# Local control matters

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Men with high-risk localized prostate cancer (PC) represent an important patient population for whom treatment decisions are complex. Compared to the average patient they have greater risk of distant metastasis (DM) and eventual PC-specific mortality (PCSM). To some this raises the question of the impact of local recurrence in the natural history of the disease. A growing body of evidence clearly demonstrates that local control in PC improves DM-free survival (DMFS) and overall survival (OS).

The recent publication by Kishan *et al.*, examined the link between local control and DMFS, PCSM, and OS in high-risk patients (1). They utilized patient-level data encompassing 992 patients with high-risk PC, by virtue of Gleason Grade Groups 4 or 5 (Gleason scores of 8–10), from six randomized trials of external beam radiation therapy (EBRT). Four of the six trials relied on palpable findings to determine local failure (LF). With a median follow-up of 6.4 years, they demonstrated a significant association of LF with OS [hazard ratio (HR) 1.7; 95% confidence interval (CI): 1.37–2.10], PCSM (HR 3.1; 95% CI: 2.33–4.12) and DM (HR 1.9; 95% CI: 1.54–2.39). Patients without LF had a significantly decreased risk of death compared to those with LF (HR 0.13; 95% CI: 0.04–0.41) while those with LF had a significantly increased risk of metastasis or death (HR 2.46; 95% CI: 1.22–4.93). Furthermore, they utilized Markov proportional hazard models to quantitatively estimate the relative contributions of transitions between each disease state (disease free, LF, DM, or death) on each outcome. As the underlying trials from which the patients data were extracted were analyzing

the role of androgen deprivation therapy (ADT), the authors were also able to further investigate the influence of ADT duration on these outcomes and found that long-term and lifelong ADT had a significant impact on the transition to LF (HR 0.34; 95% CI: 0.20–0.59 and HR 0.17; 95% CI: 0.06–0.49 for long-term and lifelong compared to no ADT respectively). This analysis supplements a trend in the literature demonstrating that the higher the risk-group the greater the benefit to local therapy.

The benefit of local control for PC was first demonstrated by the SPCG-4 trial which randomized patients to watchful waiting or radical prostatectomy (RP). With extended follow-up at 18 years there was a benefit to local therapy in the rate of DM (38% *vs.* 26%), PCSM (29% *vs.* 18%) and overall mortality (OM) (69% *vs.* 56%) (2). Notably, although this trial was intended to represent a low-risk population, it was performed in an era before prostate-specific antigen (PSA) screening, with 88% having palpable disease. As such this should not be taken to represent today's low-risk, active surveillance population.

For locally advanced disease, three randomized trials of ADT with or without EBRT also demonstrated the benefit of local therapy (3-5). SPCG-7 had the longest follow-up and demonstrated a clear benefit to the addition of EBRT on PCSM (HR 0.42; 95% CI: 0.31–0.57) and OM (HR 0.70; 95% CI: 0.58–0.84) with a 17% reduction in death from PC at 15-years (34% *vs.* 17%) and 10% improvement in OM (61% *vs.* 51%). The UK/NCIC PR.3 trial had nearly identical estimates for the benefit in OM (HR 0.70; 95% CI: 0.57–0.85) and PCSM (0.46; 95% CI: 0.34–0.61). The

French TAP-32 trial had the shortest follow-up and a sample size powered only for the primary endpoint of biochemical failure (BF), not for PCSM or OS (5). Despite a lack of difference in more concrete endpoints the TAP-32 trial did show a significant improvement in PFS (HR 0.27; 95% CI: 0.17–0.39). As such these trials clearly demonstrate that local therapy, in this case EBRT, can decrease metastasis and improve both prostate cancer specific survival (PCSS) and OS in patients with higher-risk PC treated with ADT.

Post-operative EBRT after RP with high-risk features can also be viewed as a form of local intensification. Of the three classic adjuvant EBRT trials, the SWOG 8794 trial had the highest-risk patients. A third of patients had a post-operative PSA >0.2 ng/mL prior to EBRT, and yet even with a relatively modest dose of 60–64 Gy, they were able to demonstrate significant improvements in DMFS (HR 0.71; 95% CI: 0.54–0.94) and OS (HR 0.72; 95% CI: 0.55–0.96) (6,7). The EORTC 22911 trial similarly demonstrated a benefit to BF, and 10 year loco-regional failure with adjuvant RT. This trial had ~30% of patients having PSA >0.2 ng/mL. In contrast, the ARO 96-02 trial had the lowest-risk patients and did not show a benefit in OS although adjuvant radiation therapy (RT) substantially reduced BF. The latest wave of post-operative trials, RADICALS-RT, RAVES, and the GETUG-AFU17 have undergone meta-analysis of their first reports by the ARTISTIC collaboration. These data were presented at ESMO 2019 and indicate that early salvage is a reasonable alternative to adjuvant therapy for most men, suggesting that the benefit seen in the early trials is derived from intensified treatment of persistent local disease.

