Postoperative radiotherapy in prostate cancer: acquired certainties and still open issues. A review of recent literature

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ABSTRACT

It is recognized that radiation therapy can eradicate microscopic tumor disease, even in postoperative prostate cancer patients, with extracapsular extension, positive surgical margins or increased prostate-specific antigen is found in surgical specimens. This review of recent literature analyzes and discusses acquired certainties and still open questions regarding type, timing, doses, techniques, toxicities, and associated hormonal therapies of radiotherapy prescribed after radical prostatectomy. Free full text available at www.tumorionline.it

Introduction

In organ-confined prostate cancer patients, surgical treatment is the most common therapeutic procedure to eradicate the disease. The retropubic approach is generally preferred for the perineal approach, considering the advantage to assess pelvic lymph nodes at the same moment of prostatectomy. Although a learning curve with robotic resection does exist and it is not so short, robotic-assisted laparoscopic prostatectomy is rapidly becoming the surgical procedure of choice for treating localized prostate cancer. Postoperative radiotherapy offers a potentially curative treatment for selected patients with biochemical or clinical failure after radical retropubic prostatectomy (RRP) and could reduce the risk of failure in high-risk patients. The type of postoperative radiotherapy preferred and when it could be most useful are frequently debated issues.

It is essential to distinguish two types of post-RRP radiotherapy treatment intent, considering two kinds of definition. Performing radiotherapy within 6 months of surgery and an undetectable post RRP prostate-specific antigen (PSA) represent the “temporal” and “biochemical” conditions necessary to define a postoperative as an adjuvant or immediate radiotherapy. Conversely, in the presence of detectable PSA after surgery and/or 6 months after RRP, radiotherapy should be considered a salvage approach. The “biochemical” and “timing” definition can clarify the significance of adjuvant intent to complete the surgical intervention by sterilizing microscopic disease in case of a high risk of local recurrence and the significance of salvage intent in case of failure.

Many concepts of post-RRP radiotherapy in prostate cancer are now acquired certainties, whereas many aspects still appear to be open issues.

Why is adjuvant radiotherapy preferable?

Roehl et al. published a mono-institutional study of 3478 consecutive RRP patients, with extracapsular extension (ECE) and/or positive surgical margin. The patients were monitored by a single operator, which is an important factor in reducing the bias of various surgical techniques or manual experiences. The range of local control was assessed as 10% to 50%. The probability of non-progression survival was stratified by pathological stage (P < 0.0001) and clinical stage (P < 0.0001). With a median follow-up of 65 months, the worse clinical outcomes were reported for cases with pathological specimens of nonconfined prostate disease (pT3 and/or cT3), for incomplete surgery in terms of radical intent (positive surgical margins), and when a patient was classified as cT3 before surgery. Several retrospective and three large prospective studies (Table 1) have clarified the role of early adjuvant radiotherapy (EART) in reducing the rate of recurrence after RRP in patients with high-risk carcinoma of the prostate defined by evidence of ECE, seminal vesicle involvement (pT3), and/or infiltration of surgical margins (R1). The EORTC 22901 randomized controlled trial compared radiotherapy versus no radiotherapy for prostate cancer patients with a positive surgical margin or pT3 prostate cancer. With a median follow-up of 5 years, 1065 patients (502 in the radiotherapy arm versus 503 in the wait-and-see arm) were evaluated. A statistically significant advantage in favor of the radiotherapy arm was found for cumulative incidence of local-regional failure (P < 0.0001) and was confirmed for biochemical progression-free survival (P < 0.0001) and clinical progression-free survival (P = 0.009).

The SWOG 8794 randomized, prospective, multi-institutional study analyzed 425 pT3 patients. Sixty to 64 Gy of external beam radiotherapy were prescribed to the prostatic fossa in one arm (n = 214) and observation alone in the other arm (n = 211). With a median follow-up of 10.6 years, PSA relapse (>4 ng/ml) occurred significantly later in the radiotherapy arm (P < 0.001; 10.3 years for radiotherapy versus 3.1 years for observation) and recurrence-free survival was significantly longer (P = 0.0015; 13.8 years for radiotherapy versus 9.9 years for observation). The third randomized trial on postoperative radiotherapy (ARO 96-02/AUO AP 09/95 trial) was conducted on 385 men with prostate cancer, staged as pT3 and/or R1. They were randomized to receive 60 Gy radiotherapy (n = 193) or observation alone (n = 192). With a median follow-up of 5.6 months, the number of patients with no evidence of biochemical disease at 5 years was 72% for the radiotherapy arm compared to 54% in the observation arm (P = 0.0015).

