# DEVELOPMENTS IN EXTERNAL BEAM RADIOTHERAPY FOR PROSTATE CANCER

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**Primary EBRT:**

For localized prostate cancer (PC) (T1c-T2c N0M0), external beam radiotherapy (EBRT) is one of the standard treatment options. Combined with androgen deprivation therapy (ADT) (6months-3years), EBRT is also an established treatment option for the locally advanced (T3-T4 N0M0) and high-risk PC (Gleason ≥8 and/or PSA >20 ng/ml).[1] Intensity-modulated radiotherapy (IMRT), a further improvement of 3-dimensional conformal radiotherapy (3D-CRT), is becoming the golden standard in EBRT, because of its ability to safely provide higher doses to the prostate and seminal vesicles while lowering toxicity for the organs at risk.[2] In the setting of primary EBRT, a dose of at least 74 Gy must be provided given the superior results compared to conventional dose EBRT (64-72 Gy).[3] For intermediate and high-risk PC, a further dose increase to 78 Gy has shown a significant benefit.[4] A dose-escalation to >81 Gy has shown a further reduction in local recurrence rate compared to conventional dose EBRT.[5]

**Postoperative EBRT:**

Cancer recurrence after radical prostatectomy (RP) occurs in approximately 15-50% of patients and the failure pattern is predominantly local.[6] Three randomized trials comparing adjuvant EBRT versus observation post RP (EORTC 22911[7], ARO 96-02[8] and SWOG 8794[9]) have shown a significant reduction in the risk of local recurrence and PSA progression in case of adverse pathological features (extracapsular extension, seminal vesicle invasion and/or positive surgical margin). Although the radiation dose in EORTC 22911, ARO 96-02 and SWOG 8794 was 60-64 Gy, current practice in most institutions is to deliver 64-68 Gy to the prostate bed.[10]

Salvage EBRT is performed if a rising PSA trend is apparent (defined as PSA >0,2 ng/ml with two consecutive increases) after RP without evidence of systemic failure.[11] It is the only therapeutic option offering a potential cure.[12] A low pre-radiation PSA is of utmost importance in order to achieve the best results[13]: a PSA <0,5 ng/ml is the currently recommended upper limit.[1] It is estimated that 2% PSA control is lost per 0,1 ng/ml increase in pre-treatment PSA.[13] In most institutions, a dose of ≥68 Gy is administrated in the salvage setting.[10]

**Palliative EBRT:**

In metastatic PC, painful bone metastases not responsive to systemic treatments and oral analgesics should be considered for palliative EBRT. Single-fraction radiotherapy with a dose of 8 Gy is recommended for uncomplicated bone metastases and is as effective as multifractionated radiotherapy.[14] A pain response can be expected after a few days to 4 weeks with complete and partial pain relief in respectively 20-50% and 50-80% of patients.[14] Spinal cord compression, a devastating complication of axial bone metastases, is an emergency given the risk of tetra-or paraplegia in case of delayed or inadequate treatment. Steroids and surgical decompression, followed by EBRT is the golden standard treatment and is superior to radiotherapy alone with respect to ambulatory function and pain relief. If surgical decompression is not possible, EBRT in combination with steroids should be performed.[14]