More importantly there may even be a benefit of EBRT to the prostate in men with early metastatic PC. In the STAMPEDE trial (8), patients with metastatic PC were treated with standard of care systemic therapy with or without prostate EBRT. The addition of EBRT in all patients improved failure free survival (FFS, HR 0.76; 95% CI: 0.68–0.84) but did not improve OS (HR 0.92; 95% CI: 0.80–1.06)). However, when analyzed in pre-specified subgroups, patients with low metastatic disease burden were found to have benefit in terms of OS (HR 0.68; 95% CI: 0.52–0.92), PCSM (HR 0.65; 95% CI: 0.47–0.90) and FFS (HR 0.59; 95% CI: 0.49–0.72) with a 7% improvement in prostate-cancer specific survival at 3-years (86% *vs.* 79%). High metastatic burden was defined, as in previous trials, as four or more bone metastases with at least one outside the axial skeleton and/or visceral metastases, and there was no difference in any of outcomes with RT added in

patients with a high disease burden, suggesting that there is a potential upper limit to those who benefit from local therapy. In a separate STAMPEDE report establishing the benefit of Abiraterone in the ADT sensitive status (9), the subgroup analysis for FFS demonstrates a significant interaction for an increased benefit with planned EBRT (P=0.02) and borderline significant interaction with nonmetastatic patients (P=0.08). That these two subgroups may have more of a benefit from Abiraterone potentially suggest that it contributes to the local effect of EBRT just as conventional ADT was previously demonstrated to improve local control.

As technology has improved, EBRT studies sought to identify more direct evidence of a benefit to local intensification through dose-escalation. Six randomized trials (10-15) of over 4,000 patients assessed conventionally fractionated dose-escalation and uniformly succeeded in demonstrating a dose-response effect for BF, provided evidence that LF portends a worse prognosis, and in some cases confirmed that LF may lead to a late wave of metastatic disease. The relationship between LF and DM has further gained importance as DM has recently been validated as a surrogate for PCSS by the ICECaP working group (16). The relationship between LF and DM has been directly explored in several retrospective series. Investigators from Massachusetts General Hospital noted that the hazard rate for distant failure was initially high for all patients, but in those with LF it increased with time (17). This prompted the hypothesis that early metastases represent micro-metastatic disease at the time of diagnosis that emerge after treatment, whereas subsequent LF results in a "late wave" of metastases. This was further supported by a series at Fox Chase Cancer Center while emphasizing the inverse relationship between EBRT dose and distant failure with higher RT doses appearing to decrease late distant metastases (18). These early reports relied on palpable recurrence to determine LF while investigators from Memorial Sloan Kettering included only biopsy-proven LF. In their series, post-treatment biopsy status was the strongest predictor for DM [HR 2.39; 95% CI: not reported (NR)] and DSS (HR 3.3; 95% CI: NR) (19). They also noted a dose-response effect on LF. More recently, a secondary analysis of the RTOG 9408 trial demonstrated that biopsy-proven LF is a strong predictor of DM (HR 2.4; 95% CI: 1.3–4.4), DSS (HR 3.8; 95% CI: 1.9–7.5) and OS (HR 1.23; 95% CI: 0.95–1.6) (20). In RTOG 9408, the population favored low- and intermediate-risk patients, and an important caveat noted that these findings may not

be generalizable to higher-risk patients such as those with higher Gleason scores.

The work by Kishan *et al.*, then takes this further by pooling outcomes from randomized trials of prostate EBRT and assessed the impact of LF on DM, PCSS, and OS specifically in high-risk patients. Notably it is likely that none of these individual trials had sufficient sample size to demonstrate that LF [based upon digital rectal exam (DRE)] correlated with these clinical endpoints. However, in the pooled analysis the impact of LF became evident (1). When limited to those with pathologically the most aggressive PCs—Grade Group 4 and Grade Group 5 at biopsy—there was a substantial adverse impact of LF on DMFS (HR 1.9; 95% CI: 1.54–2.39), PCSS (HR 3.1; 95% CI: 2.33–4.12) and even OS (HR 1.7; 95% CI: 1.37–2.10). These estimates correlate well with the results previously observed for biopsy proven LF from MSKCC and RTOG 9408.

Does this really mean that RT is needed in these most aggressive patients? The alternative theory argues that LF represents inherently more aggressive biology that portends both increased DM and LF. In a single institutional retrospective series of patients treated with dose-escalated EBRT (21), the presence of any Gleason pattern 5 in those with Gleason 8–10 PC as compared to those without pattern 5, predicted significantly worse outcomes for all endpoints, including time to BF, DMFS (HR 3.4; 95% CI: 1.7–7.1), PCSS (HR 12.9; 95% CI: 5.4–31) and OS (HR 3.6; 95% CI: 2.0–6.5). This finding was also borne out in a population-based SEER analysis (22). Interestingly, in a secondary analysis of two cooperative group trials, RTOG 9202 and RTOG 9902, Gleason pattern 5 disease resulted in increased distant metastases but not LF (23). This recognition of a more aggressive phenotype has made its way into the newer Gleason Grade Groups, as well as the National Comprehensive Cancer Network (NCCN) risk-stratification where the highest Gleason scores represent very-high risk disease. As a result, some have argued that LF is a sign of aggressive disease and not necessarily the cause of metastasis.