As shown in Table 1, such results confirmed a role of postoperative radiotherapy in improving biochemical results in prostate cancer patients with risk factors in the pathological specimen. Does adjuvant radiotherapy significantly reduce also the risk of metastasis and increase in survival a patient with pT3N0M0? Updates of SWOG 8794 and 22911 trials have recently been published to evaluate other end points as well as biochemical improvements. Thompson et al. reviewed SWOG 8794: patient follow-up continued after the first report, and significant advantage for metastasis-free survival with radiotherapy (P = 0.016; 93/214 events in the radiotherapy arm versus 114/211 events on observation)
was recently revealed. Survival was significantly greater with radiotherapy ($P = 0.023$; 88/214 deaths in the radiotherapy arm versus 110/211 deaths on observation). This was the first report to demonstrate that postoperative radiotherapy, despite the relatively modest dose used in the late 1980s, can significantly reduce the risk of metastasis in the presence of ECE after RRP.

### Table 1 - Comparison between postoperative randomized studies regarding patient inclusion criteria (according to the TNM classification), median age of study populations, number of patients, median follow-up, biochemical recurrence-free survival, metastatic events, and overall survival, when available

<table>
<thead>
<tr>
<th>Randomized trial</th>
<th>TNM inclusion criteria</th>
<th>Median age (yr)</th>
<th>No. of patients</th>
<th>RT dose (Gy)</th>
<th>Median follow-up (yr)</th>
<th>bRFS vs observation</th>
<th>Metastatic events RT vs observation</th>
<th>OS RT vs observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 229911</td>
<td>pT2N0XMR1 or pT3N0X0</td>
<td>65</td>
<td>1005 (502 vs 503)</td>
<td>60</td>
<td>5</td>
<td>74% vs 52%</td>
<td>49% vs 32%</td>
<td>-</td>
</tr>
<tr>
<td>SWOG 9714</td>
<td>pT2N0XMR1 or pT3N0X0</td>
<td>64.9</td>
<td>425 (214 vs 211)</td>
<td>60.64</td>
<td>&gt;12</td>
<td>13.0 vs 9.5</td>
<td>52/24 vs 14/21 (P = 0.046)</td>
<td>15.2 vs 13.3</td>
</tr>
<tr>
<td>ARO</td>
<td>pT1N0X0</td>
<td>-</td>
<td>385 (152 vs 133)</td>
<td>60</td>
<td>5</td>
<td>72% vs 54%</td>
<td>(41 5 yr)</td>
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The EORTC229911 trial investigators re-analyzed the data of the randomized trial with 1005 patients. The authors demonstrated (re-evaluating data from specimens of participants by means of pathological reassessment) that margin status, in the arm submitted to radiotherapy, was the strongest predictor of prolonged biochemical disease-free survival with EART. The investigators concluded that immediate postoperative radiotherapy should not be recommended for prostate cancer patients in case of negative surgical margins. After this clear contradiction with previous results of the same study group, strong criticisms pointed out that it was a retrospective analysis (unknown margin status in some patients) and utilized a noncentralized pathologic assessment, with consequent bias of subjective interpretation of data.

### Timing of adjuvant radiotherapy versus salvage radiotherapy

The time between postoperative radiotherapy and RRP can represent a way to define the intent of the treatment. Immediate postoperative and salvage radiotherapy have not been compared in a prospective, controlled trial. Parkin et al., in a recent complete review of the literature, concluded that adjuvant radiotherapy seems to be better than salvage therapy in terms of clinical benefit in high-risk patients, with a level I assessment of evidence (Evidence-Based Medicine score according to the National Cancer Center guidelines).

A recent monocentric Italian study retrospectively evaluated 431 post-RRP patients: 258 underwent adjuvant radiotherapy (started <6 months after RRP) and 173 underwent salvage radiotherapy. After a median follow-up of 48 months, failure-free survival, including biochemical and clinical failure, was significantly longer in the EART patients (79.8% vs 60.5%, $P < 0.00001$), whereas toxicity was instead better in the salvage group.

Several studies have dealt with the issue of the correlation between the timing of postoperative radiotherapy and the risk of subsequent toxicity, suggesting that the time of recovery for bladder/anastomosis/urethral tissue may be an important factor in the development of toxicity in postoperative radiotherapy. Likewise, the advantage of EART versus salvage radiotherapy in many studies seems to be clear from many studies, the issue of time-correlated increased toxicity of immediate radiotherapy remains to be fully addressed.

