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Treatment methods of prostate cancer recurrence after radiotherapy

Current treatment alternatives and our clinical experience

Prostatos vėžio recidyvų po spindulinės terapijos gydymo metodai

Šiuolaikinėje medicinoje naudojami metodai ir mūsų klinikinė patirtis

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Background / objective

Prostate cancer is the most common cancer among men of Lithuania. Every year about 3000 new cases of prostate cancer are diagnosed in our country. Many patients receive radiotherapy as primary treatment. Unfortunately, after several years some of the patients are diagnosed with prostate cancer recurrence. These cases are more challenging and require to apply salvage treatment methods. The aim of this article is to present our clinical experience and discuss the main features, advantages and disadvantages of the treatment methods.

Patients and methods

Retrospective analysis of 10 salvage prostate cancer recurrence treatment cases was completed. All patients previously received radiotherapy as primary treatment. 5 patients received salvage high- dose brachiterapy (group 1) and other 5- salvage cryotherapy (group 2). Prostate cancer recurrences were diagnosed by multiparametric MRI and ultrasound guided transrectal or transperineal biopsies.

Results

Average patient age was 64,2±7,9 years in group 1 and 68±3,1 years in group 2. None of the patients had prostate cancer progression to lymph nodes (N) or metastases (M) on initial diagnosis or before salvage treatment. No intraoperative complications were observed. Average time between radiotherapy and salvage therapy in both groups was 88,9±30,1 months. In both groups 1 patient suffered from salvage treatment failure- prostate cancer progression was observed.

Conclusions

Currently there is no perfect treatment method for recurrent prostate cancer. Every situation requires universal aproach. Our initial experience shows that salvage cryotherapy and brachiterapy can be a viable alternative for patients with disease progression after radiotherapy.

Key words: prostate cancer, prostate cancer recurrence, salvage treatment.

Įvadas / tikslas
Lietuvoje kasmet nustatoma apie 3000 naujų prostatos vėžio atvejų. Daugeliui pacientų taikomas spindulinis gydymas. Deja, praėjus keletui metų, kai kuriems pacientams diagnozuojamas prostatos vėžio recidyvavimas. Šiuo metu yra daug gydymo metodų, bet dažnai iškyla problemų pasirenkant optimalų. Šio straipsnio tikslas – pasidalinti mūsų klinikine patirtimi bei apžvelgti prostatos vėžio recidyvų po spindulinės terapijos gydymo alternatyvas.

Pacientai ir metodai
Retrospektyviai buvo išanalizuota dešimt pacientų, kuriems po pirminio gydymo radioterapija buvo diagnozuotas prostatos vėžio recidyvavimas. 5 pacientai buvo gydomi didelių dozių brachiterapija (1 grupė), o likusiems 5 buvo skirta krioterapija (2 grupė). Prostatos vėžio recidyvai diagnozuoti multiparametriniu kontroliuojant MRT ir ultragarsu atliktomis transrektalinėmis ir transperinealinėmis prostatos biopsijomis.

Rezultatai
Pirmoje grupėje vidutinis pacientų amžius buvo 64,2±7,9 metų, o antroje grupėje 68±3,1. Nė vienam pacientui nebuvo nustatytas prostatos vėžio išplitimas į limfmazgius (N) ar metastazavimas (M). Intraoperacinių komplikacijų nepasitaikė. Vidutiniškai tarp pirminės radioterapijos ir gelbstinčio prostatos vėžio recidyvavimo gydymo praėjo 88,9±30,1 mėnesio. Gelbstintis prostatos vėžio recidyvavimo gydymas buvo nesėkmingas dviem atvejais – po vieną atvejį abiejose grupėse.

Išvados
Šiuo metu nėra tobulo gydymo tų pacientų, kuriems prostatos vėžys recidyvavo po spindulinio gydymo. Tokiais atvejais reikalingi unikalūs sprendimai. Mūsų nedidelė pirmoji patirtis rodo, jog gelbstinčioji krioterapija ir brachiterapija – tinkami metodai gydyti pacientams, kuriems recidyvavo prostatos vėžys po spindulinės terapijos.

Reikšminiai žodžiai: prostatos vėžys, prostatos vėžio recidyvai, gelbstintis gydymas.

Introduction

Prostate cancer is the most common cancer among men of Lithuania. Every year about 3000 new cases of prostate cancer are diagnosed in our country. Many patients receive radiotherapy as primary treatment. Unfortunately, after several years some of the patients are diagnosed with prostate cancer recurrence. These cases are more challenging and require to apply salvage treatment methods. Radical prostatectomy, cryotherapy, high- dose radiotherapy, hormone therapy, high- intensity focused ultrasound or active surveillance- any of it can be used for prostate cancer reccurence treatment. The aim of this article is to present our clinical experience and discuss the main features, advantages and disadvantages of treatment methods.

