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Platinum Priority – Editorial

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Salvage Radiotherapy for Nodal Oligorecurrent Prostate Cancer: A Step Towards Predictive Criteria for Metastasis-Directed Therapy in Prostate Cancer?

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It is theorized that "oligometastatic" disease (usually defined as ≤5 lesions) represents a distinct castration-sensitive prostate cancer entity that is amenable to metastasis-directed therapy (MDT), the stated goals of which vary from avoiding the toxicities of androgen deprivation therapy (ADT) to augmenting its benefit [1]. However, the ability to predict benefit from MDT requires a pairing of comparative data based treatment with specific clinical context that synthesizes the key contributors to the natural history of the disease.

The metachronous emergence of oligorecurrent lymph-node relapse after failure of local therapy arguably represents the most promising of clinical contexts, involving staggered development of metastatic potential, a lymphotropic pattern of recurrence associated with more favorable outcomes [2,3], and typically retention of castration sensitivity. Furthermore, early detection of nodal relapse is increasingly linked to the rise of positron emission tomography (PET) agents (choline, fluciclovine, prostate-specific membrane antigen), whose superior sensitivity [4] hypothetically identifies disease still "in transit."

Thus, while ADT remains a standard of care for these patients, salvage lymph node dissection (SLND) or radiotherapy (RT) to delay progression and/or systemic therapy has been championed. Notably, studies on SLND for PET-detected oligorecurrent nodal disease [5] have consistently observed underestimation of the extent of involvement, leading to predictions that superextended SLND or extended nodal RT (ENRT) may be required [6]. Accordingly, many have concluded that comprehensive locoregional therapy should be favored, for instance as mandated for previously untreated pelvic nodes at relapse in the seminal STOMP trial [7]. However, in the absence of proof that such therapy improves clinically relevant outcomes, others reasonably ask if the costs and potential toxicities of comprehensive therapies (ie, ~5 weeks of conventionally fractionated ENRT) are justified when compared to focal MDT, such a five fraction stereotactic body RT (SBRT).

In this issue of *European Urology*, De Bleser and colleagues [8] add to this debate with their 506-patient multi-institution retrospective comparison of SBRT versus ENRT for oligorecurrent nodal disease (≤5 sites; 72% pelvic) predominantly detected via choline PET (85%). Baseline variances related to the retrospective design (ie, SBRT used more often in single-node relapse and without ADT) qualified the observation of unadjusted improved 3-yr metastasis-free survival (MFS) for ENRT versus SBRT (77% vs 68%; $p = 0.01$). Nonetheless, robust adjustment for potentially confounding factors yielded a persistent strong interaction between adjusted MFS and SBRT versus ENRT, and a second round of interaction testing further suggested that patients with single-node involvement benefitted specifically and significantly from ENRT. Patterns of failure analysis indicated that pelvic node(s) as the first relapse was more common after SBRT, whereas physician-reported toxicity was higher after ENRT.

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As comparison, a single other available retrospective study [9] in this space compared 35 patients undergoing RT to a limited involved field (83% SBRT) and 27 undergoing ENRT for pelvic/retroperitoneal oligorecurrence detected via choline PET. In loose agreement, the authors found a nonsignificant trend (hazard ratio 0.38; $p = 0.12$) on multivariate analysis for a lower biochemical failure rate for ENRT, enrichment of metastases after involved-field RT versus ENRT (10 vs 5, $p = 0.27$), and higher toxicity after ENRT.

Taken together with the literature on SLND [5], these studies suggest a benefit for ENRTin reducing short-term further progression, without ability to comment as yet on survival. Further, De Bleser et al are to be commended for compiling a sufficient volume of data to (1) propose a clinically relevant MFS benefit that may be a surrogate for overall survival [10]; (2) match a pattern of relapse to their proposed mechanism for ENRT benefit in sterilizing occult nodes; and (3) identify a potentially predictive clinical context of single-node relapse for MDT choice (ENRT) and benefit.

Nonetheless, as the authors note, the data available are not yet sufficient to define a recipe for MDT in this space. Potential issues for data interepretation remain: non-standardized selection for ENRT versus SBRT; biochemical value–driven imaging follow-up after treatment that probably skewed towards more intensive monitoring for progression among SBRT-treated patients who infrequently received ADT; and lack of direction on how to integrate ADT. In the latter regard, while low metastatic burden may be prognostic, it is not predictive of the absence of benefit from ADT and other systemic agents [11]. Whether PET-detection of nodal disease occult to conventional imaging changes this discussion is unclear and is subject to technical variance. For instance, the time from tracer injection to image acquisition affects the sensitivity of ^{18}F-fluciclovine (Fig. 1), and the choice of anatomic imaging sequence may influence where and how much disease is found. Beyond simply considering the burden of disease according to any imaging assay when assessing the 'actionability' of disease detection, it then would seem prudent to consider other prognosticators of natural history after local therapy failure [12,13], most prominently the time interval to relapse (median of 53 mo in current study, which is reassuringly consistent with slow growth).

Finally, given the increase in physician-reported toxicities with ENRT, patient-reported outcomes are needed to fully capture the quality-of-life tradeoffs for any benefit and the potential impact on tolerability of subsequent life-extending systemic therapies. In particular, as 70% of patients previously received RT (postoperative or definitive), the precise summation of treatment plans required for matching broad ENRT fields to prior RT (Fig. 2) may pose a higher risk or learning curve in comparison to relatively flexible SBRT for near- or in-field re-irradiation in some patients.