### When could salvage radiotherapy be useful?

Salvage radiotherapy showed a limited efficacy when prescribed after PSA failure or for local recurrence. However, for patients with recurrent prostate cancer after RRP, salvage radiotherapy remains the only potentially curative therapy. Early referral and careful patient selection will result in optimal benefit from salvage radiotherapy. The best results are reported in patients whose pre-radiotherapy PSA level was 0.5 ng/ml or less.

Anling et al. confirmed that, in their experience, a PSA value of 0.4 ng/ml or greater may be the most appropriate cutoff point to use, since a significant number of patients with lower PSA do not show a continuous increase in the marker. Freedland et al., evaluating biochemical relapse risk at 1 year and at 3 years, recently affirmed that a PSA value greater than 0.2 ng/ml is an appropriate cutoff point to define PSA recurrence after RRP.

An important factor leading to complications of the treatment of patients with PSA failure is the inability to distinguish patients with isolated local recurrence from those with occult distant metastases, who are unlikely to benefit from salvage radiotherapy. Several papers have reported criteria to distinguish between local and distant failure based on grading, T stage, PSA doubling time, and time after RRP.

In analyzing current imaging modalities, significant limitations in terms of specificity and sensitivity can be observed. The use of [11C]choline PET seems to be promising for restaging prostatectomy cases with a PSA rise and appears superior to 18F-FDG PET and complementary to conventional imaging. The use of [11C]choline PET/CT (computed tomography) can take advantage of the possibility to stage disease after RRP in a single step. However, the capability to identify local/regional disease, especially early in the course of recurrence with PSA lower than 1 ng/ml, when the cancer burden is lowest but most amenable to therapy, is drastically reduced.

Another discussed issue is the usefulness of vesicourethral anastomosis (VUA) biopsy in case of PSA relapse after RRP. Koppie et al. investigated the impact of anastomotic biopsy in 67 patients. Thirty-three (49%) were submitted to salvage radiotherapy (dose range, 60-74 Gy) in case of PSA failure only (2 PSA values >0.2 ng/ml); 34 (51%) were treated after a biopsy-demonstrated relapse. A recent multicentric Italian study retrospectively evaluated 431 post-RRP patients: 258 underwent adjuvant radiotherapy (started <6 months after RRP) and 173 underwent salvage radiotherapy. After a median follow-up of 48 months, failure-free survival, including biochemical and clinical failure, was significantly longer in the EART patients (79.8% vs 60.5%, $P < 0.00001$), whereas toxicity was instead better in the salvage group.

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In the recent subset analysis of the SWOG 8794 study, it emerged that the risk of failure in RRP patients not undergoing EART is predominantly local, with a surprisingly low incidence of distant failure. This awareness raises the important issue of the optimal dose of EART, which remains to be clarified.

A subsequent secondary analysis of EORTC trial 22911 identified patients with positive surgical margins as those benefiting most from early irradiation. In some reports, it was assumed that the residual tumor burden after RRP would be many logarithms smaller than in the case of radical irradiation, in which a clear dose-response effect was demonstrated. On the contrary, the radiotherapy dose used in the postoperative setting was generally 20-25% lower (around 60 vs 70-80 Gy) than that commonly used in the case of radical irradiation. Accordingly, the doses of irradiation adopted in the large randomized trials investigating the role of EART after RRP ranged between 60 and 64 Gy.

Only a few retrospective, small-sized series have dealt with the issue of the role of the EART dose. Valicenti et al. reported that EART doses >60 Gy improved biochemical control compared with lower doses. The criticism of the study was that the follow-up and sample size were limited.

King et al. investigated the role of a dose escalation in salvage radiotherapy in 122 lymph node-negative RRP patients. Median prostate bed dose was 60 Gy for 38 patients and 70 Gy for 84 patients. A dose response was found, with a 5-year biochemical recurrence-free survival rate of 25% vs 58% for prostate bed doses of 60 Gy vs 70 Gy (P<0.0001). It was concluded that a prostate bed dose of 70 Gy is recommended to achieve optimal disease-free survival.

Data from published studies of adjuvant and salvage radiotherapy after RRP were analyzed, in the context of biochemical tumor control probability dose-response curves. In this context, higher doses could potentially obtain significantly greater disease-free control rates. Considering an expected proportional gain in the biochemical recurrence-free survival rate of almost 3% per incremental Gray, a randomized trial testing a salvage radiotherapy dose of 64 vs 70 Gy or an adjuvant trial testing 60 vs 66 Gy was suggested. The proposed trial would require approximately 250 RRP patients and would be expected to find an almost 20% difference in the 5-year biochemical recurrence-free survival rate between the two treatment arms.

