Editorial

Active surveillance: minimising treatment while maximising outcomes in testis cancer

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As cure rates improve, the treatment paradigm in testicular cancer has shifted and research is now focused on allowing survivors to live longer and better, whilst minimising treatment and potential harm (1). These approaches rest on the repeated observations confirming the efficacy of treatment and importantly, preserved overall survival or 'cure', even if metastases develop (2-4).

First introduced in the 1980s, active surveillance for clinical stage 1 testicular cancer after orchidectomy has been embraced (5,6), and is now preferred to adjuvant therapy in most consensus guidelines (7-9). Whilst highly efficacious at preventing relapse (10-12), adjuvant treatment with chemotherapy or radiotherapy is associated with potential short- and long-term toxicities that may have persisting impacts on quality of life for long-term survivors and pertinently, is unnecessary for the majority (1). Attempts to stratify tumours using clinicopathologic features reduces the fraction exposed to unnecessary treatment (11), however based on contemporary data, even 'high' risk seminoma which has a relapse rate of 46% (13), will expose more than half the individuals to the perils of adjuvant treatment unnecessarily if uniformly applied.

Using an example of a young, otherwise well individual with a new diagnosis of T1b nonseminoma (i.e., no lymphovascular invasion), adjuvant treatment with a single cycle of bleomycin, etoposide and cisplatin (BEP) will improve the long-term relapse-free survival from 86.5% to 98.6% (11). However, the number needed to treat, to save one person from relapse approximates 8, and the cumulative number of chemotherapy cycles administered if an all-comer strategy is applied in the adjuvant setting, is greater than the number of definitive chemotherapy cycles recommended for those who ultimately relapse (assuming n=100, 100 × 1BEP + 1.4 × 3BEP =104.2 cycles *vs.* 0 × 1BEP + 13.5 × 3BEP =40.5 cycles). Whilst some may look favourably upon these numbers, the overall rate of cure remains unchanged, and the quality of survival of this often young population, should be forefront of our minds, with issues including cardiovascular morbidity, infertility, peripheral neuropathy, ototoxicity affecting survivors for decades after they are cured (1). While an informed discussion regarding the relative advantages and disadvantages of active surveillance and adjuvant therapy is encouraged (14), and selected clinical situations might move the pendulum towards adjuvant treatment (i.e., older age or other comorbidities that would make definitive chemotherapy challenging), limiting unnecessary chemotherapy (or radiotherapy) exposure is key to promoting long-term, quality survival of

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this population.

Active surveillance delicately navigates the risk of over-investigation and over-treatment, with the risks of recurrent testicular cancer, using a protocolised approach encompassing physical examination, regular imaging, and serum tumour biomarkers evaluation (6-9,15,16). These recommendations have been designed to proactively detect recurrences in the unlikely event they occur. However, there is room to improve surveillance protocols and Matulewicz *et al.* (17) prudently highlight three domains, which may herald forthcoming change.

Adherence to active surveillance recommendations is key to their success, however there is overwhelming evidence that adherence is sub-optimal (18). Strategies to optimise adherence, including shared care with primary health providers (which additionally offers enhanced preventative health care contact) (19), and use of Telehealth and/or health-based mobile applications offer opportunities to engage an often young and mobile population in their survivorship follow-up (20). Whilst Telehealth obviates an opportunity for physical examination of the contralateral testis, testicular self-examination can be encouraged as a surrogate between physical visits (21).

Due to the elevated risk of relapse in individuals not pursuing adjuvant treatment, an intensified imaging strategy is required, particularly during the first 24 months of follow-up. Whilst necessary to proactively detect relapse, this may reduce adherence due to impacts on time and/or finances in some jurisdictions, and exacerbate 'scanxiety' whereby fear of cancer recurrence is heightened in the lead-up to planned imaging (22). Additionally, concerns regarding radiation exposure have been raised. Strategies to de-intensify imaging in seminoma, including use of magnetic resonance imaging in preference to computerised tomography, reduction in scan frequency, and omission of pelvic imaging have been proposed and may address some of these challenges, and is reflected by some recommendations (6). Microribonucleic acids (miRNA), pertinently plasma miR-371, may obviate the need for frequent imaging in follow-up with a growing volume of evidence demonstrating superiority to existing clinical instruments and clinical utility in surveillance of both seminoma and nonseminoma with early detection of recurrence and high specificity and positive predictive value (23). Prospective studies are underway and are likely to cement this into active surveillance paradigms in the future (24-26). Unfortunately, miRNA have not yielded the same benefits in detecting teratoma (23), such that serial imaging cannot be replaced entirely, particularly in nonseminoma, which has an inherently higher risk of relapse compared with seminoma.

Despite these issues, active surveillance promotes an early return to 'normal' life, free from long-term toxicities and late effects, and balances the risks of recurrent malignancy in the setting of excellent salvage opportunities and most importantly, preserved survival (1).