Patients and methods

Recently, in Vilnius university Oncology institute 10 salvage treatment procedures for prostate cancer recurrences were performed. Retrospective analysis of these cases was completed. 5 patients (50%) received salvage high- dose brachiterapy (Group 1) and other 5 received 2-cycle salvage cryotherapy (Group 2) with real-time ultrasound guidance, urethra-warming catheter and temperature change tracking. All patients previously received radiotherapy as primary treatment for prostate cancer. Radiation dose was 68-72 Gy. Prostate cancer recurrences were diagnosed by multiparametric MRI and ultrasound guided transrectal or transperineal biopsies. MRI findings were validated with Magnetic Resonance Prostate Imaging Reporting and Data System (PI-RADS). CT, MRI, ultrasound scanning, bone scintigraphy was performed for patients before treatment. No pathological bone changes were detected.

The analyzed factors in both groups were: age, prostate cancer stage on initial diagnosis (TNM), PSA on initial prostate cancer diagnosis, PSA before salvage therapy, time between primary radiotherapy and salvage treatment, Gleason score on initial diagnosis, salvage brachiterapy radiation dose, intraoperative and postoperative complications.

Data analysis was performed using SPSS software version 17 (SPSS, Chicago, IL, USA).

Results

Average patient age was 64,2±7,9 years in group 1 and 68±3,1 years in group 2. None of the patients

had prostate cancer progression to lymph nodes (N) or metastases (M) on initial diagnosis or before salvage treatment. Cancer tumor stages on initial prostate cancer diagnosis (T) in **group 1**: 2 patients (40%) had cT1c, 2 patients (40%) cT2b, 1 (20%) patient cT3a; **in group 2**: 3 (60%) patients had cT2b, 1 (20%) patient cT3a and 1 (20%) patient cT1c. Gleason score on initial diagnosis in **group 1** was 6 in 4 cases (80%) and 8 in 1 case (20%); in **group 2** Gleason score was 6 in all cases (100%).

Time between radiotherapy and salvage treatment in group 1 was 90±36 months; in **group 2**- 87,2±26,4 months. Average time between radiotherapy and salvage therapy in both groups was 88,9±30,1 months.

In **group 1** PSA on cancer diagnosis was 14,3±6,7 ng/ml, on cancer recurrence diagnosis 7,4±4,9 ng/ml. In **group 2** PSA on cancer diagnosis was 21,5±13,4 ng/ml, on cancer recurrence diagnosis 2,7±2,3 ng/ml. In group 1 only one patient was followed up more than 6 months. Other patients received their salvage brachiterapy very recently and PSA was not checked yet. Hopefully in the near future, we will be able to share longer follow-up time results of these patients. In **group 2** PSA after salvage cryotherapy was 0,4±0,7 after 5±1,7 months of follow- up.

In **group 1** every patient had two procedures of brachiterapy with few days break between them. 4 patients (80%) received 11 Gy and 1 patient (20%) 9 Gy dose for prostate during each procedure.

No intraoperative complications were observed. No patients suffered from urinary incontinence. However, one patient (20%) who had highest PSA before treatment (15,21 ng/ml) developed dysuria like symptoms after brachiterapy. Unfortunately, 2 months after salvage brachiterapy PSA of the same patient rose up to 93,16 ng/ml and he was diagnosed with metastases in his vertebrae. Currently, he is suffering from pain syndrome and is treated with chemotherapy.

In **group 2** patients received 2-cycle cryotherapy with real-time ultrasound guidance, urethra-warming catheter and temperature change tracking.

All procedures were completed succesfully without any intraoperative complications. No patients suffered from urinary incontinence. Urinal obstruction was observed after 1 week for 1 of 5 patients. He had to stay with epicystostomy and over-went prostate transurethral resection. After these procedures patient could urinate normally. One patient had biochemical progression due to metastasis in parailiacal lymph node, and he got external beam therapy to lymph-node projection. After 6 months there were no signs of cancer progression on MRI and PSA was 1,77 ng/ml.

Discussion

Biochemical failure in men who have undergone external beam radiation therapy (EBRT) for localized prostate cancer can occur in approximately 10% to 30% [1-3]. The biochemical control rates are significantly better with high-dose radiation compared with conventional doses. PSA relapse-free survival rates after primary definitive radiation therapy are between 62% and 81%, depending on risk grouping [4].

