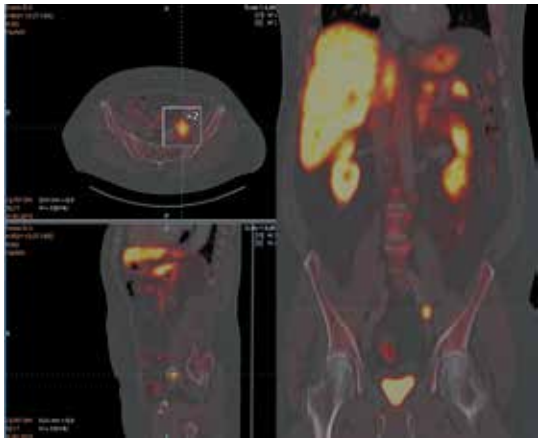

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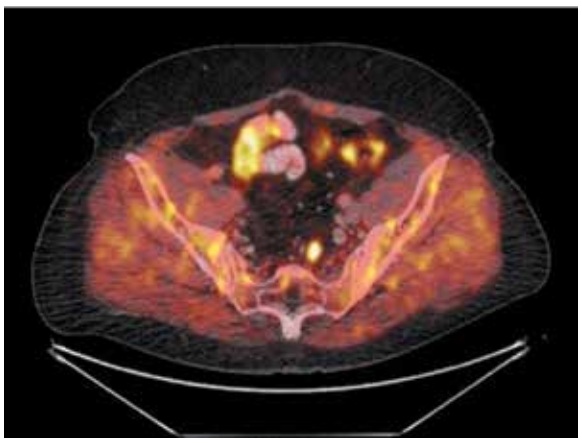


Fig. 3. *Positron emission tomography coupled with computed tomography: а – patient B., 62 years, with lymphogenic progression of the disease after radical prostatectomy in September of 2011; б – patient G., 57 years, with lymphogenic progression of the disease after radical prostatectomy in March of 2011*

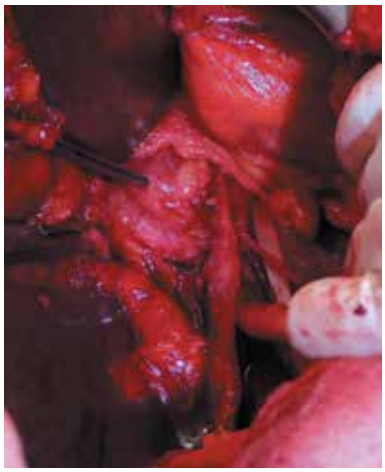
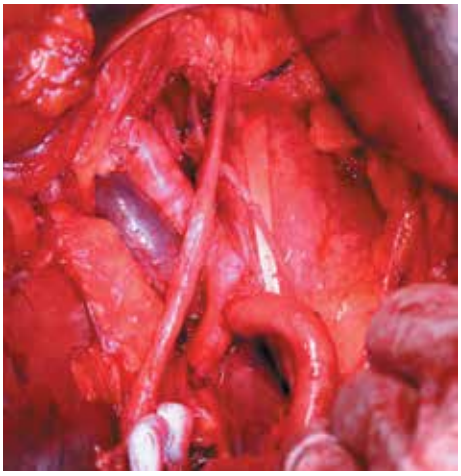


Fig. 4. *Metastasis localized in the projection of left iliac vessels*

centers, all enrolled patients underwent open or laparoscopic ePLND with excision of all metastatic LNs. Additionally, LNs from all areas in the lesser pelvic cavity were removed regardless of metastases localization (Figs. 4–7).

