

The first clinical experience in prostate cancer salvage cryotherapy

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Introduction. Prostate cancer is the most common malignant neoplasia among men in Lithuania, though it presents a low mortality rate. In 2007 more than 3 500 Lithuanians were diagnosed with prostate cancer. Many patients were treated with radiotherapy. Unfortunately, after several years the number of cases of prostate cancer recurrence after radiotherapy started to grow. This new problem requires the following difficult decision to make: which treatment method to choose? Radical prostatectomy, high-dose radiotherapy, cryotherapy, high-intensity-focused ultrasound, active surveillance or hormone therapy – all are viable salvage methods. In 2012 we performed the first cryotherapy procedures. Now we want to present our first clinical experience in prostate cancer salvage cryotherapy.

Materials and methods. Five patients diagnosed with prostate cancer were selected for prostate cryotherapy. Four patients were treated only with radiotherapy, one patient was treated with radiotherapy plus neoadjuvant hormonal treatment.

Prostate cancer recurrences were diagnosed by multiparametric MRI and ultrasound guided transrectal or transperineal biopsies. MRI findings were validated with the Magnetic Resonance Prostate Imaging Reporting and Data System (PI-RADS). CT, MRI, ultrasound scanning, and bone scintigraphy were performed for patients before treatment. No pathological bone changes were detected. All patients received 2-cycle cryotherapy with real-time ultrasound guidance and temperature change tracking.

Results. The described treatment scheme for these patients enables to deliver two freezing-thawing cycles with 10–12 probes and a urethra-warming catheter. All procedures were completed successfully without any intraoperative complications. Urinal obstruction was observed after 1 week for 1 of 5 patients. He had to stay with epicycstostomy and underwent prostate transurethral resection. After these procedures the patient could urinate normally.

One patient had biochemical progression due to metastasis in parailiacal lymph nodes, and he got external beam therapy to lymph-node projection. After 6 months there was no cancer progression signs on MRI and PSA was 1.77 ng/ml.

No patients suffered from urinary incontinence.

Conclusions. Our initial experience shows that cryotherapy can be a viable alternative for patients with disease progression after radiotherapy. Currently the biggest advantages of cryotherapy are as follows: possibility to treat patients not suitable for salvage prostatectomy, short hospitalization, low complication risk and lower overall cost than other methods. Short term data seems to be promising but longer follow-up is necessary to verify oncological and functional results.

Key words: prostate cancer, recurrence, cryotherapy, salvage cryotherapy

INTRODUCTION

Prostate cancer is the most common malignant neoplasia among men in Lithuania, though it presents low mortality rate. In 2007 more than 3 500 Lithuanians were diagnosed with prostate cancer. Many patients were treated with radiotherapy. Unfortunately, after several years the number of cases of prostate cancer recurrence after radiotherapy started to grow. This new problem requires a difficult decision to make: which treatment method to choose? Radical prostatectomy, high-dose radiotherapy, cryotherapy, high-intensity-focused ultrasound, active surveillance or hormone therapy – all are viable salvage methods. In 2012 we performed the first cryotherapy procedures. Now we want to present our first clinical experience in prostate cancer salvage cryotherapy.

MATERIALS AND METHODS

Five patients diagnosed with prostate cancer were selected for prostate cryotherapy. Four patients were treated only with radiotherapy, one patient

was treated with radiotherapy plus neoadjuvant hormonal treatment.

Prostate cancer recurrences were diagnosed by multiparametric MRI and ultrasound guided transrectal or transperineal biopsies. MRI findings were validated with the Magnetic Resonance Prostate Imaging Reporting and Data System (PI-RADS). CT, MRI, ultrasound scanning, bone scintigraphy were performed for patients before treatment. No pathological bone changes were detected.

All patients received 2-cycle cryotherapy with real-time ultrasound guidance and temperature change tracking. Figure 1 shows placement of freezing probes during the procedure.

The first case: a 71-year-old patient with initially diagnosed cT1c N0 M0 prostate cancer, Gleason 3 + 3 = 6, PSA value 8.9 ng/ml. In May 2004 the patient received 70 Gy dose for prostate treatment volume with 3D conformal radiotherapy. In 2012 prostate cancer recurrence was diagnosed on MRI, with PSA 0.3 ng/ml. Prostate volume was 26 cm³. 5 months after cryotherapy PSA was 0.07 ng/ml.