Differentiating between local recurrence and metastatic disease is very important. Traditionally, bone scans and CT scans have been the tests of choice, along with physical examination, to define disease progression. Evaluation of PSA kinetics (doubling time and velocity) may be a useful tool that further aids in differentiating between local recurrence and metastatic disease. Quickly rising PSA may indicate distant disease while a more moderate rate of PSA rise may indicate local disease recurrence [5]. In patients with local recurrence, PSA doubling time is greater than 6 months and in those with systemic recurrence PSA doubling time is less than 3 months [5]. Moreover, if PSA doubling time is < 10 months, the 7-year survival after radiation therapy is only 52% [6,7].

Other authors suggests that there is no definitive predictors of local recurrence after radiotherapy. Several features have been associated with a higher likelihood of systemic rather than local disease, including a rapidly rising post-treatment PSA level, short PSA doubling time, poorly differentiated cancer (Gleason score 8–5), and a short disease-free interval after radiotherapy, no individual factor is definitively associated with metastatic progression nor eliminates the possible benefit of local salvage therapy [8;9].

Most men who fail EBRT receive androgen-deprivation therapy (ADT), which can have an impact on quality of life and cardiac, metabolic, and bone health

[10,11]. Consistent evidence shows that ADT cannot be considered a curative treatment for patients with locally recurrent prostate cancer [12]. However, many patients have localized disease that may be suitable for local salvage therapy using surgery, brachytherapy, cryotherapy, or high-intensity focused ultrasound (HIFU).

Historically open salvage prostatectomy (SRP) is associated with high risk of complications and bad outcomes. However, recent studies reported much better results and lower complication risk. Brazilian study published some interesting facts about open salvage prostatectomy. Blood loss during operation superior to 600 mL occurred in only 14% of the patients. None of them required blood transfusion. However other complications were higher than expected: stenosis/sclerosis of the vesicourethral anastomosis 50%, urinary incontinence, defined as two or mores pads required daily was 72%, nearly 74% of the patients reported worse erectile function. Intraoperative rectal injury rate was 2% although, other authors reported rate fom 0% to 19% [13].

Other study, which is one of the biggest ones, analyzed open SRP results of 404 patients. At 5 years after SRP, the probabilities of being free from biochemical cancer recurrence, metastasis, and cancer-specific death were 48%, 83% and 92% respectively; at 10 years, the probabilities were 37%, 77% and 83%, respectively. They also concluded that higher PSA before operation, and higher Gleason score after operation are associated with higher risk of BCR and metastasis. Lymph node involment before operation is also predictor of metastasis [14]. Salvage robotic-assisted laparoscopic prostatectomy has lower complication rates than open SRP, but, unfortunately, this procedure is not currently performed in Lithuania.

Salvage radiotherapy is rarely used for prostate cancer radiation failures. Only few studies analyzed such treatment method results. Grado et al. treated 49 patients with transperineal TRUS-guided brachytherapy after radiotherapy and published that biochemical disease- free rate at 3 years is 48%, at 5 years- 34%. The incidence of serious complications after salvage brachytherapy, such as incontinence and rectal complications, was lower than that reported after other types of salvage procedures [15]. In many cases salvage brachiterapy or

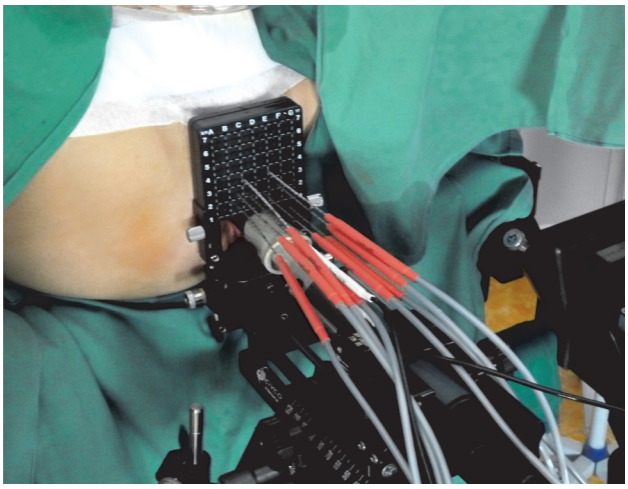

Fig. 1. Placement of freezing probes during cryotherapy
1 pav. Šaldymo adatų įvedimas krioterapijos metu.

external beam re- radiotherapy is not an option for prostate cancer recurrence treatment because of too high cummulative radiation dose (external beam therapy already brings at least 70 Gy radiation dose)

Additional radiotherapy also brings toxic complications. Moman et al. study analyzed results of salvage iodine-125 implantation in 31 patients: Grade 1, 2, or 3 toxicity of the gastrointestinal tract was reported in 45%, 10%, and 0% of the patients, respectively, in the acute phase, and in 48%, 3%, and 6%, respectively, in the late phase. Both genitourinary and gastrointestinal toxicity occur frequently [16].