A strict follow-up was established for all patients who underwent SL. One month after SL PSA level was tested in all patients. If patient's PSA level decreased, no additional



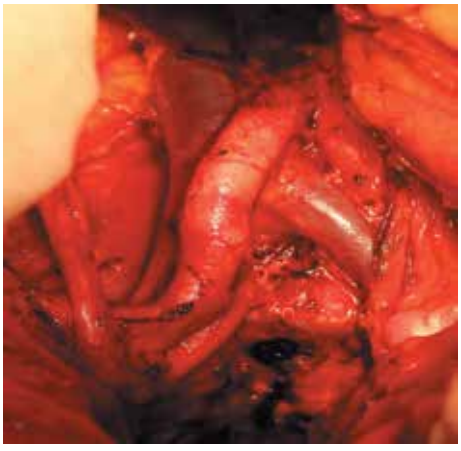


Fig. 5. *View of the operation field after extended salvage lymphadenectomy*

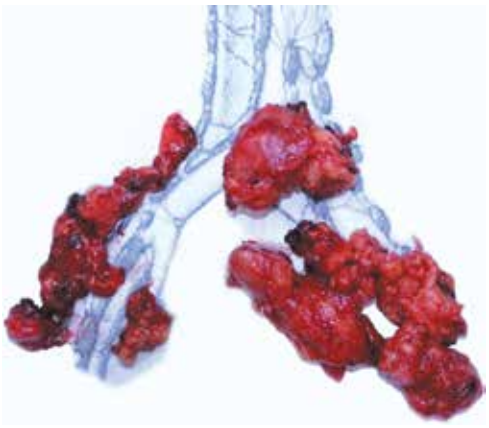


Fig. 6. *Gross specimen and a diagram of lymph node dissection boundaries*

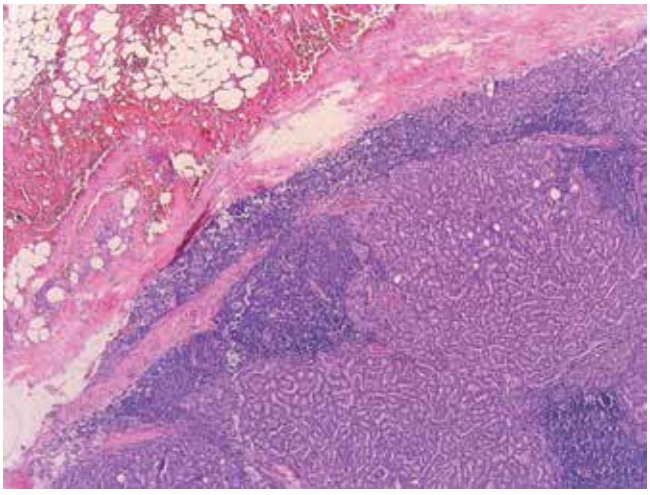


Fig. 7. *Micro-specimen. Prostate cancer metastasis in a lymph node*

drug therapy was prescribed, but the follow-up continued. HT was recommended only if symptoms of disease progression were detected, or if patient's PSA level increased. Complete remission was defined as PSA level of 0.2 ng/ml or lower after the surgery.

Results and Discussion

Routine morphological study showed that median number of excised LNs was 16 (from 3 to 40). Metastases in the removed LNs were observed in 53 (93 %) patients. It should be noted, that for some patients additional metastases in LNs, not detected by preoperative PET/CT, were found during morphological study of the samples acquired through SL. Thus, additional metastases in LNs were observed in 24 (45.3 %) of 53 patients. Median number of metastases discovered during routine morphological study was 3 (from 1 to 22 metastases). For 4 (7 %) patients no metastases in the excised LNs were found during routine morphological study, but considering persisting high PSA level HT was recommended. This group was excluded from the survival analysis.

