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Efficacy and toxicity of concurrent radiochemotherapy with gemcitabine after transurethral resection of invasive bladder cancer

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Background. To evaluate the efficacy of combination of gemcitabine and radiotherapy in conservative treatment of invasive bladder cancer: toxicity, tolerance and possibilities of bladder preservation.

Materials and methods. Fourteen patients with the invasive bladder cancer (pT2–pT4) were treated according to the protocol of clinical study. In all the cases transurethral resection was followed by radiation and chemotherapy. A total dose of 54–60 Gy of radiotherapy was delivered by daily fractions of 1.8–2.0 Gy each. Simultaneous chemotherapy was started on the same day as radiotherapy; gemcitabine was delivered once a week intravenously for six weeks. To evaluate the efficacy of treatment re-TURBT was performed on the 6th week after completion of radiotherapy. Toxicity of treatment was evaluated according to NCI CTC (National Cancer Institute Common Toxicity Criteria) scale, and unacceptable effects of radiotherapy were assessed according to RTOG / EORTC Late Radiation Morbidity Scoring Scheme.

Results. 12 patients were treated successfully with good compliance to protocol requirements. Grade I–III diarrhea, dysuria, neutropenia and mild liver function disorders were observed. In 10 patients, complete response was achieved, in one patient T2 disease was established, and extensive metastatic disease was observed in one patient

Conclusions. Our initial data showed that combined conservative bladder cancer treatment consisting of TURBT, chemotherapy and radiotherapy is reasonably effective. This treatment modality could be offered as an alternative to patients refusing cystectomy or those who are medically unfit for this operation. Further follow-up of these patients and assessment of life expectancy after bladder preserving treatment is necessary.

Key words: bladder cancer, radiotherapy, chemotherapy, gemcitabine, transurethral resection of the bladder tumour

INTRODUCTION

Radical cystectomy with or without dissection of pelvic lymph nodes is considered to be a standard treatment modality for invasive bladder cancer. Transurethral resection followed by external beam radiotherapy with chemotherapy should be offered to patients with inoperable disease and those who are seeking an alternative for radical cystectomy (1). Both surgical treatment and conservative chemo radiotherapy offer similar overall survival, and the advantage of conservative treatment is better quality of life due to the preservation of bladder and its function. However, the overall survival in both groups is comparable and not very high. A five-year survival after radical cystectomy is nearly 50% and varies according to the stage of disease (5-year survival in patients with pT4 tumours is about 30%, and for patients with pT2 tumours it is 72%). After a conservative treatment combining TUR and chemo radiotherapy the tumour response rate could be 70%–85%, and 5-year survival is 50%–64%; bladder function is preserved in more than 80% of patients. However, the stage of the disease strongly influences the results of the treatment, and survival is shorter in patients with advanced stages (2–7). Conservative treatment with cisplatin-based chemotherapy of bladder cancer was used in the majority of clinical trials. Due to unacceptable toxicity, a considerable number of patients fail to finish the scheduled treatment course (3, 8). Therefore, new optimal combinations of radiotherapy and chemotherapy with novel chemotherapy agents, especially those with radio sensitizing properties, should be investigated, e. g. gemcitabine which is widely used for the treatment of solid tumours, including bladder cancer (9).

Gemcitabine demonstrated radio sensitizing properties both in experiments *in vitro* and in chemo radiotherapy of cancer pa-

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tients. Up to now, several phase I clinical trials of the combination of gemcitabine and radiotherapy in the conservative treatment of invasive bladder cancer were performed; gemcitabine was given once or twice a week together with conventional radiotherapy (10–12). According to literature, maximum tolerance dose of gemcitabine once a week together with radiotherapy is 400 mg/m^2, and twice a week is 27 mg/m^2. In all the cases tumour response was 100%.

According to the experience of the above authors, it could be assumed that gemcitabine combined with radiotherapy is rather effective in the treatment of the advanced bladder cancer. These date encouraged us to start a clinical trial in order to establish an optimally effective and tolerable dose of gemcitabine combined with radiotherapy and to evaluate the immediate tumour response.