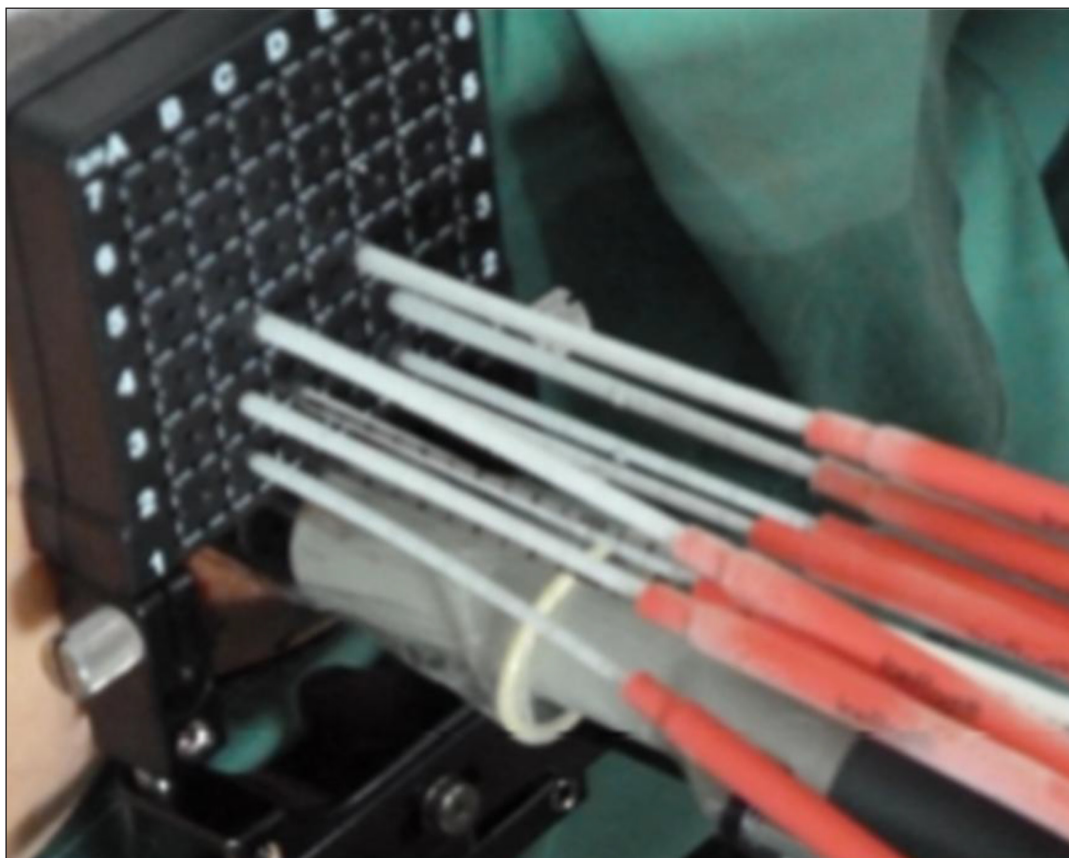


Fig. 1. Placement of freezing probes

The second case: a 68-year-old male, with initially diagnosed cancer cT2b N0 M0, Gleason 3 + 3 = 6, PSA value 17.6 ng/ml. In January 2007 the patient received 70 Gy dose treatment with radiotherapy. In 2012 prostate cancer recurrence was diagnosed on MRI, with PSA 2.7 ng/ml. Prostate volume was 28.5 cm³. Cryotherapy was used, but after 4 months PSA was 21.6 ng/ml. Metastasis was spotted in the parailiacal lymph node on MRI. The patient received 60 Gy dose radiotherapy. After 6 months there were no cancer progression signs on MRI and PSA was 1.77 ng/ml.

The third case: A 64-year-old patient, initially diagnosed with cT3aN0M0, Gleason 3 + 3 = 6 prostate cancer. In 2004 the patient with initial PSA 44 ng/ml received 70 Gy dose 3D conformal radiotherapy with neoadjuvant hormonal treatment. In 2012 local recurrence was diagnosed with PSA 5.2 ng/ml. Prostate volume was 27.9 cm³. Cryotherapy was used and after 6 months PSA was 0.002 ng/ml.

The fourth case: In 2001 a 71-year-old patient with initial PSA 22 ng/ml had prostate treatment with 3D conformal radiotherapy. In 2012 biochemical recurrence occurred with PSA 5.9 ng/ml. Prostate volume was 27 cm³. MRI showed extra-capsular extension. PSA was 0.21 ng/ml

6 months after cryotherapy. MRI showed no cancer progression signs. Figure 2 shows the MRI perfusion map before cryotherapy (prostate cancer recurrence) and Fig. 3 shows this map six months after the procedure.