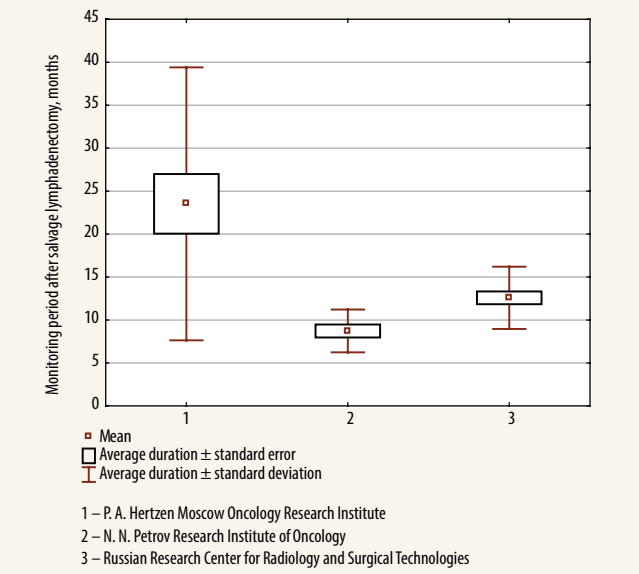


Fig. 8. *Average duration of monitoring in the 3 research centers*

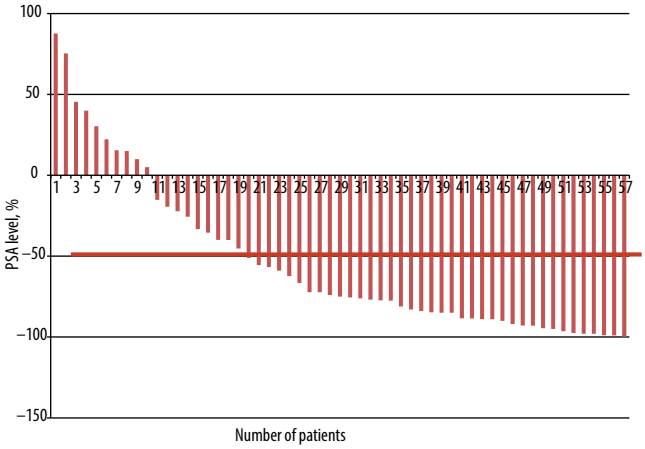


Fig. 9. *PSA level dynamics 1 month after salvage lymphadenectomy*

Mean follow-up duration for the patients in the total group was 16.8 ± 12.3 months, median duration was 12 months (6–48 months). Subgroup analysis revealed statistically significant differences in the follow-up duration for patients from different medical centers. Thus, mean follow-up duration at the P.A. Hertzen Moscow Oncology Research Institute was 23.5 ± 15.9 (6–48) months, at the N.N. Petrov Research Institute of Oncology – 8.7 ± 2.5 (6–12) months, at the Russian Research Center for Radiology and Surgical Technologies – 12.6 ± 3.6 (6–18) months; $p = 0.0056$. Therefore, follow-up durations at the 3 centers were significantly different. This may be explained by the fact that surgeries were performed at different times (Fig. 8).

Evaluation of PSA level dynamics after SL has shown response to the therapy (in the form of marker level decrease) in 47 (82.5 %) patients. In 10 (17.5 %) patients stabilization or increase of PSA level was observed.

Dynamics of PSA level 1 month after SL are presented in Fig. 9. The plot shows ≥ 50 % decrease in PSA level in 38 (66.7 %) patients 1 month after the surgery compared to the initial value established at biochemical progression diagnosis before SL. Complete response defined as marker level ≤ 0.2 ng/ml was observed in 13 (22.8 %) patients.

The plot shows a significant PSA level decrease in the majority of patients 1 month after SL. Routine extended SL with excision of both verified by PET/CT metastases and residual LNs form the lesser pelvis cavity was associated with satisfactory biochemical response in the majority of patients included in the study. Absence of therapy response and an increase in marker level were observed in 10 (17.5 %) patients, of which 4 (7 %) didn't have metastases in the excised LNs, 6 had widespread lymph node metastases. Presumably, absence of positive dynamics in the form of PSA level decrease in patients with multiple metastases in LNs is associated with further disease progression and metastases in other organs. Absence of metastases in distant LNs can be explained by unsatisfactory quality of lymph node dissection or inaccuracy of PET/CT (false positive results). Patients without therapy response in the form of PSA level decrease 1 month after SL were recommended adjuvant HT. This patient cohort was excluded from the survival analysis.