According to the hypothesis of dose gain of postoperative radiotherapy, Cozzarini et al. in a mono-institutional analysis on 334 high-risk, node-negative patients with undetectable postoperative PSA levels, obtained a gain of 12% in terms of biochemical recurrence-free survival rate when doses were increased from <70.2 to ≥70.2 Gy in an EART setting. Similar findings were shown after the exclusion of patients receiving androgen deprivation. At univariate analysis, both 5-year biochemical recurrence-free survival and disease-free survival were significantly higher (83% vs 71% [P = 0.001] and 94% vs 88% [P = 0.005], respectively) in the high-dose group.

Postoperative radiotherapy: is it really so toxic and poorly tolerated?

The reluctance of urologists to refer high-risk patients to postoperative radiotherapy may be related to the potential expected toxicity. Timely postoperative irradiation it is not offered to a significant number of patients due to the concern regarding the possible risk of genitourinary and gastrointestinal toxicity. While a large number of retrospective and prospective studies have dealt with the issue of clinical outcome following EART, few papers have reported the toxicity profile of postoperative irradiation.

Most of the data were reported in three randomized trials. In the EORTC trial at 5 years, the cumulative incidence of grade 3 toxicity was 4.2% in the adjuvant radiotherapy arm and 2.6% in the observation arm (P = 0.073). The cumulative incidence of any-grade toxicity, however, was significantly greater in the adjuvant radiotherapy arm (64.9% vs 54.3%; P = 0.005).

Graded acute and late gastrointestinal and genitourinary toxicity data were not reported in the SWOG trial. Considered together, such complications were more common in the adjuvant radiotherapy arm than in the salvage radiotherapy arm (23.8% vs 11.9%; P = 0.0024). The German Cancer Society trial recorded the frequency of acute and late toxicity in the adjuvant radiotherapy arm only. Acutely, the rates of grade 3 bladder and grade 2 rectal toxicity were 3% and 12%, respectively. No acute grade 3 rectal toxicity was found. The rate of late grade 2 and 3 bladder toxicity was 10% and 2%, respectively, whereas the rate of late grade 2 rectal toxicity was 10%.

It is fundamental to consider that these studies started in the late 1980s and used huge radiation portals and not modern techniques. The installation of CT simulators in daily practice has modified the way to identify target volumes, from two-dimensional to three-dimensional customized targets. In the modern era of radiotherapy, the even more frequent use of image-guided radiotherapy and intensity-modulated radiotherapy allow better positioning control of patient and target and a drastic reduction of high dose involvement of organs at risk.

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What are the treatment volumes for postoperative radiotherapy?

There is no consensus on correct contouring and definition of target volume in three-dimensional conformal radiotherapy. The definition of a "volume including surgical limits from seminal vesicles to apex with security margin to encompass peri-prostatic area" was described as an initial phase of radiotherapy in the EORTC 22911 study. A boost to "reduced volume circumscribing the previous definition of a "volume including surgical limits from seminal vesicles to apex with security margin to encompass peri-prostatic area" was described as an initial phase of radiotherapy in the EORTC 22911 study. A boost to "reduced volume circumscribing the previous definition of a "volume including surgical limits from seminal vesicles to apex with security margin to encompass peri-prostatic area" was described as an initial phase of radiotherapy in the EORTC 22911 study. A boost to "reduced volume circumscribing the previous definition of a "volume including surgical limits from seminal vesicles to apex with security margin to encompass peri-prostatic area"

Recently, Poortmans et al. published consensus guidelines for target volume definition in postoperative radiotherapy for prostate cancer, on behalf of the EORTC Radiation Oncology Group. The end point of the report was to achieve a standardization of the target volume definition and delineation, as well as of the clinical quality assurance when three-dimensional conformal radiotherapy, intensity-modulated radiotherapy or image-guided radiotherapy are applied for patients undergoing postoperative radiotherapy for prostate cancer. It was estimated that the sites of recurrence in prostate fossa are involved in order of high to low for relapse as follows: anastomosis in 63%, retrovesical site in 17%, bladder neck in 10%, and other sites in 10%. It was suggested that the VUA and the bladder neck centrally, the space behind the lower bladder posteriorly, and the apex be included in the clinical target volume.

Members of the RTOG Genitourinary Committee have demonstrated that substantial qualitative variability exists among prostate cancer experts. Using a model-derived CTV from these expert contours, a consensus CTV has been established to be used in RTOG clinical trials. The consensus CTV should extend superiorly from the level of the caudal vas deferens remnant to >8-12 mm inferior to the VUA. Below the superior border of the pubic symphysis, the anterior border extends to the posterior aspect of the pubis and posteriorly to the rectum, where it may be concave at the level of the VUA. At this level, the lateral border extends to the levator ani. Above the pubic symphysis, the anterior border should encompass the posterior 1-2 cm of the bladder wall posteriorly, it is bound by the mesorectal fascia. At this level, the lateral border is the sacrorectogenitopubic fascia. Seminal vesicle remnants, if present, should be included in the CTV if there are pathologic evidence of their involvement.