The fifth patient, 66-year-old, was diagnosed with cT2b N0 M0 prostate cancer, Gleason 3 + 3 = 6, PSA value of 15.2 ng/ml. In 2007 the patient received 70 Gy dose treatment with 3D conformal radiotherapy. In January 2013 prostate cancer recurrence was diagnosed on MRT, with PSA 4.9 ng/ml. Prostate volume was 20.1 cm³. In February 2013 cryotherapy was applied and after 2 months PSA was 0.29 ng/ml.

RESULTS

The described treatment scheme for these patients enables to deliver two freezing-thawing cycles with 10–12 probes and a urethra-warming catheter. All procedures were completed successfully without any intraoperative complications.

Urinal obstruction was observed after 1 week for 1 of 5 patients. He had to stay with epicystostomy and overwent prostate transurethral resection. After these procedures the patient could urinate normally.

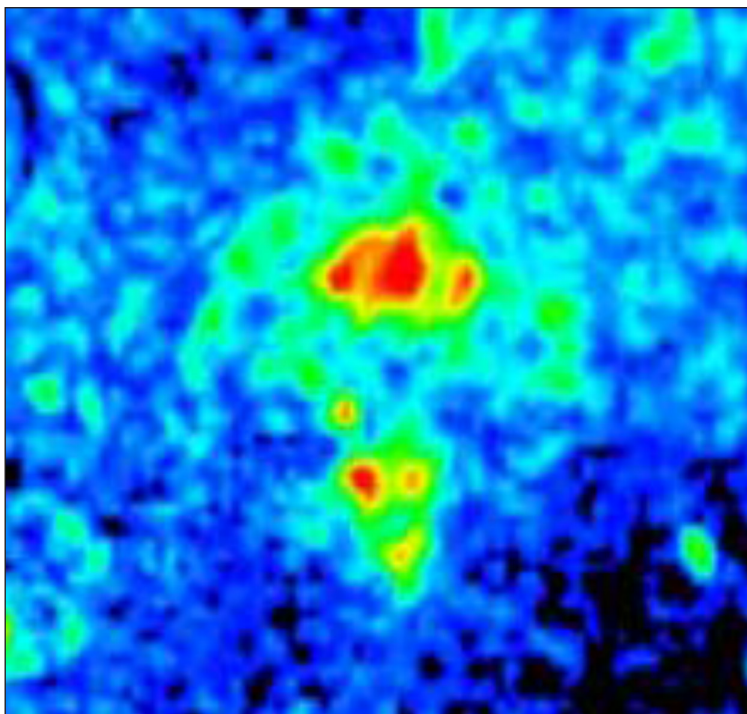


Fig. 2. MRI perfusion map shows intensive blood flow, which is increased in prostate cancer cells

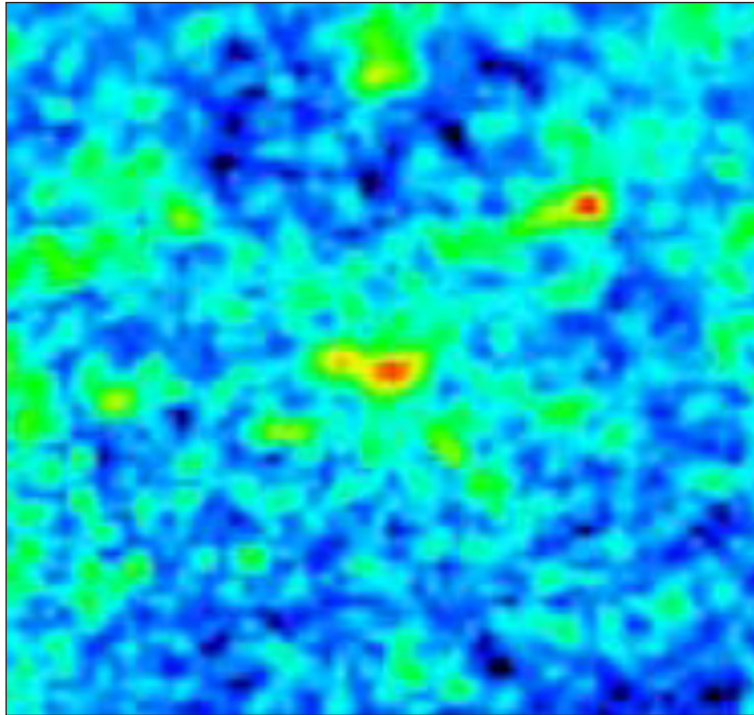


Fig. 3. MRI perfusion map after cryotherapy. There are no increased blood-flow spots in prostate

One patient had biochemical progression due to metastasis in the 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.