Happily, ongoing prospective randomized controlled trials are poised to provide complementary answers to our most critical questions regarding whether (1) adding ENRT to intermittent ADT extends progression-free survival (OLIGOPELVIS-2, NCT 03630666) and (2) ENRT improves 2-yr MFS over SLND or SBRT when added to 6 mo of ADT (STORM, NCT 03569241). Both trials critically include validated quality-of-life secondary endpoints that equally may drive patient decision-making, especially as systemic therapy evolution inevitably affects the interpretability of efficacy endpoints.

In the interim, we again thank the authors for providing much-needed direction on discussing the trade-offs currently apparent between ENRT and more selective SBRT/SLND when offering locoregional treatment of oligorecurrent nodal disease. While ADT omission/duration remains controversial, it is encouraging to see meaningful progress towards establishing benchmarks for MDT options that may change the natural history of the disease or even offer a cure with acceptably low risk and towards predictive criteria for differentiating between types of MDT.

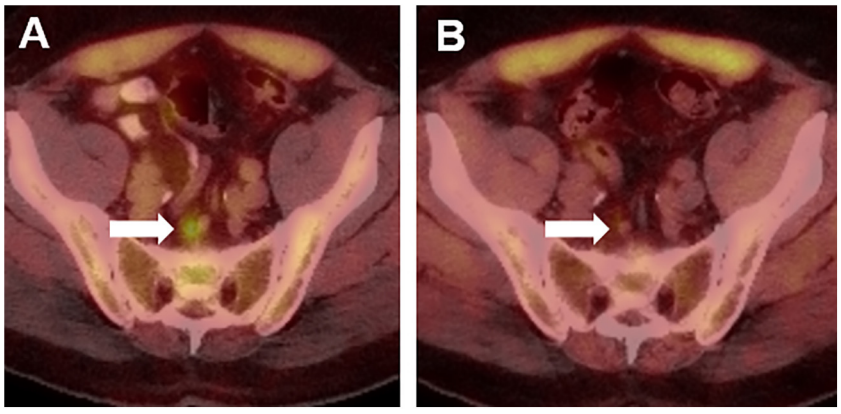

Fig. 1 – Example of the dependence of the tracer-ligand uptake signal on time to acquisition in positron emission tomography (PET) with ^{18}F-fluciclovine in a patient with oligorecurrent relapse (white arrows) in a presacral lymph node following prior radiotherapy for localized prostate cancer. (A) The time from injection to image acquisition for the early pelvic image set was 3 min, resulting in a maximum standard uptake value of 4.3 for the node. (B) Images collected at 15–20 min from injection in a whole-body scan following the pelvic scan, resulting in a qualitatively worse tumor/normal tissue ratio.

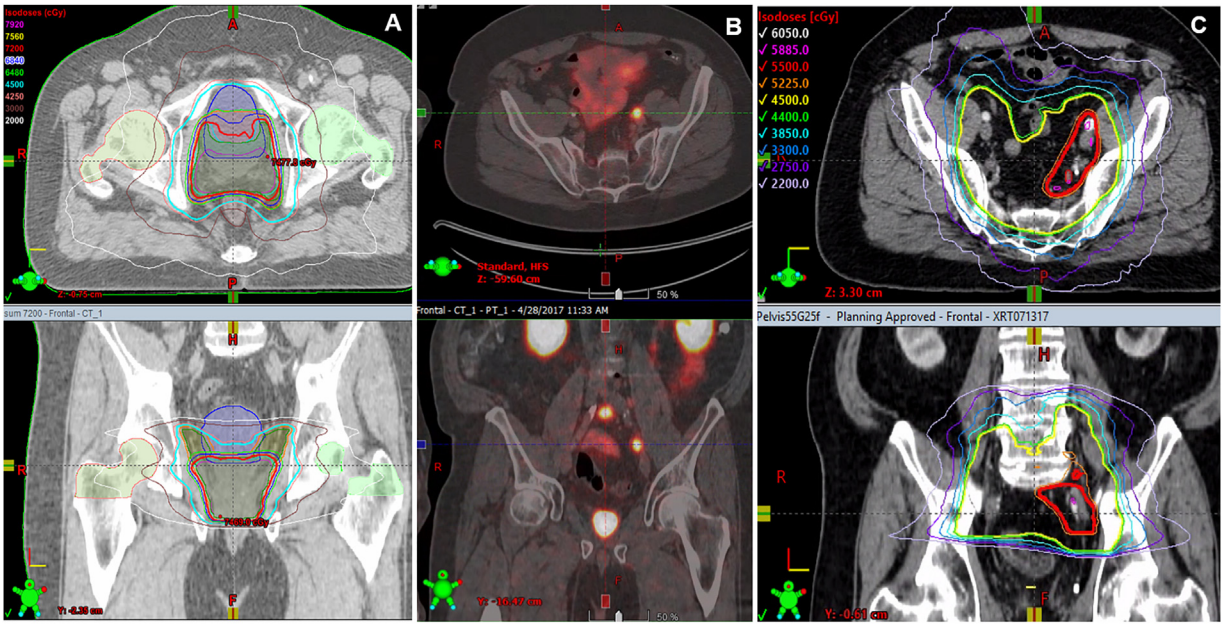

Fig. 2 – Example of patient with (A) prior postoperative salvage radiotherapy to the prostate fossa (7020 cGy in 39 fractions) now experiencing (B) oligorecurrent pelvic nodal relapse detected via ^{18}F-fluciclovine positron emission tomography and (C) undergoing carefully matched extended nodal radiotherapy to the upper pelvic nodes (4500 cGy in 25 fractions) with a simultaneous integrated boost (5500 cGy in 25 fractions) to tracer-avid disease, along with androgen deprivation therapy.

Conflicts of interest: The authors have nothing to disclose.

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