What about pelvic nodes?

The role of whole pelvic radiotherapy (WPRT) involving drainage lymph nodes in patients with prostate cancer is not well established. In the RTOG 9413 study, a clinical advantage of WPRT combined with neo-adjuvant hormone therapy was suggested. However, pelvic nodes area was usually not involved in postoperative radiotherapy.
In some surgical series, it was suggested that the extent of the pelvic lymphadenectomy is crucial. Hidenreich et al. performed extended pelvic lymphadenectomy during RRP in 100 consecutive patients: this procedure was compared with RRP and standard lymphadenectomy. Extended pelvic lymphadenectomy was associated with a high rate of lymph node metastasis outside of the fields of standard lymphadenectomy.

In some institutions, the inclusion of the whole pelvis could be considered clinically useful in selected cases after a limited lymphadenectomy or in the presence of high risk of lymphatic re-colonization, although there is no evidence in the literature of a clinical advantage of WPRT in the postoperative setting.

Tolerability data of WPRT with new radiotherapy techniques, reducing bowel in intestinal cavity involvement, are promising. A retrospective analysis of 172 postoperative prostate cancer patients, treated to prostatic fossa and whole pelvis, showed that acute gastrointestinal, upper gastrointestinal and rectal toxicities were reduced with tomotherapy and intensity-modulated radiotherapy when pelvic nodes after WPRT were treated. The tomotherapy approach and Linac intensity-modulated radiotherapy also resulted in greater safety in minimizing gastrointestinal G2-3 acute toxicity and interruption of diarrhea.

Node involvement represents an important prognostic factor in prostate cancer patients. For node-positive patients, the impact of postoperative radiotherapy was shown with excellent long-term outcome in a series of 250 consecutive patients with pathologic lymph node invasion. The results of 129 patients (51.6%) treated with a combination of radiotherapy and hormone therapy, and 121 patients (48.4%) who received adjuvant hormone therapy alone, were analyzed; the mean follow-up was 95.9 months. This was the only study reporting a significant protective effect for radiotherapy on biochemical recurrence-free survival and cancer-specific survival.

A small number of patients showed lymph node involvement. Most of these patients received WPRT, which can play a significant role in distortion of clinical results.

Conclusion and future directions

Currently, the optimal treatment for patients at high risk of local recurrence after WPRT seems to be EART, as confirmed in the three randomized trials. Positive surgical margins may represent the most important element for the decision to prescribe EART. Salvage radiotherapy can be useful after a PSA increase (almost >0.20 ng/ml) in the context of clinical T stage and pre-radiotherapy PSA levels were statistically significant. Finally, a small number of patients showed lymph node involvement. Most of these patients received WPRT, which can play a significant role in distortion of clinical results.

Thus, it can be concluded that the potential benefit deriving from the addition of adjuvant androgen deprivation to postoperative radiotherapy remains to be clarified.

References

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Hormone therapy in the postoperative setting: why, when, how?

Multiple randomized trials in the radical setting have shown a clinical benefit of adding androgen suppression therapy to radiotherapy in several subsets of prostate cancer patients. The rationale for incorporating hormone therapy with radiotherapy in prostate cancer treatment is based on the observation that hormone therapy can cause involution changes in prostate cancer cells and reduce prostate tumor volume. If prostate cancer cells remain in prostatic fossa or in other sites, a control effect on them is expected.

Consensus exists in terms of timing, duration, type or side effects of androgen deprivation. The treatment is usually prescribed according to the preference of the referring urologist or radiation oncologist. Eulau et al. reported a study of 105 consecutive patients treated with pelvic irradiation (60-70 Gy to the prostatic bed in all patients, 50 Gy to the whole pelvis in 50 patients) after RRP. Of the 105 patients treated, 31 received adjuvant deprivation in combination with radiotherapy. The median duration of adjuvant deprivation was 6 months (range, 2-10). Freedom from biochemical relapse was significantly better among patients who received transient androgen blockade before and during radiotherapy than among those treated with radiotherapy alone (56 vs 27% at 5 years, P = 0.004). Freedom from clinical relapse was also superior for the combined treatment group (100 vs 70% at 5 years, P = 0.014). An important criticism of the study is that the follow-up was short considering the end points, and the duration of hormone therapy varied in the study population.

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