No patients suffered from urinary incontinence.

DISCUSSION

Nowadays many urologists are trying to solve new dilemma: How to treat patients who were diagnosed with prostate cancer recurrence after radical radiotherapy? According to new literature, in eight years biochemical prostate cancer recurrence will be diagnosed for 15–20% low risk cases and about 40% high risk cases of prostate cancer (1, 2).

Data of the Cancer of the Prostate Strategic Urologic Research Endeavour comprising 2 336 patients with prostate cancer (4) demonstrated that 92% of patients who had initially been irradiated received ADT for the secondary treatment of PSA progression. In the absence of salvage procedures, the mean time interval from biochemical to clinical progression was approximately 3 years. After radiotherapy for prostate cancer, it has been demonstrated that up to one third of patients with biochemical failure will have a positive biopsy (5).

According to the 2008 American Urological Association (AUA) Best Practice Consensus Statement, ideal candidates for salvage cryoablation also should have absence of seminal vesicle invasion, a PSA less than 10 ng/mL (preferably <4 ng/mL), a PSA doubling time of 16 months or more, and at least a 10-year life expectancy. Factors such as gland volume larger than 50 to 60 cm³ or prior transurethral resection may exclude patients in some cases (5–7). On the other hand, the European Association of Urology (EAU) guidelines state that ideal candidates for cryotherapy are those who have organ-confined prostate cancer and those identified as having minimal tumour extension beyond the prostate (1–3). The prostate should be <40 mL in size. Prostate glands >40 mL should be hormonally downsized to avoid any technical difficulty in placing cryoprobes under the pubic arch. Prostate-specific antigen (PSA) serum levels should be <20 ng/mL, and the biopsy Gleason score should be <7. It is important that patients with a life expectancy >10 years should be fully informed that there are no data, or only minimal data, on the long-term outcome for cancer control at 10 and 15 years (10). We analyzed and adapted these AUA and EAU statements for our hospital. In our opinion, excellent candidates for prostate cryotherapy are

diagnosed with local prostate cancer, no metastases (checked with CT, MRI or bone scintigraphy scans), The prostate-specific antigen (PSA) serum level is lower than 10 ng/mL, the biopsy Gleason score is <7 and the prostate volume should be lower than 50 mL. Patients with life expectancy longer than 10 years must be informed that there is no or there is only minimal data on the long-term outcome for prostate cancer control.

Currently there are many treatment alternatives for prostate cancer recurrence: prostate cryotherapy, high dose rate brachytherapy (HDR), prostatectomy, high-intensity focused ultrasound (HIFU). In rare cases active surveillance can be used.

In our experience surgery after radical radiotherapy is associated with high mortality rate and high risk of postoperative complications. EAU guidelines propose not to perform radical prostatectomy for patients who had radiation therapy because of high complications risk. Various authors reported that 30–67% of the patients, who had salvage prostatectomy after radiotherapy, suffered from urinary incontinence, anastomosis stenosis occurred in 11–30% and 1–10% had rectal injuries (8, 9). Erectile dysfunction seems frequently not to be a major problem in this setting as it is often present after radiotherapy (10, 11). It is important to remember that many patients with prostate cancer recurrence are old with many comorbidities and are after radiotherapy. Quite often surgery cannot be applied in such settings. Other salvage treatment options are brachytherapy or external beam re-radiotherapy. Unfortunately, these treatment methods cannot be used in a lot of cases because of too high cumulative radiation dose (External beam therapy already brings at least 70 Gy radiation dose). In addition to this, experience with salvage brachytherapy for radiation failures is very limited. Hormonal therapy brings many negative side-effects and desperately decreases the quality of life. Hormonal treatment lasts for a long period of time and cost of the treatment is very high. 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 is still experimental due to the short follow-up periods reported.

On the other hand, cryotherapy is well known for a low complication rate, good quality of life, short

procedure time and hospitalization. Cryosurgery may offer an option for treating cancers that are considered inoperable or that do not respond to standard treatment methods. Furthermore, it can be used for patients who are not good candidates for conventional surgery because of their age or other medical conditions. The technology of cryoablation devices has been improved, 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. Gas-driven miniaturized equipment, ultrasonographic ice-ball monitoring, and the use of thermal sensors have allowed more efficient freezing of the prostate gland while reducing collateral damage to surrounding tissues. Various studies reported outcomes and complication rates of salvage cryotherapy: 4.4–13% urinary incontinence, 1–3.4% rectal injuries. The same studies followed up patients for 3–10 years after salvage cryotherapy and reported biochemical recurrence-free survival rates varying from 39 to 66% (9).