MATERIALS AND METHODS

Patients' selection

Clinical trial was started after the approval by the Lithuanian Bioethics Committee and the State Medicines Control Agency of Lithuania. All the patients enrolled in the study underwent cystoscopy, possibly, a macroscopically wide transurethral resection (TURBT) of the bladder tumour. In all the patients, invasive urothelial carcinoma of bladder was verified by histological examination. TNM staging was performed for all the patients, and patients with pT2–pT4, N0–N1, M0 were enrolled into the study. Chest X-ray, abdominal/pelvic ultrasound examination and CT were performed to assess the stage of the tumour. WHO performance was 0–2, renal function satisfactory, creatinine clearance > 65 ml/min, bladder closed, urine culture sterile, neutrophils $\geq 1.5 \cdot 10^9$/l, platelets $\geq 100 \cdot 10^9$/l, Hb ≥110 g/l, liver enzymes elevated no more than 3 times, bilirubin elevated no more than 1.5 times above the normal. All the patients have signed the informed consent form before the enrolment. (Table 1).

Exclusion criteria were: superficial, metastatic or advanced urothelial cancer, bad performance status (WHO > 2), renal insufficiency, cystostomy, pregnancy, lactation, severe mental disorders and tumours of other localizations.

Clinical trial design

According to the clinical trial protocol, patients underwent a complete (if possible) transurethral resection of bladder tumour (TURBT). 2 weeks later, chemo radiation was started. Radiotherapy was delivered to a total dose 54–60 Gy, its duration was 6 weeks, and 1.8–2.0 Gy per fraction were delivered. On the first day of radiotherapy, chemotherapy with gemcitabine was started. Gemcitabine was given intravenously, 300 mg/m^2, once a week for 6 weeks in combination with radiotherapy. In two patients, the dose of gemcitabine was 175 mg/m^2 once a week for 6 weeks. The dose of gemcitabine was selected taking into account the results of phase I–II clinical trials, in which gemcitabine in combination with radiotherapy was used to treat advanced pancreatic, non–small cell lung cancer, head and neck cancer and invasive urothelial cancer, especially. Chemo radiation was stopped in case febrile neutropenia, grade 4 toxicity of digestive tract or any other grade 4 nonhaematologic toxicity (according to the National Cancer Institute Common Toxicity Criteria) occurred.

