Implications of local failure on overall prognosis in aggressive prostate cancer

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High-risk prostate adenocarcinoma (PCa), consisting of patients with either Gleason Score (GS) of 8 to 10, prostate-specific antigen (PSA) more than 20 ng/mL, or clinical tumor-stage T3 or T4, portends a significant risk of relapse and cancer-specific mortality (1). Compared to low-risk PCa, these patients have a more than 3-fold increased risk of PCa-related death. The combination of long-term androgen deprivation therapy (ADT) and radiotherapy remains a standard management option for these patients (2). Despite combined modality treatment, a significant proportion of men with high-risk PCa, especially those with relatively aggressive features, eventually relapse after first line treatment (3). Stratification of GS into grade groups (GG) has improved the discriminatory ability of the existing risk stratification system in determining the overall prognosis for all risk groups including the high-risk category (4). In a study by Pierorazio *et al.*, 10-year biochemical relapse-free survival was approximately 63% and 35% for patients with GG4 and GG5 disease, respectively (4). Another study by Gnanapragasam *et al.* showed approximately 5- and 17-times higher risk of prostate cancer-specific mortality (PCSM) in patients with GG4 and GG5 PCa, respectively (5). The high relapse rates highlight the importance of further optimization of treatment for men with GG4 and GG5 PCa.

We read with great interest the individual patient-based meta-analysis reported by Kishan *et al.* (6) in this context. A

total of 992 patients were included in the study—593 with GG4 and 399 with GG5 PCa. Patients in this meta-analysis were originally enrolled and treated with radiotherapy and ADT in one of the following 6 randomized trials: Radiation Therapy & Oncology Group (RTOG) 8531 (7), RTOG 8610 (8), RTOG 9202 (9), European Organization for Research and Treatment of Cancer (EORTC) 22863 (10), EORTC 22961 (11) and EORTC 22991 (11) (*Table 1*). Considering local failure as a time-varying covariable, the authors demonstrated an approximate doubling of the risk of distant metastasis and PCSM in patients who had local failure. Using a multi-state disease model and Markov proportional hazard model, they found that transition to local failure was associated with approximately 7 times higher risk of subsequent PCSM and approximately 2 times higher risk of subsequent distant metastasis or death. Long-term ADT in conjunction with radiotherapy yielded reduced risk of PCSM or overall mortality in patients who had experienced local failure. These findings are consistent with a secondary analysis of RTOG 9408 where importance of local control was demonstrated based on a planned biopsy after treatment (12). The presence of a viable tumor on biopsy had a significant association with PSA failure [hazard ratio (HR): 1.7; 95% confidence interval (CI): 1.3–2.1], distant metastasis (HR: 2.4; 95% CI: 1.3–4.4), cause-specific survival (HR: 3.8; 95% CI: 1.9–7.5), and in those with GS ≥7 even overall mortality (HR: 1.6; 95% CI: 1.04–2.35), thus lending credibility to the influence of local

Table 1 Individual trials in the meta-analysis

Trial & period	Total patients	Included (%)	Arms	RT dose	ADT period
RTOG 8531 [1987–1992]	977	216 (21.8)	RT	65–70 Gy	Indefinite period
			RT + LL-ADT		
RTOG 8610 [1987–1991]	456	128 (12.8)	RT	65–70 Gy	4 months
			RT + STADT		
RTOG 9202 [1992–1995]	1,554	337 (34)	RT + ST-ADT	65–70 Gy	4 months
			RT + LT-ADT		28 months
EORTC 22863 [1987–1995]	415	43 (4.3)	RT	70 Gy	36 months
			RT +LT-ADT		
EORTC 22961 [1997–2001]	970	186 (18.8)	RT + STADT	70 Gy	6 months
			RT + LTADT		36 months
EORTC 22991 [2001–2008]	819	82 (8.3)	RT	70 (25%)	6 months
			RT + STADT	74 (51%)	
				78 Gy (24%)	

LT-ADT, long-term ADT; ST-ADT, short-term ADT; LL-ADT: lifelong ADT.

control on distant metastasis and PCa-specific survival (12).

The main strengths of this meta-analysis include a large patient population and a unique but robust statistical design. Overall findings allude to an important hypothesis that site of local failure could act as a potential nidus for subsequent distant dissemination in men with GG 4 or 5 PCa. However, the interpretation of the results needs careful attention to some of the underlying limitations of this meta-analysis. These include heterogeneity in the patient population, differences in management protocols, and more importantly variability in the definition of local failure and absence of central pathology review among others. Furthermore, these co-operative group studies were conducted between 1987 to 2008. As a result, majority of the patients were treated with conventional doses (65–70 Gy) of radiotherapy which might be considered suboptimal compared to the modern standard of dose-escalated external beam radiotherapy (EBRT) (12) or combination of EBRT with brachytherapy boost (13). Similarly, radiotherapy delivery techniques for PCa have evolved over the decade. Use of magnetic resonance imaging (MRI) in radiotherapy treatment planning, delivery of intensity modulated radiotherapy (IMRT) or volumetric modulated arc therapy (VMAT), practice of image-guidance and use of hydrogel spacer between rectum and prostate include some of the notable examples of these advancements (14,15). These

technological advancements have resulted in reduced risk of morbidity and have ensured safe dose-escalation. Nonetheless, it remains undefined whether reduction in the risk of treatment-related morbidity potentially improves treatment adherence and thereby oncologic outcome. Extrapolation of the findings of this meta-analysis to the current era should be done with careful consideration to these inconsistencies in radiotherapy dose and treatment techniques.

