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

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DOI https://doi.org/10.1200/OP.23.00191

ABSTRACT

PURPOSE International guidelines advocate for active surveillance as the preferred treatment strategy for patients with stage 1 testicular cancer after orchidectomy although a personalized discussion is required.

MATERIALS AND METHODS We conducted an analysis of individuals registered in iTestis, Australia's testicular cancer registry, to describe the patterns of relapse and outcomes of patients treated in Australia where the Australian and New Zealand Urogenital and Prostate Cancer Trials Group Surveillance Recommendations are widely adopted.

RESULTS A total of 650 individuals diagnosed between 2000 and 2020 were included, 63% (411 of 650) seminoma and 37% (239 of 650) nonseminoma. The median age was 34 years (range 14-74). 26% (106 of 411) with seminoma and 15% (36 of 239) nonseminoma received adjuvant chemotherapy. After a median follow-up of 43 months (range 0-267) postorchidectomy, relapse occurred in 10% (43 of 411) of seminoma and 18% (43 of 239) of nonseminoma. The two-year relapse-free survival was 92% (95% CI, 89 to 95) and 82% (95% CI, 78 to 87) in seminoma and nonseminoma, respectively. All relapses (86 of 86) were detected at a routine surveillance visit; 98% (85 of 86) were asymptomatic and detected solely through imaging (62 of 86, 72%), tumor markers (6 of 86, 7%), or a combination (17 of 86, 20%). The most common relapse site was isolated retroperitoneal lymphadenopathy (53 of 86, 62%). No nonpulmonary visceral metastases occurred. At relapse, 98% (84 of 86) had International Germ Cell Cancer Collaborative Group (IGCCCG) good prognosis; 2 of 86 intermediate prognosis (both nonseminoma). No deaths occurred.

CONCLUSION In our cohort of stage 1 testicular cancer, where national surveillance recommendations have been widely adopted, recurrences were detected at routine surveillance visits and, almost exclusively, asymptomatic with IGCCCG good-prognosis disease. This provides reassurance that active surveillance is safe.

ACCOMPANYING CONTENT

Appendix

Accepted April 28, 2023
Published June 16, 2023

JCO Oncol Pract 00:1-8

View Online Article

INTRODUCTION

Multiple international guidelines advocate for active surveillance as the preferred treatment strategy for patients with clinical stage 1 testicular cancer after orchidectomy although adjuvant chemotherapy remains an option.[1-3] For individuals whose cancer is destined to never relapse, active surveillance avoids the potential morbidity associated with treatment.[4,5] However, for some individuals with high-risk disease, where there are concerns regarding adherence to active surveillance recommendations or other patient factors, adjuvant chemotherapy may be preferred.[3,6] Regardless of whether adjuvant treatment is applied, protocolized follow-up is key to the detection of early recurrences to maintain excellent survival outcomes in this population.[1-3,7-9]

CONTEXT

Key Objective

In a contemporary real-world population, does active surveillance offer individuals with stage 1 testicular cancer a satisfactory relapse-free survival and, in turn, safely spare them from potential chronic and late effects of additional treatment?

Knowledge Generated

In an environment where the Australian and New Zealand Urogenital and Prostate Cancer Trials Group Surveillance Recommendations have been widely adopted, we showed that almost all relapses were asymptomatic and discovered through routine imaging, with most having International Germ Cell Cancer Collaborative Group good-risk disease. Monitoring serum tumor biomarkers for seminoma and extending computerized tomography to the pelvis in both seminoma and nonseminoma/mixed germ cell tumors may be less valuable than other elements of the recommendations.

Relevance

Our data renders further support for active surveillance as the preferred treatment pathway for most individuals after orchidectomy.