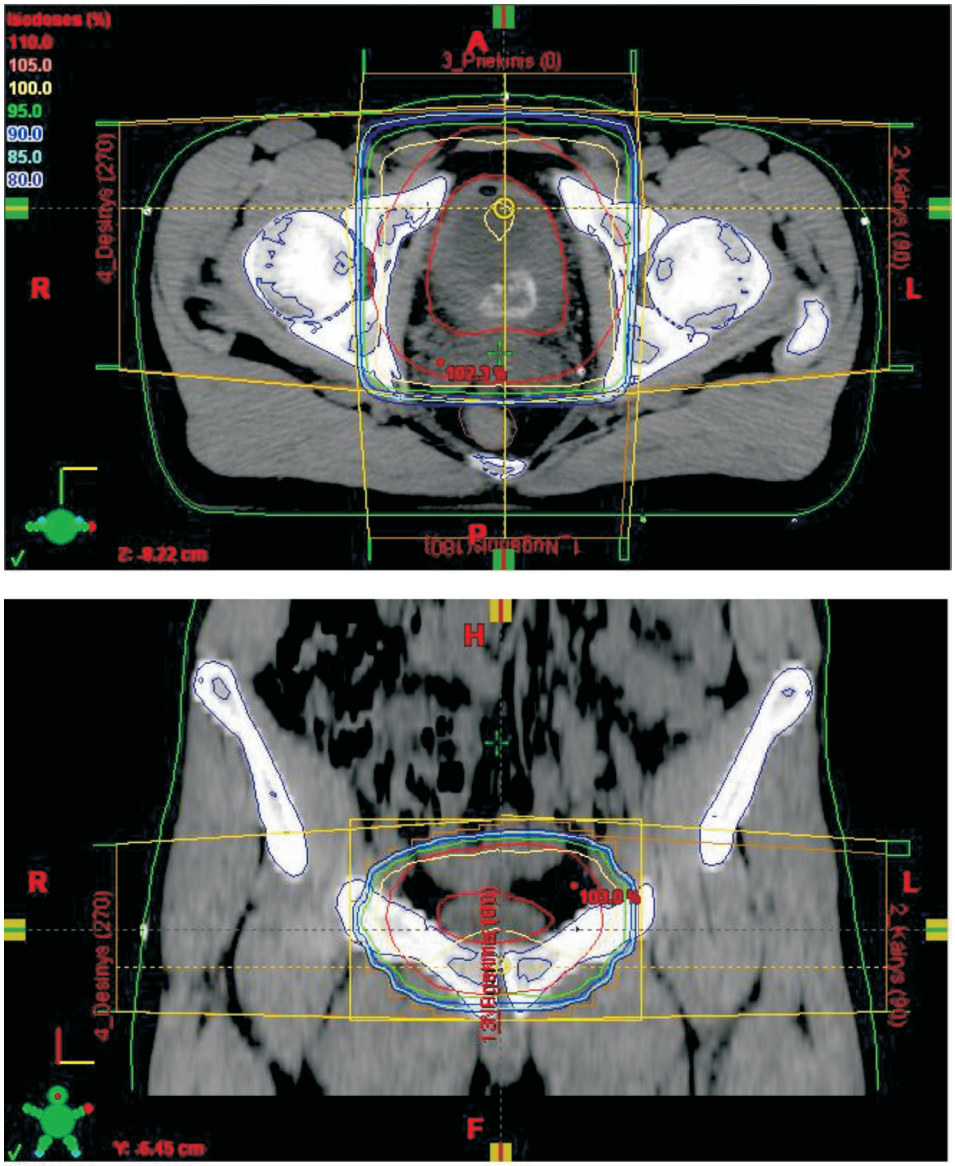
Radiation therapy

Equipment: SATURN and CLINAC accelerators were used. The energy of irradiation was 15–15 MeV. A dose of 1.8–2.0 Gy per fraction was given, a total dose of 54–60 Gy was given in 30 daily fractions in 6 weeks.

Patients' position: Patients were lying on their back with their feet at the width of shoulders, their hands over the head, and their bladder was empty during radiotherapy. Four-field planning technique ("box" technique) was used. 3D planning systems were used. CTV (clinical target volume) and PTV (planning target volume) were delineated (CTV 1–2 cm), and critical organs (rectum and femoral heads) were established (Figs. 1–3). For patients with regional metastases (N1) or T3–T4 tumours, a total doze of 44–46 Gy in 22–23 fractions (1.8–2.0 Gy per fraction) to the pelvis was given. Irradiation zone included the whole bladder and regional (parailiacal, presacral) lymph nodes. After that, boost covering bladder was applied with 5–7 fractions of 1.8–2.0 Gy per fraction up to the total dose of 54–60 Gy. The

Table 1. **Patients' characteristics**

Patient's No.	Dose (mg/m^2)	Gender	Age	Body surface (m^2)	Performance status (WHO)	Stage	Hydronephrosis	TURBT extent	Response
1	175	Male	73	2.10	1	T2N0	No	Complete	Complete
2	175	Male	64	2.05	2	T2N0	No	Complete	Complete
3	300	Male	74	1.90	1	T2N0	Yes	Incomplete	T2 disease
4	300	Male	58	1.75	0	T4N0	No	Incomplete	Complete
5	300	Male	69	1.90	1	T2N0	No	Incomplete	Complete
6	300	Male	42	1.75	0	T2N0	No	Complete	Complete
7	300	Male	41	1.75	0	T2N0	No	Complete	Complete
8	300	Male	73	1.90	0	T2N0	No	Complete	Complete
9	300	Female	75	1.55	2	T2N0	No	Complete	Complete
10	300	Male	66	1.75	1	T2N0	No	Incomplete	Interrupted
11	300	Male	65	1.97	0	T2N0	No	Incomplete	Complete
12	300	Female	77	1.50	0	T2N0	Yes	Incomplete	Interrupted
13	300	Male	77	1.70	1	T2N0	No	Complete	Complete
14	300	Male	60	1.55	0	T2N0	No	Incomplete	Metastatic disease



Figs. 1 and 2. Planning of radiation therapy: CTV and PTV (clinical target volume and planning target volume)