Some of the additional concerns with this meta-analysis include lack of a priori stratification based on GS in the individual studies, omission of baseline PSA as a covariable from the multivariable regression models or omission of T-stage from the multivariable Markov proportional hazard model for prostate cancer-specific survival (PCSS). Impact of inter-physician and inter-institutional variability in radiotherapy planning and delivery on collective outcomes were not reported and finally, the causes of non-cancer-specific deaths were not mentioned. One should interpret the results in light of the prognostic influence of relative burden of the primary and secondary Gleason patterns on the overall outcome. This has been highlighted in a retrospective study by Huynh *et al.* They found 2.77-fold increase in the risk of PCSM and 1.75-fold increase in the risk of all-cause mortality for men with GS 3+5/5+3 relative to men with GS 4+4 PCa (16). Similarly, Lim

et al. found that presence of pathological Gleason 5+4 adenocarcinoma yielded a significantly inferior biochemical relapse-free survival compared to those with Gleason 4+5 adenocarcinoma in post-operative biopsy (17). Finally, the results of this study should be construed with due consideration to the use of molecular imaging techniques in PCa which have shown improved precision in staging of newly diagnosed prostate cancer or identifying relapse after first line treatment (18).

The findings of this meta-analysis lead to some intriguing questions which merit further validation in future randomized controlled studies. One such question is whether escalation of local treatment can spare men with high risk prostate cancer from long-term ADT for 2–3 years which is the backbone of systemic treatment in high-risk prostate cancer (9,10). In ASCENDE-RT study, 12 months of ADT in conjunction with pelvic and low-dose rate brachytherapy boost to prostate yielded commendable biochemical control at 9 years; however, the study does not provide confirmatory evidence on local failure rates (13). In addition, the current study (6) and a previous study from the same group (19) has showed lack of benefit in terms of local control or mortality with continuation of ADT for indefinite period relative to long-term ADT. However, these findings are only hypothesis-generating and need further validation in a randomized clinical trial adequately powered to estimate outcomes such as PCSS or overall survival (OS) with planned stratification for grade group in addition to other relevant prognostic factors.

Intensification of systemic treatment should be revisited considering the findings of this meta-analysis. Findings of the trials from Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) platform favor intensification of systemic treatment in men with locally advanced or high-risk non-metastatic PCa. In two studies from STAMPEDE platform, where approximately 1/3rd of patients harbored locally advanced or high-risk non-metastatic disease, significant OS benefit was obtained with addition of docetaxel and abiraterone to upfront ADT (20,21). These findings bear important ramifications on the findings of this meta-analysis because patients with GG4 or GG5 PCa could potentially harbor metastases in nodes or distant organs often undetectable by conventional imaging. Further, in RTOG 0521 study (22), where 84% patients had GS of 8 to 10, administration of 6 cycles of adjuvant docetaxel after EBRT with concomitant and adjuvant ADT for 2-year improved 6-year OS by approximately 5% (HR: 0.69; 90% CI: 0.49–

0.97). Although addition of chemotherapy improved distant control by 5% at 6-year, no information was available on the local failure rates in the two arms. Overall, these findings suggest that intensification of systemic treatment has the potential to synergize with the effect of local treatment which could further improve prognosis in men with highly aggressive PCa. These hypotheses should be tested in future randomized controlled trials.

Along with intensification of systemic treatment, its optimal sequencing with local radiotherapy also merits careful attention. This is even more relevant in the era of hypofractionated radiotherapy for localized PCa where higher dose (3–8 Gy) per fraction is delivered to the prostate and often proximal part of the seminal vesicles (23). Results from two phase III randomized studies have demonstrated that there could be a sequence dependent interaction between ADT and radiotherapy target volume (24,25). Further studies are necessary to determine the impact of this interaction on outcome in men with GG4 or GG5 PCa and identify those who could potentially benefit from addition of pelvic nodal radiotherapy along with prostate radiotherapy.

To summarize, local control remains an important endpoint in patients with aggressive PCa. Therefore, combination of optimal local and systemic treatment aimed at enhancing local control and thereby cancer-specific or overall survival should be an integral part of for these patients whenever possible. Use of advanced molecular imaging or genomic classifier could aid in better patient selection and maximizing benefit from treatment escalation. Future clinical trials with planned stratification for grade grouping and other relevant prognostic factors will provide further clarity on the ideal treatment regimen for these patients. Such studies could also help unveil potential mechanistic pathways linking local failure with distant metastasis and cancer-specific survival in this patient population.

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