## RECENT DEVELOPMENTS AND INDICATIONS OF EBRT

### 1. Simultaneous integrated boost in the primary setting for PC

With IMRT high doses can be delivered safely while respecting maximal doses to organs at risk, thus not increasing toxicity. Despite higher doses, local failure still occurs in up to 20% of cases.[3] Several studies have demonstrated that local recurrence predominantly originates at the primary tumor site.[15] This led to the hypothesis that local control could be increased by simultaneously delivering a boost dose to the primary tumor within the prostate. An intraprostatic lesion (IPL) can be detected by magnetic resonance imaging (MRI), MRI spectroscopy (MRS) and to a lesser extent (18F-)choline PET-CT.[16] This macroscopic IPL can be targeted by a simultaneous integrated boost (SIB), delivering a higher dose to the IPL while maintaining the standard high dose to the rest of the prostate.[17] Several planning studies have demonstrated the feasibility of SIB-IMRT to the IPL, while not delivering the treatment itself. Most included a dose increase to the IPL up to 90-95 Gy[17,18], although there are theoretical possibilities for further dose escalation up to 150 Gy.[19] Since most tumors are located in the peripheral zone, in close vicinity to the anterior rectal wall, Housri et al. concluded that the most important factor predicting favorably for receiving very high dose SIB-IMRT is an IPL-to-rectum distance >4,2 mm.[19] In accordance Fonteyne et al. reported the rectum to be the dose limiting organ in 88,3% of patients treated with SIB-IMRT.[20] Few studies have reported on the outcome after delivering SIB-IMRT.[20-22] Fonteyne et al. detected an IPL in 118 of 221 PC patients using MRI and MRS. Median dose delivered to the prostate and the IPL was 78 Gy and 81 Gy respectively in 38 fractions. After a median follow-up of 9 months, acute gastrointestinal (GI) and genitourinary (GU) toxicity grade $\geq 2$ was 11% and 48% respectively.[20] Although only a modest dose increase to the IPL was achieved, Eade et

al. estimated a gain in biochemical relapse-free survival rate of 2,2% for every 1 Gy added based on 8-year dose response analyses.[23] Ippolito et al. treated 40 patients with a dose of 72 Gy to the prostate and dose escalation to 80 Gy in 40 fractions to the MRI-detected IPL. Acute and late toxicity grade ≥ 2 were 20% and 9,5% respectively for GI and 32,5% and 13,3% for GU symptoms. After a median follow-up of 19 months no biochemical recurrence was recorded.[21] The results of these SIB-IMRT feasibility studies show similar incidences for acute toxicity as earlier published studies using standard high-dose IMRT.[24] So far no data are published on long-term toxicity after SIB. However, Zelefsky et al. demonstrated an association between acute and late toxicity in their study on 1.571 patients treated with primary IMRT.[24] Longer follow-up is required to evaluate biochemical and clinical outcome.

## 2. Hypofractionation in the primary setting for PC

Primary EBRT for PC is classically delivered in 2 Gy fractions, which for a dose of 74-80 Gy results in an overall treatment time of 7-8 weeks. Each tissue has a different sensitivity to EBRT fractionation that can be quantified by the α/β ratio in the linear-quadratic model. It has been suggested that the α/β ratio in prostate cancer is low, which would imply that hypofractionated regimens, in which a bio-equivalent dose is administered in less fractions with a higher dose per fraction, could improve oncological outcome and decrease late toxicities while overall treatment time is shortened and treatment cost is reduced.[25] So far, 3 randomized controlled trials have been published comparing oncological outcome of hypofractionated EBRT with conventionally fractionated EBRT. In the study of Yeoh et al. and Arcangeli et al. biochemical control was significantly better after hypofractionated EBRT.[26,27] However, Yeoh et al. only used a dose of 55 Gy in 20 fractions in the hypofractionated group and 64 Gy in 32 fractions in the conventionally fractionated EBRT

group, which nowadays is considered a low dose.[26] Arcangeli et al. used high dose EBRT in both groups but only included high-risk PC patients and had a limited follow-up time (median 33,5 months).[27] In contrast Lukka et al. reported a 7% difference in biochemical or clinical failure favoring patients treated with a dose of 66 Gy in 33 fractions compared to the hypofractionated group who received 52,5 Gy in 20 fractions.[28] These poor results, however, can be explained by the low dose given in both groups. Recently Fonteyne et al. conducted a multicentric phase II trial including 113 patients treated with a dose of 56 Gy in 16 fractions over 4 weeks.[29] After a median follow-up of 47 months, 5-year biochemical recurrence-free survival rates of 98%, 94% and 83% were calculated for low-, intermediate- and high-risk PC patients respectively, who received no, 6 months and 36 months of concomitant ADT respectively. These results are better than other observational reports of hypofractionated schemes that saw 3- to 5-year biochemical control rates of 91%-100%, 76%-85% and 71%-78% for low-, intermediate- and high-risk PC respectively. However, in most of these studies intermediate- and high-risk patients did not receive ADT.[30] No significant differences in late toxicity are reported, although acute GI and GU toxicity seems to develop earlier in hypofractionated than in conventionally fractionated EBRT.[27] High dose hypofractionated EBRT has shown promising results, although long-term biochemical and clinical outcome and late toxicity reports are eagerly awaited. Furthermore, the ideal fractionation schemes are yet to be determined.