After an earlier review of Australian practice, which demonstrated wide variation in the active surveillance strategy,[10] the Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group Germ Cell Tumour Subcommittee, comprising consumers and clinicians, developed local Surveillance Recommendations to guide the frequency and nature of surveillance after orchidectomy in 2017[9,11] (Appendix Figs A1A and A1B, online only). The ANZUP Surveillance Recommendations advocate for semiregular clinical evaluation for at least 60 months after orchidectomy, with intensified follow-up in the first 24 months reflecting the natural history of testicular cancer and elevated risk of relapse during this period. Similar to other available surveillance protocols,[1-3,7,8] recommendations vary by histologic subtype, pathologic factors such as the presence of lymphovascular invasion in nonseminoma/mixed germ cell tumors (NSGCT), and use of adjuvant therapy;[9] however, there are important differences, including inclusion of serum tumor biomarker evaluation routinely for individuals with seminoma.[3,8] Uptake of the ANZUP Surveillance Recommendations has evidently been high, with visits to the website exceeding 17,000 since its publication (ANZUP, personal communication, March 2023).

Testicular cancer remains an uncommon cancer in Australia, with an incidence of approximately 950 cases per year.[11] To facilitate research and better understanding of treatment patterns,[12] iTestis, Australia's national, prospectively maintained testicular cancer registry, was also established in 2017 to collect standard-of-care clinical data and biospecimens. At the time of interrogation for this study, iTestis contained >1,000 patients diagnosed with stage 1 and advanced testicular cancer from 15 Australian sites. We report a real-world cohort of individuals in Australia with stage 1 testicular cancer to describe patterns of relapse.

MATERIALS AND METHODS

We conducted a retrospective analysis of patients diagnosed with stage 1 testicular cancer within iTestis. Clinicopathologic information and demographic information were extracted, including age/year of diagnosis, orchidectomy and any adjuvant treatment details, and relapse events including method of detection, metastatic sites, International Germ Cell Cancer Collaborative Group (IGCCCG) prognostic group, and date of death or last follow-up. Data related to adherence to the ANZUP (or other) Surveillance Recommendations were unavailable.

Individuals were identified sequentially by their treating center, with clinical data extracted from medical records locally and updated in iTestis at participating sites. Ethics approval for use of deidentified individual patient-level data was obtained from the Melbourne Health Human Research Ethics Committee (MH2017.372). iTestis is available to participating centers and provided by the Walter and Eliza Hall Institute of Medical Research, an independent research organization affiliated with the University of Melbourne and Royal Melbourne Hospital (Australia).

Descriptive statistics of discrete data were performed, including median, range, and proportion, where relevant. Odds ratios (ORs) were used to explore associations with categorical data, and the log method was used to calculate 95% CIs in univariable analyses. Where an event rate was zero, a continuity correction was used. Statistical significance was defined as a two-tailed P value of ≤.05. Binary logistic regression was performed in a multivariable analysis of covariates identified in univariable analysis, except for those calculated using continuity corrections because of risk of introducing bias. Time-to-event end points including relapse-free survival (RFS) were estimated using the

Kaplan-Meier method. RFS was defined as the time from orchidectomy to first documented metastatic relapse event (or death). Follow-up was estimated using reverse Kaplan-Meier methodology, with follow-up defined as time from orchidectomy to last recorded follow-up in iTestis or relapse, whichever occurred earlier. All statistical analyses were performed using IBM SPSS Statistics, Armonk, NY (version 28.0.1.0) and Microsoft Excel for Mac, Redmond, WA (version 16.5).

RESULTS

Our study examined 650 individuals with stage 1 testicular cancer registered in iTestis and diagnosed between 2000 and 2022 (Table 1). The median year of diagnosis was 2018; 33% (212 of 650) were diagnosed before the introduction of iTestis and the ANZUP Surveillance Recommendations. Of the individuals, 63% (411 of 650) had pure seminoma and 37% (239 of 650) had NSGCT. The median age at diagnosis was 34 years (range 14-73). Other relevant clinicopathologic and demographic details were as expected and are displayed in Table 1.

Almost all individuals (602 of 650, 93%) continued in follow-up at the time of data extraction, with only 3% (16 of 650) lost to follow-up. Of the remaining individuals, 31 (5%) were discharged and one (0.2%) died, with this death considered unrelated to testicular cancer diagnosis and treatment.

