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Editorial Comment

Cancer registries and randomised clinical trials in rare tumours: At the two extremes of daily clinical practice

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In a recent issue of *Lancet Oncology* [1], a group of US investigators reported a thorough retrospective analysis about retroperitoneal sarcoma (RPS) and the use of radiation therapy (RT) in the adjuvant/neo-adjuvant setting making use of the US National Cancer Database (NCDB).

Primary aim of the study was to understand whether the use of adjuvant/neoadjuvant RT had any impact on post-resection RPS overall survival (OS). This question is presently addressed in a European Organisation for Research and Treatment in Cancer (EORTC) – Soft-Tissue and Bone Sarcoma Group (STBSG) randomised study (partially funded through the European project Eurosarc FP7 278472), comparing surgery alone, as the present standard of care, with preoperative external beam RT and surgery, as the experimental arm [2].

The attempted comparison made by the US colleagues between patients receiving surgery alone with those receiving either preoperative RT or post-operative RT in a propensity score-matched fashion was sound. Nevertheless, the inherent weaknesses of the US National Cancer Data Base, shared with all cancer registries, have inevitable implications, hampering the matching and therefore their results.

1 While a large national database generates a large sample size, it includes a great deal of heterogeneity in practice patterns and patient selection. It is widely recognised that due to the complexity and rarity of RPS, its treatment should be restricted to high-volume centres with specialist multidisciplinary teams [3–10]. To try to derive meaningful conclusions about the impact of a single aspect of RPS treatment from data collected from all types of institutions across the United States, with no oversight or standardisation in practice, is potentially overly ambitious and unrealistic. The retrospective, multi-institutional nature of this study with its acknowledged paucity of data about key aspects of sarcoma care such as surgical technique and margin status, is a massive limitation. The authors' attempt to address this by suggesting that restricting the time frame to the modern era is sufficient to ensure standardised care is inadequate, as there remains much heterogeneity in the treatment of sarcoma among high-volume centres, much less among those who see very little of this disease. While it is relatively easy to achieve statistical significance in large

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database studies with high N values, the clinical significance of these findings is much more difficult to discern.

2 One other major problem in running such a comparison is to understand why RT is associated with a better outcome: because it selects better patients or because it truly improves local control. This may be particularly true for post-operative RT, but also for preoperative RT. In other words – given the complexity of this disease and the variability in presentations – the prognostic factors used to match the cohorts, although widely recognised, may not be enough to control for all possible differences among the groups, for instance, tumour location (which may contra-indicate radiotherapy precisely in preoperative situations). Of note, on the one end, the use of preoperative RT was far more frequent in academic centres. The association of the use of preoperative RT and better OS may well simply reflect the better quality of surgery in the academic centres [4,6,7,11]. On the other end, the use of post-operative RT, given its well-known limitations in volume, dosages and related toxicities, may well just select the better patients, which would have fared better anyway, because they had better tumour to operate coinciding with an easier site to irradiate. This is not enough emphasised in their findings, while they tend to over-interpret their results.

3 The lack of information of disease-related events other than death in cancer registries is a major problem in putting in perspective the results of this analysis. Of note, large series of patients surgically treated at single institutions have 5-year OS similar to – if not better than –either RT groups of the present series.

4 Given the heterogeneous findings of the previous studies of perioperative RT in RPS [12–27] and the ongoing equipoise that has led to the EORTC trial, the dramatic differences shown here – not in recurrence-free survival (RFS) where one might expect to see considerable variability, but rather in OS – are difficult to believe. The question arises whether these differences are related to a stochastic effect of well-conducted statistical analyses rather than to a ground-breaking discovery in a field that has been unable to demonstrate a significant difference even in lesser outcomes. The authors' own recent conflicting results somewhat support this. The disparity in the findings of their recent studies [28] cannot be accounted for by the few hypotheses they put forward.

5 We are dealing with a rare subgroup of tumours (RPS), with an expected incidence of <0.5/100,000/year. Moreover, at least five main histological subtypes (well-differentiated, intermediate-grade dedifferenatiated, high-grade dedifferentiated liposarcoma, leiomyosarcoma and solitary fibrous tumours) are represented in RPS. Their different natural histories and patterns of failures have been recently well described [4,5,29]. The interpretation of the results reported by Nussbaum et al. [1] should take this heterogeneity into consideration. As an example, the likelihood that the use of RT does impact the outcome of retroperitoneal leiomyosarcoma or high-grade dedifferentiated liposarcoma is very limited, given the fact that their systemic risk largely outreaches the local one and is not addressed by the use of RT.

The authors should be congratulated for putting this study together, but all the limitations above clearly point to the fact that this analysis cannot impact significantly on our daily practice, as the patients included herein are too much lumped together to be able to derive from this analysis the best approach for the single patient.

While we suggest that such a study should be interpreted with caution, we acknowledge that the task of studying these tumours only by means of prospective randomised trials is also challenging, especially when subgroups need to be considered. We are fully aware of the limitations that the ongoing EORTC-STBSG randomised trial has and that it will represent a critical step forward only if interpreted in light of all other available evidences.

1 As mentioned by Nussbaum et al. [1] in the discussion of their paper[1], the trial plans to enrol 256 subjects to provide 90% power to detect a 20% improvement in 5-year abdominal RFS, the primary end-point. While OS is a secondary end-point, the trial is very likely underpowered to detect a significant difference in OS, as a maximum power of 52% would be observed only after all 256 patients died. A hypothetical as well as unrealistic randomised control trial adequately powered to detect a difference in OS would probably require more than 1000 patients.

2 Indeed, if a difference in abdominal RFS were detected in favour of the use of preoperative RT, we could well speculate that this difference will translate into a survival benefit on the long run, especially for the subgroup of patients at high risk of death for loco-regional recurrences (i.e. well-differentiated and G2 dedifferentiated liposarcoma), but this will be far from being formally sustained by the study.

3 We may discuss how 'standard treatment' can be defined in rare tumors, particularly 'very rare' ones. Clearly, we must take most profit from 'any' evidence we have in our hands, by fairly balancing it by consensus within the medical community [3], even when the results of a randomised study become available.

4 Well-constructed prospective registries are a key to understand in depth the variegated presentation of tumours like these in the real life. Collaboration among large referral institutions is critical to join forces to improve evidence. In this perspective, a large collaborative Trans-Atlantic Retroperitoneal Working Group (TARPSWG) has been established in 2013, with the aim to provide better evidence to complement the one obtained by clinical studies and cancer registries.

In conclusion, we would like to thank Nussbaum and his co-authors for their analysis of the NCDB concerning management of RPS, but we firmly disagree on the conclusive nature of their findings. Evidence forthcoming from retrospective database investigations, no matter how large they are, have never and will never outweigh results from well-designed prospective phase III randomised trials.

It is now critical to conclude this specific ongoing randomised EORTC 62092/STRASS study [2]. All participating sites are invited to do their best to complete the accrual. On the other hand, we invite Nussbaum and all other researchers working in sarcoma referral institutions, who have not yet done so, to join the TARPSWG and participate to build the prospective registry, which will be a key to interpret the present and future evidence in the years to come.

Conflict of interest statement

None declared.

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