The Markov models utilized by Kishan *et al.*, attempt to tease out this interaction and illustrate the relative impact of *de novo* DM and DM following an initial LF. Accounting for the impact of ADT duration, they note that in the first 5 years, as much as 81–96% of failures are directly transitioning from recurrence-free to metastatic, suggestive of a significant proportion of patients with occult metastatic disease at diagnosis which manifest after treatment. In contrast, after 5 years of follow-up, the proportion of

DM that present following an initial LF increases to approximately 50% in those treated without or with a short duration ADT but not in those treated with long-term or lifelong ADT, suggesting that without adequate ADT LF can become a significant contributor to DM (1). These data strongly support that local control dose matter even in those with the highest pathologic risk disease.

One logical way to increase radiation dose to the prostate and improve local control is through the use of brachytherapy (BT). Three randomized trials have explored dose-escalation through the combination of BT and EBRT. The first was a single-center study from Ontario, performed in the era before 3D-based treatment planning with conventional fractionation (24). This is the only study reporting long-term outcomes, with a median follow up of 14 years, and found significant improvement in biochemical progression free survival (bPFS) (HR 0.53; 95% CI: 0.31–0.88) but not DMFS, PCSM, or OM. The next single-institution randomized trial utilized more modern technique but has only reported 7-year results (25). They also found a significant improvement in median bPFS (116 *vs.* 74 months, P=0.04), but no difference in OS. The Canadian multicenter ASCENDE-RT utilized 12 months of ADT for all and randomized between a low-dose rate (LDR) BT or dose-escalated EBRT of 78 Gy (26). Biochemical PFS was significantly inferior in the control arm (HR 2.04; 95% CI: 1.25–3.33) but no significant differences in DMFS, PCSS, or OS were noted. All three trials enrolled intermediate and high-risk patients, and all found significant improvements in biochemical and clinical relapse-free survival with the addition of a BT boost. Nevertheless, none have thus far demonstrated an OS benefit, although only the earliest trial has published long-term results.

Just as the current study by Kishan *et al.* focused upon LF in those with the highest Gleason scores, the addition of BT boost to improve local control has shown promising results in a retrospective multi-institutional study (27). Collecting data from 12 centers and focusing on those with Gleason scores of 9–10 allowed for a comparison of RP, EBRT and EBRT + BT with an enriched event rate. After propensity score adjustment they reported a significant improvement in DMFS with BT boost (HR 0.27; 95% CI: 0.17–0.43 and HR 0.30; 95% CI: 0.19–0.47 for EBRT + BT *vs.* RP and *vs.* EBRT alone, respectively) and PCSM (HR 0.38; 95% CI: 0.19–0.73, and HR 0.36; 95% CI: 0.18–0.70). Tilki *et al.* followed this analysis with one of their own and noted that EBRT + ADT + BT is the most intensive RT that can be offered ("MaxRT"), while RP can be supplemented

with adjuvant RT, ADT, or both ("MaxRP"). In their multi-institutional retrospective analysis both of these "Max Therapies" yielded similar risk for PCSM and all-cause mortality (28) with each showing improvements with intensified local therapy compared to less aggressive RT or surgical approaches. A recent systematic review supports these findings showing EBRT alone to be inferior to RP, with this difference mitigated with the addition of ADT. While MaxRT was superior to RP and MaxRP was comparable to MaxRT (29). These analyses, although constituting weaker evidence than a randomized trial, point to a benefit to further intensification of local therapy.

While Grade Groups 4 and 5 portend a poorer prognosis, there may be additional patients at higher risk for whom local intensification may play a role. Several investigators have attempted to risk stratify patients with the use of genomic classifiers in the adjuvant setting. Den *et al.* reported in a retrospective two-center cohort that a genomic classifier was able to better classify patients according to their risk of DM compared to the best available contemporary nomograms in the post-operative setting. Furthermore, they were able to demonstrate that in patients classified as average or high-risk, an adjuvant approach decreased rates of DM significantly compared to a salvage radiotherapy approach (30).

In conclusion, for PC local control matters and it appears to matter most in those with the highest-risk disease up to and including even those with low-volume metastatic disease. How best to optimize local control remains to be seen. Randomized trials of ADT provide the strongest data with the highest level of evidence while dose escalation with a BT boost or the addition of post-operative RT for early salvage are also important strategies, but with weaker evidence. Importantly, these data further strengthen the argument that we should not give up on those with the highest-risk disease. Despite the substantially higher risk of DM in Grade Group 4–5 disease, this does not mean that local control does not play a role. Randomized trials of newer agents and improved diagnostics for risk stratification, such as more accurate imaging and genomic classifiers, may also help us to identify those patients who benefit from intensified local therapy. Taken together, there is a compelling case that just as active surveillance is most appropriate in those with low-risk PC for whom local therapy is unlikely to change OS, treatment with radiotherapy and potentially even intensified RT for local control in higher risk patients appears to be more relevant than previously appreciated.

## Footnote

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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