### 3. Dose-escalation in the adjuvant setting for PC

In the adjuvant setting, the standard dose used in randomized trials was 60-64 Gy delivered by conventional radiotherapy and was rarely associated with severe long-term side effects (<5% grade 3 GI and GU toxicity).[7,8] However, a recent survey in the US has revealed that less than

4% still uses doses below 64 Gy.[10] It is indeed hypothesized that dose-escalation could improve PSA control with an estimated 3% gain per incremental Gy.[31] However, this dose-escalation might be hampered by toxicity when conventional radiotherapy is used. IMRT is able to improve dosimetric parameters for the rectum and bladder, allowing for safe dose-escalation.[32] Few studies have reported on long-term outcome of dose-escalation in the adjuvant setting with 2 studies reporting doses above 70 Gy.[33,34] In a retrospective series, doses of 68-69 Gy resulted in an absolute increase in biochemical recurrence free survival (bRFS) of 12% compared to lower doses (5-year bRFS 83% vs 71%).[35] A recent multicenter analysis of patients treated to doses > 69 Gy pointed out that doses above 70 Gy might be situated at the steep end of the dose-escalation curve.[33] The toxicity profile was reassuring with less than 1% grade 3 GI sequelae. However, a 29% probability of late grade 2-3 GU toxicity was observed with a 10% absolute incidence of grade 3 toxicity.[33] This is higher compared to doses of 60-66 Gy using conventional radiotherapy.[36] The observed increase in grade 3 GU toxicity with a dose of 68 Gy[37] or higher compared to 60-66 Gy is probably caused by the need to include the bladder neck and vesico-urethral anastomosis in the "high dose" region. As a result, improvements in treatment techniques such as 3D-CRT and IMRT might not improve GU toxicity.

## 4. Dose-escalation in the salvage setting for PC

It is suggested that the dose-response relationship of salvage and definitive primary EBRT are similar.[31] According to the analysis of Bernard et al. and King et al., there is a strong dose-response relationship and they both concluded that it is appropriate to consider doses above 66.6 Gy.[38,39] A recent review by Ohri et al., estimated that there is a potential 2.5% gain in PSA control per incremental Gy.[13] This is in agreement with the advise of the American

Society for Therapeutic Radiology and Oncology Consensus Panel, suggesting to use "the highest dose of radiation therapy that can be given without morbidity is justifiable".[40] When using conventional radiotherapy techniques it is estimated that dose-escalation above 72 Gy would result in an unacceptably high rate (20%) of grade 3 toxicity.[13] Consequently, EAU guidelines still recommend only 64-66 Gy.[11] Nevertheless, the recent survey among US physicians revealed that 55% delivers doses of at least 70 Gy and 91% uses IMRT, although only 2 groups have published their 5-year results using such doses with this technique.[41,42] From these studies it can be concluded that high dose salvage EBRT is probably safe when IMRT is used with 1% and 3% grade 3 GI and GU toxicity, respectively. For patients with pre-treatment PSA <0,5 ng/ml, the 5-year PSA control is promising with >70% of patients having their disease controlled.[41,42] Currently, Swiss Group for Clinical Cancer Research (SAKK) is conducting a phase 3 trial (SAKK 09/10) that compares salvage radiotherapy with 64 Gy versus 70 Gy without hormonal treatment in patients without macroscopic biochemical recurrence after prostatectomy (ClinicalTrials.gov identifier: NCT01272050). This trial will help us further define the role of dose-escalation in the salvage setting.