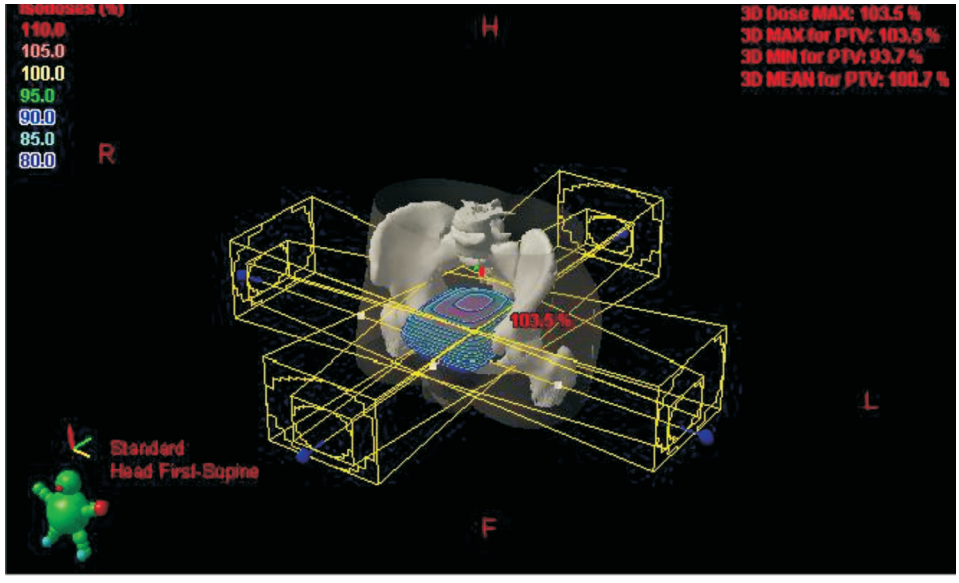


Fig. 3. Radiation therapy: 4-fields technique

dose to the 30% volume of rectum and femoral heads was limited to 60 Gy. For patients without regional metastases the treatment volume included the whole and paravesical tissue, the total dose was 54–60 Gy in 27–30 fractions (1.8–2.0 Gy per fraction).

Chemotherapy

Chemotherapy was started on the same day with radiotherapy. Gemcitabine was administered intravenously, the dose of 300 mg/m^2 once a week together with standard 3D radiotherapy on days 1, 8, 15, 22, 29, 36. Gemcitabine was diluted with 500cc normal saline and delivered intravenously over 30 minutes. Two patients received the dose of 175 mg/m^2 of gemcitabine.

Clinical tests during the treatment

During the treatment by chemo radiotherapy routine blood count (haemoglobin, WBC, neutrophils, platelets) and blood chemistry (liver and renal function tests, glucose level, serum electrolytes) were performed. A medical oncologist and a radiotherapist evaluated the performance status once a week, and the decision concerning the continuation of treatment according to the protocol was made. All the decisions concerning proceeding of the treatment, dose adjustment, patients' exclusion and patients' examination were made by a multidisciplinary team of experienced oncologists.

Follow-up procedures

In order to evaluate response to treatment, cystoscopy and TUR were performed 6 weeks after the completion of the treatment. Then, ultrasound examination of pelvis and abdomen, chest X-ray, cystoscopy and, if necessary, TUR would be performed. No additional treatment would be prescribed to patients with complete remission. In the case of superficial bladder tumour, intravesical chemotherapy or immunotherapy would be applied after TUR. In the case of invasive urothelial carcinoma, cystectomy would be offered. In the case of progressive disease and distant metastases, systemic chemotherapy would be applied.

RESULTS

Patients' characteristics

From March, 2004 to November, 2006 fourteen patients (12 males and 2 females) were enrolled into the study. Their performance status was 0–2 (WHO), mean age was 65.7 years (ranging from 41 to 77). Stage T2 tumour was detected in 13 of patients after TUR, and for one patient T4 cancer was found (invading prostate and seminal vesicles). TUR was radical in 9 patients, and in 5 patients it was incomplete. Hydronephrosis was found in 2 patients. In all the patients a highly malignant (grade 3) urothelial carcinoma was established after histological investigation of TUR specimen. Two patients received 175 mg/m^2 of gemcitabine, whereas 12 patients were given 300 mg/m^2, twelve patients completed chemo radiotherapy, 1 patient refused to continue the treatment, and 1 patient terminated the treatment.