Of 411 individuals with seminoma, 26% (106 of 411) received adjuvant chemotherapy and one (1 of 411, 0.2%) received adjuvant radiotherapy after orchidectomy. Administration of adjuvant chemotherapy in individuals with NSGCT was also uncommon, with only 15% (36 of 239) receiving chemotherapy, most commonly bleomycin, etoposide, and cisplatin for one to two cycles (29 of 36, 81%). Adjuvant chemotherapy was more often applied if seminoma was >4 cm (multivariable OR, 1.6; 95% CI, 1.0 to 2.7) or associated with rete testis invasion (multivariable OR, 2.1; 95% CI, 1.3 to 3.5); however, risk factors classically associated with high-risk NSGCT did not predict the use of adjuvant chemotherapy including lymphovascular invasion (univariable OR, 2; 95% CI, 1.0 to 4.3) or the presence of embryonal carcinoma (univariable OR, 1.7; 95% CI, 0.6 to 5.1; Appendix Table A1, online only).

After a median follow-up from orchidectomy of 43 months (range 0-267; IQR, 15.9-57.8), 13% of individuals relapsed (86 of 650) with metastatic disease, including 43 individuals each with seminoma (43 of 411, 10%) and NSGCT (43 of 239, 18%). Contralateral testicular cancer was diagnosed in 1% (7 of 650). The estimated 2- and 5-year RFS was 92% (95% CI, 89 to 95) and 86% (95% CI, 83 to 90) for individuals with seminoma and 82% (95% CI, 78 to 87) and 80% (95% CI, 75 to 86) in NSGCT, respectively (Table 1 and Appendix Fig A2).

In a univariable analysis, the only clinicopathologic factor associated with metastatic relapse in seminoma was the use of chemotherapy (OR, 0.1; 95% CI, 0.03 to 0.5; Appendix Table A1). By contrast, the presence of embryonal carcinoma (OR, 3.2; 95% CI, 1.2 to 8.5), rete testis invasion (OR, 3.3; 95% CI, 1.6 to 6.7), tunica albuginea invasion (OR, 2.5; 95% CI, 1.0 to 6.2), and use of adjuvant chemotherapy (OR, 0.1; 95% CI, 0 to 0.84) were associated with relapse in NSGCT in a univariable analysis.

Late metastatic relapse (>36 months) was rare (5 of 86, 6%; Table 1), with individuals with NSGCT relapsing predominantly within 12 months (range 0.7-67, IQR, 2.9-7.7) and seminoma within 24 months (range 3-54, IQR, 6.6-24.7) of orchidectomy. After a median follow-up from relapse of 26 months (range 0-255), no deaths have been documented.

Method of Detection and Pattern of Relapse

Of the seven individuals who developed contralateral testicular cancer, 43% (3 of 7) were detected through routine testicular ultrasound (2 of 7, 29%) or other undefined imaging (1 of 7, 14%). The remainder were self-detected or discovered during routine clinical examination (4 of 7, 57%), which, in one individual, was accompanied by elevated tumor markers (1 of 7, 14%).

Conversely, all 86 metastatic relapses were detected at a routine surveillance visit, with 98% (85 of 86) asymptomatic and detected through imaging alone (62 of 86, 72%), tumor markers (7%, 6 of 86), or a combination (20%, 17 of 86; Table 2). Only one individual was symptomatic at relapse, with back pain, scrotal swelling, and weight loss at the 36-month surveillance visit for seminoma. Routine imaging confirmed retroperitoneal lymph node (RPLN) recurrence, and serum tumor biomarkers, beta-human chorionic gonadotropin (bHCG), and lactate dehydrogenase (LDH) were elevated.

At the time of metastatic relapse, the RPLN was the most common site of disease in individuals with seminoma, seen in 74% (32 of 43) as an isolated site of recurrence and in 5% (2 of 43) in association with pelvic (1 of 43, 2%) or supraclavicular (1 of 43, 2%) nodal metastases (Fig 1). Similarly, individuals with NSGCT frequently had RPLN metastases, which were a solitary site of disease in 49% (21 of 43) or in association with pulmonary and/or mediastinal lymph nodes (5 of 43, 12%) or supraclavicular metastases (2 of 43, 5%). Pulmonary-only relapses were uncommon and seen in 13% (11 of 86) overall and mostly in NSGCT, where they were observed in 21% (9 of 43). Pelvic-only relapses were rare (6%, 5 of 86). No risk factors for pelvic recurrence such as previous pelvic surgery nor cryptorchidism/orchidopexy were identified.