## 5. Whole pelvis irradiation for lymph node metastasized PC

Patients with lymph node invasion (LNI) are presumed to have incurable disease and therefore it is recommended to start immediate androgen deprivation therapy (ADT).[11] However, patients with minimal LNI have a favorable prognosis after RP and extended pelvic lymph node dissection (ePLND), even in the absence of immediate ADT. Bader et al. reported a 5 year CSS of 90% if only one lymph node was invaded.[43] Schumacher et al showed a 10 year cancer specific survival (CSS) of 78,6% if maximum 2 lymph nodes were involved.[44] Patients with minimal LNI might thus not be incurable and one might question whether

adding adjuvant whole pelvic EBRT to the postoperative setting might further improve local control and might prevent metastatic disease and PC death. In a subgroup analysis, Cozzarini et al. reported a better 5 and 8 year CSS for lymph node positive patients by adding adjuvant EBRT compared to no or late EBRT.[45] Da Pozzo et al. retrospectively investigated the combination of adjuvant EBRT and ADT versus ADT alone after RP and ePLND.[46] On multivariation analysis, delivery of adjuvant EBRT was associated with a significant better bRFS and CSS. It is noteworthy that not all patients in the series of Cozzarini[45] and Da Pozzo[46] received whole pelvis EBRT. Briganti et al. performed a matched analysis comparing adjuvant whole pelvis EBRT with ADT versus ADT alone in patients with LNI after RP and ePLND.[47] Adjuvant whole pelvis EBRT consisted of a 4-field whole pelvis irradiation to a median dose of 50.4 Gy followed by a 3-field boost to the prostatic bed to a median dose of 68.4 Gy. There was a significant benefit of adding whole pelvis EBRT to ADT: 10 year CSS and OS were 86% and 74% respectively versus 70% and 55% for ADT alone. Not only patients with minimal LNI (≤2 nodes positive), but also patients with gross LNI (>2 nodes positive) benefit from the combination of whole pelvis EBRT and ADT: 10 year CSS was 86% and 87% respectively. If ADT was used alone, 10 year CSS was 74% and 62% for respectively patients with ≤2 and >2 positive lymph nodes. The gain in survival benefit seems thus most pronounced in patients with gross nodal disease.[47] Some patients are unfit or refuse to undergo RP. In these patients, primary EBRT is indicated. No recommendations are provided in the EAU guidelines on whether or not to perform a prior staging PLND (although there is the same risk of having LNI as when they would undergo RP). If LNI is present, it is likely that primary whole pelvis EBRT might improve local control, prevent metastatic spread and thus ultimately PC death. Given the low sensitivity and specificity of conventional CT and MRI, ePLND remains the most reliable method to assess LNI.[1] In order to avoid morbidity (mainly lymphocele and lymphedema) of additional ePLND[48], prophylactic whole

pelvis irradiation has been proposed in patients at risk for LNI. The results of the 2 main randomised trials evaluating whole pelvis versus prostate only EBRT are conflicting. RTOG 9413 compared whole pelvis versus prostate only EBRT and neo-adjuvant versus adjuvant combined ADT[49]. Patients with a risk of LNI >15% were included (n=1.323). EBRT consisted of a conventional four-field "box" technique with a pelvic dose of 50,4 Gy. Upper limit of pelvic irradiation was L5-S1. Patients receiving whole pelvis EBRT were treated with an additional 19,8 Gy to the prostate using a cone down boost technique. Prostate only EBRT was limited to the prostate and seminal vesicles, with a total central dose of 70,2 Gy. Whole pelvis EBRT showed a significant better 4 year PFS compared to prostate only EBRT (resp. 54% versus 47%, p=0.02). Patients in the group whole pelvis EBRT combined with neo-adjuvant ADT had the best progression free survival (PFS). This trial was updated in 2007 and surprisingly, whole pelvis EBRT no longer had a significant better PFS compared to prostate only EBRT, although a trend in favor for the group whole pelvis EBRT combined with neo-adjuvant ADT remained.[50] It is noteworthy that late GI toxicity grade ≥ 3 was highest for whole pelvis EBRT with neo-adjuvant ADT compared to other subgroups (5% vs 1-2%). The GETUG-01 trial included 444 patients with T1b-T3, N0pNx, M0 PC randomly assigned to whole pelvis or prostate only EBRT.[51] In whole pelvis EBRT, the pelvic dose was 46 Gy with the upper limit at S1-S2. The dose to the prostate changed during the study from 66 to 70 Gy. The 5 year PFS and OS was similar in both groups. Acute and late GI and GU toxicity didn't differ among both groups. This study is criticized because only 45% of patients had a risk of LNI >15%. Both the GETUG-01 and RTOG 9413 can be criticized because of the relative low dose to the prostate (≤70 Gy) and because of insufficient coverage of lymph nodes at risk. Hypofractionated intensity-modulated arc therapy is able to increase the dose to the prostate (25 fractions with a biochemical equivalent dose of 80 Gy), is able to provide higher doses to the lymph nodes with SIB to lymph nodes at risk and is able to better

