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Professional paper

WHICH PATIENTS SHOULD RECEIVE RADIOTHERAPY IN POSTOPERATIVE DISEASE RECURRENCE?

Mate Matić[1,2] and Suzana Matić[1,3]

[1]Osijek Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia;
[2]Department of Oncology, University Hospital Osijek, Osijek, Croatia;
3University Eye Clinic, University Hospital Osijek, Osijek, Croatia

SUMMARY – After radical prostatectomy (RP), up to 60% of patients with high-risk prostate cancer (PC), such as high Gleason score, extracapsular prostatic extension (ECE), positive margins, seminal vesicle involvement (SVI), will develop biochemical relapse and they will require further local treatment. Radiotherapy (RT) to the prostate bed has been used as adjuvant (ART) or salvage (SRT). In patients with high-risk PC, radiotherapy immediately after RP or adjuvant radiotherapy may eradicate residual localized microscopic disease and improve biochemical, progression-free survival, and overall survival. Only a few observational studies have compared RP patients who have received only RT with patients who have received RT with some form of hormonal therapy. A few of them have reported improved progression-free survival with addition of hormonal therapy to SRT, but benefit in overall survival (OS) is not yet known.

Key words: *Radical Prostatectomy, Adjuvant Radiotherapy, Salvage Radiotherapy*

Introduction

Three randomized controlled trials (RCTs) have analyzed the effect of RT after radical prostatectomy. Primary outcomes in these trials have been different: clinical progression-free survival (cPFS), biochemical progression-free survival (bPFS) and metastases-free survival. It is of significance that a certain number of patients in the RT arms were treated with 60 Gray (Gy), which is less than currently used doses of 66 Gy and more. These trials have reported improvement in bRFS in patients with high-risk pathological features, with the use of ART in comparison to observation only (1).

If radiation is conducted when PSA level is less than 0,1 ng/ml within four months after RP it is called adjuvant therapy. Radiation usually starts after normalization of urination. Salvage radiation therapy means administration of RT to the prostatic bed in patients with biochemical recurrence (PSA level > 0.2 ng/ml).

EORTC 22911 trial at median 10.6 years of follow-up reported reduction in locoregional recurrence (8,4% in the ART group and 17,3% in the RP only group) (2).

EORTC 2219 and SWOG 8794 showed improved clinical PFS in patients with ART compared to RP only.

SWOG 8794 reported significantly improved OS in ART patients comparing with RP only, at more than 12 years of follow-up (74% vs 66%) (3). This trial also reported improved metastatic recurrence-free survival (mRFS) (71% for ART vs 61% for RP only).

In patients with positive surgical margins, these trials demonstrated statistically significant improvement in bRFS in men who received RT in comparison to RP only. These trials did not report difference in OS between two groups of patients.

In patients with GS 7-10, only one study demonstrated significant improvement in bRFS in patients who have received RT (4).

Corresponding to: *Mate Matić, MD, PhD*, University Hospital of Osijek, Department of Oncology, Osijek Faculty of Medicine, Josip Juraj Strossmayer University of Osijek, J. Huttlera 4, 31 000 Osijek, Croatia
E-mail: matematic99@gmail.com

SWOG 8794 at median 12,6 years of follow up demonstrated that 9 patients would need to be treated with ART after RP compared to RP only to prevent one death of any cause (5).

At same median of follow-up EORTC 22911 documented that about 56 patients would need to be treated with ART after RP to prevent one case of death from PC compared to RP-only patients.

Few studies have demonstrated that SRT improves outcomes in patients with local or PSA recurrence compared to RP patients, but the benefit is not present in all groups of patients (6).

Adjuvant radiation therapy given to all high-risk patients will over-treat about 50% of patients who are cancer-free, exposing them to unnecessary toxicity and causing poorer quality of life.

Approximately 60% of high-risk patients with PSA recurrence after RP will develop metastatic disease if left untreated (7).

If salvage radiation therapy is initiated at first sign of recurrence after RP, approximately 50% of patients will have long PSA response.

Many of prostate cancer patients if left untreated will not die from the disease and even those with biochemical recurrence will not certainly become symptomatic from the disease.

Discussion

It is always a question in high-risk post-RP patients when to administer RT - before or after biochemical recurrence. ART may be given to a number of patients that would never experience recurrence. SRT could lead to metastatic disease because of later onset.

Many studies have shown that ART patients have better outcomes compared to SRT patients. In patients with ART rates of biochemical recurrence and metastasis are lower than in patients with SRT at similar follow-up period. Cause specific survival (CSS) and OS are less clear. It is not well documented if ART leads to superior outcomes in the absence of randomization.

SRT and ART trials differ in numerous factors such as RT protocols (ART trials often used lower RT doses than SRT trials) and different techniques, follow-up period, different pathological profile. Despite various studies there is not enough clinical data to answer the question if ART is superior to SRT. A recent trial at 5 years follow-up found no difference in bRFS rates between pT3N0 patients (PSA ≤ 0.5 ng/ml) who have received ART in comparison to ESRT (9).