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References

1. Feldman DR. State-of-the-Art Management of Germ Cell Tumors. Am Soc Clin Oncol Educ Book 2018;38:319-23.
2. Kollmannsberger C, Tandstad T, Bedard PL, et al. Patterns of relapse in patients with clinical stage I testicular cancer managed with active surveillance. J Clin Oncol 2015;33:51-7.
3. Beyer J, Collette L, Sauvé N, et al. Survival and New Prognosticators in Metastatic Seminoma: Results From the IGCCCG-Update Consortium. J Clin Oncol 2021;39:1553-62.
4. Gillessen S, Sauvé N, Collette L, et al. Predicting Outcomes in Men With Metastatic Nonseminomatous Germ Cell Tumors (NSGCT): Results From the IGCCCG Update Consortium. J Clin Oncol 2021;39:1563-74.
5. Leveridge MJ, Siemens DR, Brennan K, et al. Temporal trends in management and outcomes of testicular cancer: A population-based study. Cancer 2018;124:2724-32.
6. Conduit C, Lewin J, Weickhardt A, et al. Patterns of Relapse in Australian Patients With Clinical Stage 1 Testicular Cancer: Utility of the Australian and New Zealand Urogenital and Prostate Cancer Trials Group Surveillance Recommendations. JCO Oncol Pract 2023. [Epub ahead of print]. doi:10.1200/OP.23.00191.
7. Stephenson A, Eggener SE, Bass EB, et al. Diagnosis and Treatment of Early Stage Testicular Cancer: AUA Guideline. J Urol 2019;202:272-81.
8. National Comprehensive Cancer Network. Testicular Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology 2022 [updated Jan 04, 2022]. Available online: https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
9. Patrikidou A, Cazzaniga W, Berney D, et al. European Association of Urology Guidelines on Testicular Cancer: 2023 Update. Eur Urol 2023;84:289-301.
10. Oliver RT, Mason MD, Mead GM, et al. Radiotherapy versus single-dose carboplatin in adjuvant treatment of stage I seminoma: a randomised trial. Lancet 2005;366:293-300.
11. Tandstad T, Dahl O, Cohn-Cedermark G, et al. Risk-adapted treatment in clinical stage I nonseminomatous germ cell testicular cancer: the SWENOTECA management program. J Clin Oncol 2009;27:2122-8.
12. Cullen M, Huddart R, Joffe J, et al. The 111 Study: A Single-arm, Phase 3 Trial Evaluating One Cycle of Bleomycin, Etoposide, and Cisplatin as Adjuvant Chemotherapy in High-risk, Stage 1 Nonseminomatous or Combined Germ Cell Tumours of the Testis. Eur Urol 2020;77:344-51.
13. Boormans J, Sylvester RJ, Anson-Cartwright L, et al. European Association of Urology (EAU) Testicular Cancer Guidelines Panel: A new prognostic factor risk group classification for patients with clinical stage 1 seminoma in active surveillance. J Clin Oncol 2023;41:abstr 410.
14. Oldenburg J, Aparicio J, Beyer J, et al. Personalizing, not patronizing: the case for patient autonomy by unbiased presentation of management options in stage I testicular cancer. Ann Oncol 2015;26:833-8.
15. Sturgeon JF, Moore MJ, Kakiashvili DM, et al. Non-risk-adapted surveillance in clinical stage I nonseminomatous germ cell tumors: the Princess Margaret Hospital's experience. Eur Urol 2011;59:556-62.
16. Lieng H, Warde P, Bedard P, et al. Recommendations for followup of stage I and II seminoma: The Princess Margaret Cancer Centre approach. Can Urol Assoc J 2018;12:59-66.
17. Matulewicz RS, Fankhauser CD, Sheinfeld J, et al. Novel approaches to redesign surveillance strategies following orchiectomy for localized testicular cancer: a narrative review. Transl Androl Urol 2023;12:1016-22.
18. Moynihan C, Norman AR, Barbachano Y, et al. Prospective study of factors predicting adherence to medical advice in men with testicular cancer. J Clin Oncol 2009;27:2144-50.
19. Boer H, Lubberts S, Bunskoek S, et al. Shared-care survivorship program for testicular cancer patients: safe and feasible. ESMO Open 2022;7:100488.
20. Hamilton RJ, Landoni L, Kuhathaas K, et al. WATChmAN: A randomized trial of virtual surveillance versus standard in-person care for clinical stage I testicular cancer. J Clin Oncol 2020;38:abstr 396.
21. Chong RIH, Leow JJ, Choo ZW, et al. Testicular self-examination for early detection of testicular cancer. World J Urol 2023;41:941-51.
22. Derry-Vick HM, Heathcote LC, Glesby N, et al. Scanxiety among Adults with Cancer: A Scoping Review to Guide Research and Interventions. Cancers (Basel) 2023;15:1381.
23. Nappi L, Saxena N, Pautasso S, et al. Long term follow-up analysis of plasma miR371 expression to detect early relapse in patients with clinical stage I testicular germ cell tumors on surveillance. J Clin Oncol 2023;41:abstr 5006.
24. Conduit C, Grimison PS, Lewin JH, Hansen AR, Lynam JF, Weickhardt AJ, et al. CLIMATE: Assessing the clinical

utility of miR-371a-3p as a marker of residual disease in stage 1 testicular germ cell tumour (TGCT) following orchiectomy: ANZUP 1906. J Clin Oncol 2023;41:abstr TPS5100.
25. Morin Coulombe A, Ozgun G, Johnson R, et al. SWOG S1823/CCTG GCC1: Translational observational investigational study of the liquid biomarker microRNA 371a-3p in newly diagnosed germ cell tumours—Real-world trial design, rapid accrual, and robust secondary use of data opportunities. J Clin Oncol 2023;41:abstr TPS5103.
26. Shaikh F, Bagrodia A, Amatruda JF, et al. AGCT1531: Evaluating the utility of circulating microRNA in the management of children, adolescents, and adults with malignant germ cell tumors. J Clin Oncol 2023;41:abstr TPS5104.

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