Serum Tumor Biomarkers and IGCCCG Prognostic Group at Relapse

Serum tumor biomarkers led to a diagnosis of relapse in a minority of the cohort overall (24 of 86, 28%) and were

TABLE 1. Clinicopathologic Features of the Whole Cohort

Baseline Characteristic			Seminoma (n = 411)	Nonseminoma/Mixed Germ Cell Tumors (n = 239)	Total (N = 650)
Median age, years (range)			36 (14-74)	29 (17-73)	34 (14-74)
Histopathologic details	pT stage, No. (%)	1	315 (77)	137 (57)	452 (70)
		2	69 (17)	85 (36)	154 (24)
		3	5 (1)	3 (1)	8 (1)
		4	3 (<1)	0 (0)	3 (<1)
		Unknown	19 (5)	14 (6)	33 (5)
	Tumor size	Median, mm (range)	32 (2-136)	34 (7-85)	32 (2-136)
		Tumor >4 cm, No. (%)	136 (33)	74 (31)	210 (32)
		Unknown, No. (%)	34 (8)	29 (12)	63 (10)
	Lymphovascular invasion present, No. (%)		49 (12)	85 (36)	134 (21)
	Rete testis invasion present, No. (%)		105 (26)	51 (21)	156 (24)
	Embryonal carcinoma present, No. (%)		NA	176 (74)	NA
Adjuvant treatment, No. (%)	Chemotherapy regimen and number of cycles, where available	All	106 (26)	36 (15)	142 (22)
		Carboplatin ×1	104 (25)	1 (<1)	105 (16)
		Carboplatin ×2	1 (<1)	0 (0)	1 (<1)
		BEP ×1	0 (0)	21 (8)	21 (3)
		BEP ×2	0 (0)	8 (3)	8 (1)
		EP ×2	0 (0)	5 (2)	5 (<1)
		Others	1 (<1)	1 (<1)	2 (<1)
	Radiotherapy		1 (<1)	0 (0)	1 (<1)
	Active surveillance only		304 (74)	203 (85)	507 (78)
Relapse with contralateral testicular cancer, n (%)			5 (1)	2 (1)	7 (1)
Metastatic relapse	All, No. (%)		43 (10)	43 (18)	86 (13)
	Median time to relapse, months (range)		15.6 (3-54)	5.2 (0.7-67)	6.9 (0.7-67)
	2-Year relapse-free survival, % (95% CI)		92 (89 to 95)	82 (78 to 87)	NA
	5-Year relapse-free survival, % (95% CI)		87 (83 to 90)	80 (75 to 86)	NA
	Months postorchidectomy to relapse, No. (%)	<12	19 (44)	35 (81)	54 (63)
		12-24	9 (21)	5 (12)	14 (16)
		24-36	13 (30)	0 (0)	13 (15)
		>36	2 (5)	3 (7)	5 (6)

Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; NA, not applicable; pT, pathologic tumor stage.

usually in association with abnormal radiology (Table 2). In individuals with seminoma, 21% (9 of 43) had elevated serum tumor biomarkers at relapse (Appendix Table A2); however, elevated tumor markers *alone* did not prompt diagnosis of relapse in any case. The most common patterns were elevation in LDH alone (5 of 9, 56%) or elevation in both LDH and bHCG (2 of 9, 22%), and while one individual had an LDH approximating three times the upper limit of normal (ULN), minor elevations were mostly recorded. By contrast, 65% (28 of 43) of individuals with NSGCT had elevated tumor biomarkers at the time of relapse, with alteration in alpha-fetoprotein (AFP) and bHCG (13 of 43, 46%), bHCG alone (5 of 43, 18%), AFP alone (3 of 43, 11%), or both bHCG and LDH (3 of 43, 11%) being the most common patterns. Notably, of those with NSGCT and available biomarkers at relapse, 39% (11 of 28) were elevated, despite normal markers at their original diagnosis.