Early toxicity

There was no dose limiting toxicity in patients receiving 175 mg/m^2 of gemcitabine. Grade I elevation of liver aminotransferase was observed in one patient, and grade I dysuria was also observed in 1 patient. The dose limiting toxicity was observed in two patients treated with 300 mg/m^2 of gemcitabine once a week, and the treatment was interrupted due to grade III diarrhoea. Later the treatment proceeded, and patients completed the treatment according to the study protocol. Grade II neutropenia was observed in two patients. Grade I dysuria was observed in three patients, grade II in two, and grade III dysuria was observed in one patient. Grade II diarrhoea was observed in two patients, grade I elevation of liver tests was observed in one patient, and grade II elevation of liver tests was also observed in one patient. (Table 2)

Table 2. **Early toxicity**

	I°	II°	III°	IV°	Overall
Hemoglobin	2	1			3
WBC	1	1			2
Neutrophiles		2			2
Platelets	1				1
Diarrhea		4	2		6
Dysuria	3	2	1		6
ALT, AST	3	1			4

Response to treatment

Immediate response to treatment could be assessed in 12 patients out of 14. One patient terminated the treatment. Complete histological remission was diagnosed in 10 patients, pT2 disease was established in one patient, and advanced metastatic disease was determined in one patient.

DISCUSSION

Up to now cisplatin, carboplatin or 5-fluoruracile as radio sensitizing medications were involved into most protocols of chemo radiotherapy for the treatment of invasive bladder cancer. These are the clinical protocols of Paris University, France, Erlangen University, Germany, and Harward University in Massachusetts, USA, RTOG protocols and some smaller trials. These medications are good for young patients with good general status and without renal impairment; however, most patients with invasive urothelial cancer are elderly patients with concomitant diseases, hydronephrosis and impaired renal function. The average age of our study patients was 65.7 years, and seven patients were with only satisfactory performance status (5 were with status 1, and two were with status 2, according to WHO). Cisplatin based chemotherapy used for neoadjuvant treatment or chemo radiotherapy is often not tolerated by patients with bad performance status and does not protect from distant metastases. In Paris University trial, cisplatin was given in radio sensitizing doses of 15 mg/m^2 together with 5-fluorouracil, therefore, only a few side effects were observed during the treatment, and there was no necessity to stop the treatment; however, a complete response was found in 74% of patients (5). During Erlangen University (Germany) trial, higher doses of cisplatin, 25 mg/m^2, were given for 5 days consecutively. Only 68% patients completed the protocol treatment successfully (2). The reason was haematological toxicity, digestive tract and urinary system toxicity. A complete response was observed in 72% of patients. Difficulties occurred in Massachusetts, USA, where, according to the protocol, neoadjuvant MCV chemotherapy was given, and

70 and 100 mg/m^2 of cisplatin were administered together with radiotherapy. Approximately 80% of patients finished the treatment according to the protocol. One patient died due to sepsis after neoadjuvant chemotherapy, 5 patients had severe cardiovascular adverse effects and severe nephrotoxicity, severe weakness and vomiting were observed in 44% of patient. Complete response was observed in 70% of patients, 5-year survival was 52% (15). We did not observe any cardiovascular adverse effects, nephrotoxicity, or vomiting in our study. All the side effects of patients in our study were haematological and connected with pelvic organs (rectum and bladder). RTOG protocols of chemo radiotherapy were hardly tolerable. During RTOG 89–03 protocol treatment, 3 patients died due to treatment-induced neutropenia and sepsis. In 21 patients taking part in RTOG 95–06 protocol, grade III hematological toxicity developed, only 40% of patients finished the treatment according to this protocol successfully. These data (a lot of treatment-induced side effects, unsatisfactory survival) reinforce the need to look for other optimal combinations of chemo radiotherapy (13).

A number of preclinical studies proved gemcitabine to be a radio sensitizer even when doses used are not cytotoxic. Successful preclinical studies enabled investigators to start phase I and II clinical trials of chemo radiotherapy with gemcitabine in patients with pancreatic, non-small cell lung, head and neck, rectal and bladder cancers. Gemcitabine demonstrated low toxicity and it was used in regimes for treatment of advanced urothelial cancer (9). Taking into account these clinical features of gemcitabine, several investigators started clinical trials of gemcitabine combination with radiotherapy in the conservative treatment of invasive urothelial cancer.