The study of Pfister et al. reported that outcomes are better when SRT is initiated at the lowest PSA values. Several studies have reported that, if pre-radiotherapy PSA is lower than 0,5 ng/ml, the biochemical relapse-free survival can be improved (10). The term ESRT refers to patients with undetectable PSA after prostatectomy who have subsequent PSA rise ≤0.5 ng/ml. At 2 years follow-up, Siegmann reported bPFS of 83% in patients with PSA ≤0.2 ng/ml at the time of SRT compared to 61% when PSA is ≥0.28 to ≤1 ng/ml (11).

Jereczek-Fossa compared two groups of patients with 4 years of follow-up. One group received immediate RT with PSA raising between 0.1 and 4 ng/ml vs. other group who received SRT >6 months after RP for biochemical recurrence lower than 13,7 ng/ml. Study reports that bPFS is significantly longer in the immediate RT group (79.8 vs. 60.5%). Recent trials have reported that pre-radiotherapy PSA ≥0.2 ng/ml correlates with worse clinical outcome (12).

It is confirmed that the minimum radiation dose that should be delivered to the prostate bed is 64-65 Gy (13).

One of the questions regarding the use of hormonal therapy in post-RP patients is when and for how long it should be administered.

In a study conducted by Parker et al., patients who have received SRT with bicalutamide (150 mg daily) had statistically significantly fewer number of metastases and improved freedom from biochemical progression (14).

Some trials compared patients after radical prostatectomy who received ART and patients who received ART+hormonal therapy (15). Only one study has confirmed significant difference between these two groups. Bastide compared patients treated with ART + hormone therapy vs ART alone and reported that hormone therapy group had higher bRFS rates (82,8% vs 44,4%) (16).

As far as we know, early ADT reduces incidence of pathologic fractures and spinal cord compression and improves cancer-specific survival, but there is no benefit in OS (17).

RTOG 9601 has shown that survival was improved with SRT+ bicalutamide in most subgroups of patients

with positive surgical margins, PSA 0,7-4,0 ng/ml and GS 7, after a follow-up of 13 years. For now, the role of hormone therapy remains uncertain.

At 5 years follow-up GETUG-AFU 16 trial reported that patients who were treated with SRT + goserelin have improved progression-free survival especially those with postoperative PSA ≥ 0,2 ng/ml (18).

In conclusion, the 3 studies which included over 1,110 patients reported that ART compared to watch and see strategy reduced the risk of PSA relapse by 20%.

The question of whether all patients with high-risk pathological features and without measurable PSA should undergo immediate ART or early SRT at biochemical recurrence remains a subject of controversy.

Conclusion

Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly improves survival and reduces risk of distance metastases. Patients with locally advanced disease, positive margins and high GS are candidates for postoperative radiotherapy.

ART and ESRT seem to be equivalent in reducing the risk of biochemical recurrence (BCR), distant metastases and death in pT3N0 patients.

There is significant impact of ART on bRFS, but neither time to the onset of metastatic and hormone-refractory disease nor prostate cancer specific and overall mortality differed significantly. For patients with only positive margins adjuvant radiotherapy is questionable because only some patients will have BCR.

ART in comparison to observation prolongs bPFS, but its benefit in prolonging OS is questionable.

Hormonal therapy should be offered to patients treated with salvage radiotherapy, especially to patients with postoperative PSA ≥ 0,2 ng/ml.

The role and length of ADT given with post-prostatectomy irradiation remains unknown.

There are no published randomized clinical trials comparing ART and SRT.

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Sažetak

KOJI BI PACIJENTI TREBALI PRIMITI RADIOTERAPIJU U POSTOPERATIVNOM RECIDIVU BOLESTI?

M. Matić i *S. Matić*

Nakon radikalne prostatektomije (RP) više od 60% pacijenata s visokorizičnim patološkim pokazateljima, kao što su visok Gleason score, ekstrakapsularno širenje, pozitivni rubovi, zahvaćeni sjemeni mjehurići, razviti će biokemijski relaps, te će zahtijevati daljnji lokalni tretman. Radioterapija na ležište prostate može biti adjuvantna i (salvage) odgođena. Kod karcinoma prostate visokog rizika, radioterapija odmah nakon RP ili adjuvantna radioterapija, može uništiti lokalnu rezidualnu mikroskopsku bolest i povezana je s poboljšanim biokemijskim preživljenjem do progresije bolesti i ukupnim preživljenjem. Malo je istraživanja koja su uspoređivala operirane pacijente koji su proveli zračenje ležišta prostate s pacijentima koji su uz RT primili i neku vrstu hormonske terapije. Neka od njih su pokazala poboljšano preživljenje do progresije bolesti dodatkom hormonske terapije uz SRT, ali učinak na ukupno preživljenje je upitan.

Ključne riječi: *radikalna prostatektomija, adjuvantna radioterapija, odgođena radioterapija*