Almost all individuals had IGCCCG good-prognosis disease at relapse (Table 2). Serum tumor biomarkers rarely met thresholds to increase the IGCCCG prognostic group; only one individual in whom biomarkers were available (1 of 39, 3%) had an LDH > 2.5 times the ULN, corresponding to a marginally poorer prognostic group on the basis of contemporary IGCCCG prognostic grouping.[13] Similarly, only two individuals (2 of 38, 5%) with NSGCT had significant LDH elevation, resulting in IGCCCG intermediate-risk classification. Increases in AFP or bHCG never met thresholds to elevate the IGCCCG prognostic group. No non-pulmonary visceral metastases were observed.

DISCUSSION

Although a personalized approach is required,[14] most individuals with stage 1 testicular cancer can be spared adjuvant

TABLE 2. Clinical Data at Metastatic Relapse

Relapse Characteristic		Seminoma (n = 43)	Nonseminoma/Mixed Germ Cell Tumors (n = 43)	Total (n = 83)
Initial method of relapse detection, No. (%)	Radiology alone	39 (91)	23 (53)	62 (72)
	Serum tumor biomarkers alone	0 (0)	6 (14)	6 (7)
	Clinical symptoms alone	0 (0)	0 (0)	0 (0)
	Radiology and serum tumor biomarkers	3 (7)	14 (33)	17 (20)
	Radiology, serum tumor biomarkers, and clinical symptoms	1 (2)	0 (0)	1 (1)
IGCCCG prognostic group at relapse	Good	38 (89)	36 (91)	74 (86)
	Good with LDH > 2.5 × ULN	1 (2)	NA	NA
	Intermediate	0 (0)	2 (5)	2 (2)
	Poor	NA	0 (0)	NA
	Unknown[a]	4 (9)	5 (12)	9 (10)

Abbreviations: IGCCCG, International Germ Cell Cancer Collaborative Group; LDH, lactate dehydrogenase; NA, not applicable; ULN, upper limit of normal.

[a]Serum tumor biomarkers not available; otherwise, they met criteria for the IGCCCG good-prognosis group.

treatment because of effective salvage options in the event of relapse.[15,16] We report on a real-world cohort of 650 individuals diagnosed with stage 1 testicular cancer across the past two decades in Australia and receiving ongoing follow-up at the time of the launch of iTestis in 2017. Notably, almost all relapses in our cohort were asymptomatic and discovered through routine imaging, with most having IGCCCG good-risk disease and no deaths observed after a median follow-up of 26 months after relapse, rendering ongoing support for active surveillance after orchidectomy.

The shift away from routinely recommending adjuvant treatment is recognized by international clinical management guidelines, with active surveillance being the preferred strategy for most individuals.[1–3] Accompanying this trend, the local ANZUP Surveillance Recommendations have provided a pathway to guide monitoring of individuals entering active surveillance in Australia and New Zealand, balancing risk of relapse with risk of overinvestigation since their introduction in 2017, while offering deintensified follow-up recommendations also for those who do pursue adjuvant treatment.[9] Although the primary focus of this review was not to evaluate the adherence of the ANZUP Surveillance Recommendations, there has been broad consensus nationally with their adoption.

In line with other contemporary literature studies,[17] a minority of our population who received adjuvant therapy and landmark RFS rates at 2 and 5 years postorchidectomy remained satisfactory, with few late relapses. Similar to previous reports,[6,18] adjuvant chemotherapy offered a clinically meaningful reduction in risk of relapse in our cohort and a personalized approach considering clinicopathologic