During median follow-up time (12 months), biochemical disease relapse defined as PSA level increase during 3 consecutive measurements was observed in 28 (49.1 %) patients from the total group. Mean time between SL and PSA level decrease in the general patient group was 12.6 ± 10.3 months (6–48 months). Mean time between the surgery and PSA level increase for patients who underwent surgery at the P.A. Hertzen Moscow Oncology Research Institute was 18.5 ± 14.9 (6–48) months, at the N.N. Petrov Research Institute of Oncology – 6.8 ± 1.45 (6–9) months, at the Russian Research Center for Radiology and Surgical Technologies – 10.0 ± 4.2 (6–18) months; $p = 0.03$ (Fig. 10).

Presumably, significant differences between the 3 centers are associated with shorter follow-up duration for patients who underwent surgery at the N.N. Petrov Research Institute of Oncology and the Russian Research Center for Radiology and Surgical Technologies.

It should be noted that some patients in the satisfactory response subgroup had PSA level decrease of more than 90 % compared to the preoperative level accompanied by a long relapse-free period. Thus, in 11 (23.4 %) of 47 patients with PSA response after the surgery disease stabilization lasting more than 12 months was observed. During this time these patients didn't receive any additional treatment. Cox one-factor regression analysis showed that PSA level decrease of more than 90 % compared to the baseline

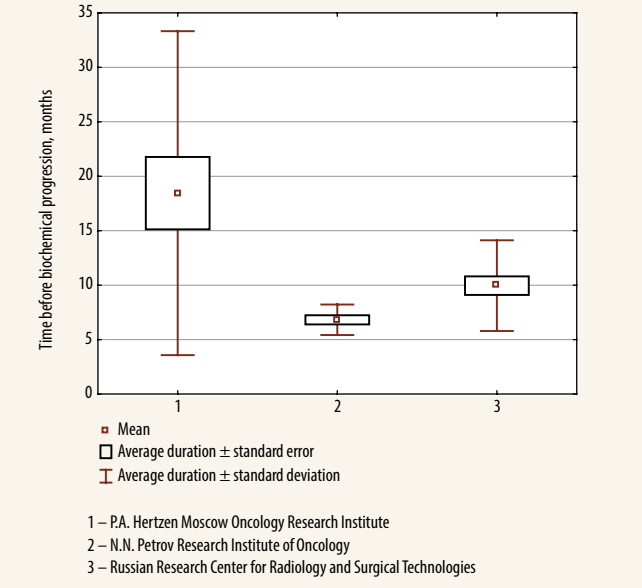


Fig. 10. *Average time before biochemical progression in subgroups of patients who underwent surgery at the 3 different centers*

before the surgery is a statistically significant predictor of favorable prognosis (odds ratio (OR) was 1.6; 95 % confidence interval (CI) was 1.2–2.1; $p = 0.002$). Results of the one-factor regression analysis are presented in Table 3.

Presence of extracapsular tumor extension beyond the LN capsule was a significant predictor of biochemical recurrence in patients after SL (OR was 2.8; 95 % CI was 1.0–8.1; $p = 0.05$). Multifactor regression analysis showed that PSA level 1 month after the surgery is an independent predictor of PSA relapse-free survival (OR was 1.5; 95 % CI was 1.1–2.1; $p = 0.02$).