Several small phase I–II studies of gemcitabine combination with radiotherapy were performed (10–12, 14). Gemcitabine was given in doses of 100–500 mg/m^2 once a week during the treatment with radiotherapy. A dose limiting toxicity was observed in patients receiving 400 and more mg/m^2 of gemcitabine; grade III and IV diarrhoea and neutropenia developed. No dose limiting toxicity was observed in patients receiving 100–300 mg/m^2 of gemcitabine. Chemo radiotherapy with low doses of gemcitabine (100–300 mg/m^2) was well tolerated. The gemcitabine dose of 175 mg/m^2 used in our trial was based on the data of these authors. As there were no serious side effects we switched to the dose of 300 mg/m^2. Twelve patients completed the study protocol without significant deviations. Side effects were presented by diarrhoea, dysuria, moderate neutropenia and elevation of liver enzymes. We did not observe grade IV toxicity and death linked to the treatment according the protocol. Two patients interrupted the treatment. We could not explain moderate elevation of liver enzymes in some cases. A complete remission was observed in 10 patients out of 12 patients; pT2 disease was established in 1 patient, and advanced metastatic disease in 1. These results were satisfactory, because patients' population was heterogeneous (especially TURBT extent, presence of hydronephrosis).

CONLUSIONS

Gemcitabine in combination with conventional radiotherapy in dose of 300 mg/m^2 once a week has low toxicity and satisfactory response to the treatment. Because only a small number of patients took part in this trial, further studies with more patients are necessary. Further follow-up is necessary to evaluate the overall survival of these patients.

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GEMCITABINO IR RADIOTERAPIJOS DERINIO EFEKTYVUMAS IR TOKSIŠKUMAS PO TRANSURETRINĖS REZEKCIJOS KONSERVATYVIAI GYDANT INVAZINĮ UROTELIO VĖŽĮ

Santrauka

Tyrimo tikslas. Įvertinti gemcitabino ir radioterapijos efektyvumą konservatyviai gydant invazinį urotelio vėžį: šio gydymo toksiškumas, toleravimas, šlapimo pūslės išsaugojimo galimybės.

Pacientai ir gydymo metodika. Pagal klinikinio tyrimo protokolą buvo gydyta 14 pacientų, sergančių invaziniu urotelio vėžiu (pT2–pT4). Jiems buvo atlikta transuretrinė rezekcija, po jos taikytas chemospindulinis gydymas – bendra židininė dozė 54–60 Gy po 1,8–2,0 Gy frakcijai. Chemoterapija pradėta tą pačią dieną kaip ir radioterapija, pacientams i/v kartą per savaitę 6 savaites skirtas gemcitabinas. Pasibaigus chemospinduliniam gydymui, po 6 savaičių pakartota TUR gydymo efektui įvertinti. Gydymo toksiškumas buvo įvertintas pagal NCI CTC skalę (National Cancer Institute Common Toxicity Criteria), spindulinio gydymo reakcijos – remiantis RTOG / EORTC spindulinio gydymo toksiškumo vertinimo kriterijais.

Rezultatai. 12 pacientų pabaigė gydymą pagal protokolą be ryškesnių nukrypimų. Kaip pašaliniai reiškiniai buvo pastebėta diarėja, dizurija, saikinga I–II laipsnio neutropenija ir kepenų fermentų padidėjimas. Iš šių 12 pacientų po taikyto gydymo 10-iai buvo remisija, 1 pacientui – pT2 liga, 1 pacientui – išplitusi metastazinė liga.

Išvados. Pradiniai mūsų duomenys rodo, kad taikant šlapimo pūslę išsaugantį konservatyvų gydymą – transuretrinę rezekciją, chemoterapiją ir radioterapiją, gauti pakankamai geri rezultatai. Šis gydymo metodas gali būti alternatyva pacientams, kurie atsisako cistektomijos, arba kai jos negalima atlikti dėl medicininių priežasčių. Reikalingas tolesnis šių pacientų stebėjimas ir išgyvenamumo išsaugant šlapimo pūslę vertinimas.

Raktažodžiai: šlapimo pūslės vėžys, radioterapija, chemoterapija, gemcitabinas, transuretrinė rezekcija