Many doctors consider that cryotherapy is an expensive procedure. However, 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 (12).

CONCLUSIONS

Our initial experience shows that cryotherapy can be a viable alternative for patients with disease progression after radiotherapy. Currently the biggest advantages of cryotherapy are as follows: possibility to treat patients not suitable for salvage prostatectomy, short hospitalization, low complication risk and lower overall cost than other methods. Short term data seems to be promising but longer follow-up is necessary to verify oncological and functional results.

Received 30 September 2013

Accepted 16 January 2014

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PIRMIEJI GELBSTINČIOSIOS PROSTATOS KRIOTERAPIJOS REZULTATAI

Santrauka

Įžanga. Prostatos vėžys yra dažniausias Lietuvos vyrų piktybinis susirgimas. 2007 m. buvo nustatyta daugiau kaip 3 500 prostatos vėžiu sergančių pacientų. Daugelis jų buvo gydomi radioterapija. Deja, praėjus keletui metų daliai pacientų prostatos vėžys progresavo net ir po spindulinio gydymo. Šiems pacientams siūlomas įvairus gelbstintis gydymas: radikali prostatektomija, didelių dozių radioterapija, krioterapija, hormoninis gydymas ar aktyvus stebėjimas. 2012 m. mūsų įstaigoje buvo pradėtos pirmosios gelbstinčiosios krioterapijos procedūros, todėl ir norime pasidalyti patirtimi ir rezultatais.

Tiriamieji ir metodika. Penkiems pacientams, sergantiems prostatos karcinoma, buvo atlikta gelbstinčioji krioterapija. Visi pacientai prieš tai buvo gydomi radioterapija, o vienam jų papildomai buvo skirtas ir neoadjuvantinis hormoninis gydymas.

Prostatos karcinomos recidyvus nustatėme multiparametriniais magnetinio rezonanso tyrimais (mMRT), taip pat paėmę transrektalines ar transperinealines biopsijas. mMRT radiniai buvo vertinami remiantis Prostatos magnetinio rezonanso atvaizdavimo ir duomenų sistema (PI-RADS). Prieš gydymą krioterapija buvo atlikta įvairių kūno dalių kompiuterinė tomografija, magnetinis rezonansas, ultragarsinis tyrimas ar kaulų scintigrafija. Patologinių pakitimų kauluose, būdingų metastazėms, neaptikta.

Visiems pacientams paskirta dviejų ciklų krioterapija. Procedūros buvo stebimos echoskopu, fiksuoti temperatūrų pokyčiai audiniuose.

Rezultatai. Per tarpvietę į norimas prostatos zonas buvo įkišta 10–12 specialių adatų, kuriomis šaldyti audiniai. Specialiu šildančiuoju kateteriu buvo mažinama šlaplės pažeidimo rizika. Visiems pacientams krioterapijos procedūros atliktos be intraoperacinių komplikacijų.

Pooperacinės komplikacijos: šlapimas susilaikė vienam pacientui. Jam teko atlikti cistostomą bei transuretrinę prostatos rezekciją. Po šių intervencijų pacientas galėjo normaliai šlapintis.

Kitam pacientui, remiantis PSA tyrimu, buvo diagnozuotas prostatos karcinomos progresavimas dėl metastazavimo į pasaito limfmazgius. Jam buvo skirtas išorinis spindulinis gydymas. Po 6 mėnesių prostatos vėžio progresavimo požymių magnetinio rezonanso tyrimu neaptikta, o PSA buvo 1,77 ng/ml.

Nė vienas pacientas neturėjo problemų dėl šlapimo nelaikymo.

Išvados. Mūsų pirmoji krioterapijos naudojimo patirtis atskleidė, jog šis gydymo metodas yra efektyvus pacientams, kurių liga progresavo po radioterapijos. Didžiausi krioterapijos privalumai: galimybė gydyti pacientus, kuriems dėl tam tikrų priežasčių negali būti atlikta radikali prostatektomija, trumpa hospitalizacija, nedidelė komplikacijų rizika ir mažesnės nei kitų gydymo metodų išlaidos. Manome, jog geri pirminiai rezultatai atskleidžia krioterapijos efektyvumą, tačiau būtina toliau stebėti gydytų pacientų būklę. Tai padėtų tiksliai įvertinti šio metodo naudą, trūkumus bei komplikacijas.

Raktažodžiai: prostatos vėžys, recidyvavimas, krioterapija, gelbstinčioji krioterapija