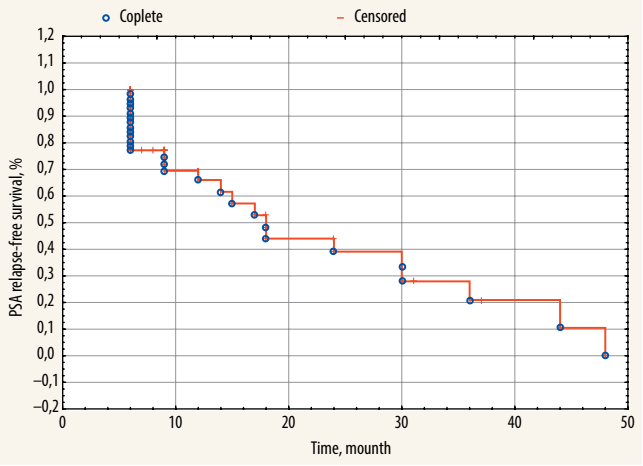


Fig. 11. *Three-year PSA relapse-free survival in all patients*

In the total patient group, 3-year PSA relapse-free survival was 21.0 ± 9.4 %. No significant differences in PSA relapse-free survival between the patient subgroups of the 3 different centers were found ($p = 0.09$). This may be explained by short follow-up duration and a small number of patients in the subgroups. Nonetheless, a trend for an increase in PSA relapse-free survival in the medical center with the longest follow-up was observed (Fig. 11, 12).

During the follow-up, 2 (3.5 %) patients died due to disease progression. Therefore, 5-year survival and TSS were comparable and amounted to 92.8 ± 6.8 %.

Table 3. *Results of Cox one-factor regression analysis of the main prognostic factors affecting probability of biochemical relapse development*

Prognostic factor	*p*	Odds ratio	95 % confidence interval
Clinical stage (cT)	0,90	1,02	0,72–1,44
Morphological stage (pT)	0,13	1,78	0,84–3,78
Total Gleason score at biopsy	0,57	1,04	0,46–1,53
Total Gleason score after RP	0,62	1,11	0,76–1,75
Time between initial therapy and SL	0,64	0,90	0,96–1,01
PSA level before SL	0,30	1,01	0,99–1,04
Number of lymph nodes removed by SL	0,34	0,97	0,92–1,03
Number of metastases after SL	0,08	1,12	0,98–1,45
Presence of extracapsular tumor extension beyond lymph node capsule	0,05*	2,80*	1,00–8,10*
PSA level 1 month after SL	0,0006*	1,60*	1,23–2,11*

**Statistically significant difference.*

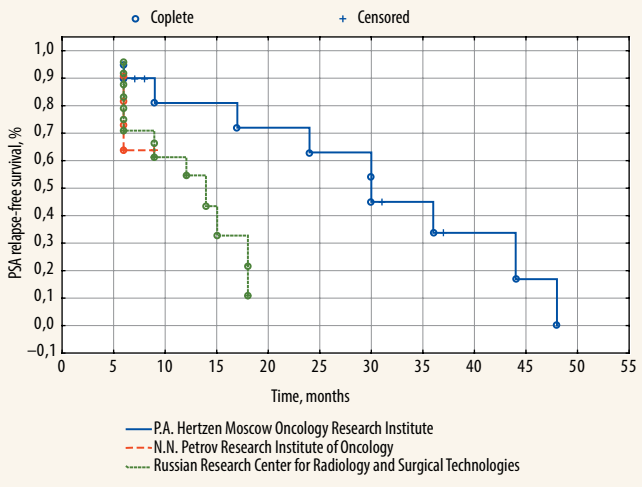


Fig. 12. *Three-year PSA relapse-free survival in patients who underwent surgery at different centers*

Conclusion

Therefore, SL is an effective therapy demonstrating satisfactory oncological results for patients with lymphogenic PC progression after primary radical treatment. In the majority of patients, SL is associated with satisfactory therapy response in the form of PSA level decrease and prolonged recurrence-free period. In some patients, removal of lymphogenic metastases allows to postpone HT or abandon it altogether, and still anticipate an increase in general survival. Despite substantial shortcomings of this article, such as lack of randomization, heterogenous patient groups (recurrences after surgical, beam radiation and focal treatments), and employment of different surgical techniques (open or laparoscopic surgery), this work is the first Russian study of innovative SL approach at 3 large medical centers. Encouraging results of the study demand further research of SL in PC patients and systematization of the collected data for widespread introduction of SL into clinical practice.

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