Other local salvage therapy- cryotherapy. It can be used for patients who are not good candidates for conventional surgery because of their age or other medical conditions.

Patients undergoing salvage cryoablation tend to have a significantly higher complication rate compared with men undergoing primary treatment due to the retreatment of irradiated, poorly vascularized, anatomically altered tissue. Although now over a decade old, in perhaps the largest study among salvage cryotherapy patients, 72% of men reported some degree of dribbling or leakage at a mean follow-up of 16.7 months [16]. The technology of cryoablation devices has been improved, urethra warming catheter was added and the development of new-generation real-time

ultrasound probes as a guide for freezing ablation allows safer and more precise treatments than in the first experiences. More recent Finley et al. study analyzed up-to-date oncologic and functional outcomes, as well as complications of salvage cryotherapy for radiation-recurrent prostate cancer and reported 21.7% urinary incontinence rate [18]. Other new study reported even better results: long term incontinence rate was 12% (using 1 pad per day beyond 6 months post-salvage cryotherapy) and fistula rate of 1.8% [19].

Biochemical failure rates after salvage cryotherapy vary not only according to the definition of failure, but also due to the generation of the cryounit, cycling parameters, clinicopathologic characteristics, and length of follow-up. Across most definitions, biochemical failure-free rates vary from 59% to 74% [20]. Recently, a large multi-institutional study comprising a pool of 450 salvage patients was published by Spiess and colleagues with the intent to create a pretreatment nomogram. At a median follow-up of 3.4 years, the overall rate of biochemical failure was 66% (PSA >0.5 ng/mL) [21]. Williams et al. reported an 87% 10-year overall survival rate in men undergoing salvage cryoablation; the disease-specific survival and disease-free survival were 64% and 39%, respectively. In terms of prognostic factors, they found a PSA nadir above 1.0 ng/mL was significantly associated with poor prognosis [22].

One study evaluated financial implications of localized prostate cancer treatment methods. Despite the relatively increased surgical expense of cryotherapy compared with conventional surgical prostatectomy (open, laparoscopic or robotic), the overall direct costs were offset by the significantly lower nonoperative hospital costs. The cost advantages associated with cryotherapy included a shorter length of stay in the hospital and the absence of pathologic costs and the need for blood transfusion [23].

High- intensity focused ultrasound

The experience of high-intensity focused ultrasound (HIFU) for the treatment of locally recurrent prostate cancer after radiation therapy is limited to a few retrospective studies and nature of this treatment modality still is experimental due to the short follow-up periods reported. A pilot study reported results of focal salvage therapy using high-intensity focused ultrasound. The actual progression-free survival rate (including PSA nonresponders) was 69% at 1 year and 49% at 2 years according to Phoenix criteria [24]. Almost same authors previously published results of salvage whole prostate HIFU. 1- and 2-year progression-free survival rates were 59% and 43%. Complication rates were: 38% urinary incontinence, erectile function scores decreased significantly, rectourethral fistula rate after 1 treatment was 2.4%, but 33% after a redo-salvage procedure [25].

Conclusions

Currently there is no perfect treatment method for recurrent prostate cancer. Every situation requires universal aproach.

Salvage radical prostatectomy (SRP) is a good option for patients who has less co- morbidities and can survive major surgery. At 5 years after SRP, the probabilities of being free from biochemical cancer recurrence, metastasis, and cancer-specific death were 48%, 83% and 92% respectively; at 10 years, the probabilities were 37%, 77% and 83%. However, higher risk of complications must be considered.

Cryotherapy is another really effective treatment which can be used if patient can not be operated. It brings similar oncological outcomes: biochemical failure-free rates vary from 34% to 74% for follow up periods up to 10 years. Other advantages are: cheaper overall cost than SRP, lower complication risk.

Experience of salvage radiotherapy and high-intensity-focused ultrasound is limited and should be reserved for experimental studies until more longer term data will be available.

Androgen deprivation therapy cannot be considered as a curative treatment for patients with locally recurrent prostate cancer and should be used for metastatic disease progression or patients with local disease recurrence who reject any other treatment alternatives.

Our initial experience shows that salvage cryotherapy and brachiterapy can be a viable alternative for patients with disease progression after radiotherapy. However, larger study with longer follow-up time is necessary to verify oncological and functional results.

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