delineate the organs at risk. Fonteyne et al demonstrated a favorable acute toxicity profile associated with this technique.[52] Evaluating acute toxicity in 31 patients, no one suffered acute GI toxicity grade ≥3 and only 2 patients (6%) suffered grade 3 GU toxicity. This compares favorably with acute toxicity reported in the GETUG-0185. The safety of hypofractionated dose-escalation in whole pelvis EBRT with IMRT has been demonstrated by other authors.[53] The role of whole pelvis irradiation in the primary setting in patients with LNI (after PLND or on radiographic imaging) has been evaluated by Robnett et al. In combination with ADT, 12 year PFS and OS was 81% and 53% respectively.[54] In RTOG 85-31, the majority of patients with LNI didn't undergo radical prostatectomy and thus it is a trial on whole pelvis irradiation mainly in the primary setting.[55] The 5 year bRFS was 54% when whole pelvis EBRT was compared with ADT, and this was significantly higher than when no immediate ADT was provided (33%).

## 6. Radiotherapeutic treatment of oligometastatic PC

Metastatic PC will lead to symptoms with a negative impact on the patient's quality-of-life and ultimately to PC death. Currently, the EAU guidelines recommend to start with ADT at time asymptomatic metastases are detected to defer progression to symptomatic stages.[11] However, ADT is associated with numerous side effects. Consequently, strategies aimed at deferring the start of ADT, second-line hormonal treatments and cytotoxic treatments as long as possible are important. Additionally, the standard treatment with ADT was recently challenged by the observation that a subset of PC patients develop metastases in limited numbers (termed oligometastases) and that survival and response to ADT varies as a function of the number of metastases.[56-59] It is hypothesized that local treatment of limited metastases, with surgery or radiotherapy, might delay the start of potentially toxic systemic treatments.[59]

Moreover, patients with an initial low-volume metastatic disease were more likely to progress locally during ADT instead of distant, while the opposite was true for patients with high-volume metastatic disease.[56] However, traditional imaging studies (bone scan, CT and MRI) lack sufficient sensitivity to detect low volume metastatic disease at low PSA levels. The role of functional imaging modalities such as choline PET-CT has shown promising results to detect low volume metastases at low PSA levels.[60] As a consequence, close PSA monitoring and timely PET-CT evaluation is able to detect patients with oligometastatic PC. Surgical and/or radiotherapeutical eradication of oligometastases might delay ADT and cancer progression.[61] Recently, the first studies addressing salvage stereotactic body radiotherapy (SBRT) for low-volume metastatic disease were published[61-64], showing that clinical progression can be, at least temporarily, slowed down. SBRT is a non-invasive modality allowing the delivery of ablative doses to the tumor while sparing the surrounding normal tissue.[65] From these studies it can be concluded that SBRT can be safely used to treat lymph node and bone metastases and has the potential to postpone systemic treatment.[61,62] However, SBRT doses are not standardized and several fractionation schedules co-exist.[62,63] Further prospective trials are necessary investigating the potential of this approach.

## CONCLUSIONS

EBRT is a standard treatment for localized and locally-advanced PC. IMRT has been a substantial improvement in the field of EBRT. IMRT is able to give SIB in the primary setting with improved cancer control. Hypofractionation tends to improve cancer control and reduces treatment time. Dose-escalation with IMRT in the adjuvant and salvage setting improves cancer-related outcomes without additional toxicity. Although EBRT has an established place in the palliative treatment of metastatic PC, there is an emerging therapeutical role for EBRT in the lymph node metastasized and oligometastatic PC.

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