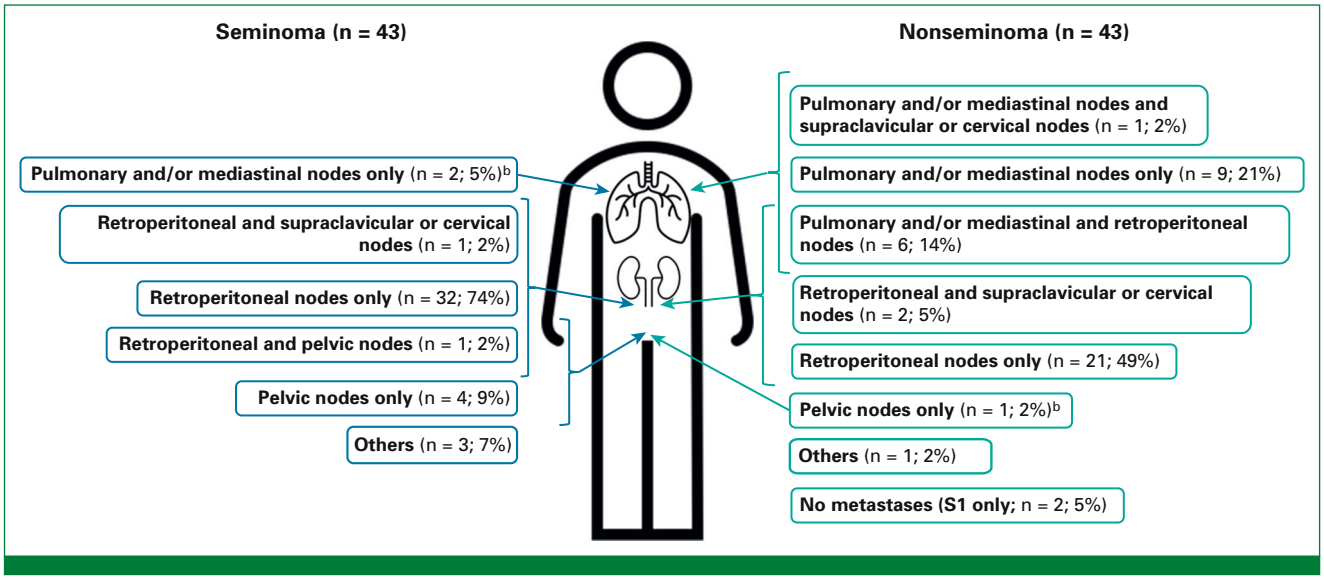

FIG 1. Sites of disease at metastatic relapse. [a]Neither had serum tumor biomarker elevation and [b]associated with clinically significant elevation in alpha-fetoprotein and beta-human chorionic gonadotropin at the time of relapse.

and patient factors and risk of late toxicities[4] in the setting of effective salvage therapies should be encouraged.

The most common site of relapse in our cohort was the RPLNs, which was seen in almost three quarters of the population. Relapse above the diaphragm was uncommon, particularly in seminoma. Although most surveillance recommendations do not recommend routine pulmonary imaging in surveillance of stage 1 seminoma and the ANZUP Surveillance Recommendations align with this, 5% of relapsed seminoma in our cohort would be missed if strict adherence to the recommendations was applied, highlighting the need for clinical discretion. In NSGCT, however, relapse above the diaphragm represented a significant proportion of relapses and pulmonary imaging, as endorsed by ANZUP and other organizations,[1-3,7-9] remains important to permit proactive detection of relapse.

As we place increasing focus on the quality of survivorship after a testicular cancer diagnosis, late effects become relevant. Although radiation associated with a single computerized tomography (CT) scan is significantly less than therapeutic radiation doses, the risks associated with cumulative exposure are increasingly recognized[19] and ultra-low–dose strategies are used at some centers to mitigate hazards.[20] The additive value of pelvic imaging has recently been examined by other contemporary data sets.[21] In a multi-center study of 270 individuals in follow-up of stage 1 testicular cancer (55% with seminoma), pelvic-only relapses were detected in 6% and, commonly, malignant pelvic adenopathy was captured on existing abdominal imaging,[21] raising a question about the value of routine CT of abdomen *and* pelvis. Our cohort mirrored these results, with five individuals (<1% of all individuals in follow-up) experiencing pelvic-only relapses, more commonly in seminoma. Unfortunately, we were unable to centrally review images to determine potential overlap with abdominal slices; however, given the uniform pattern of testicular cancer metastasis, it is possible that omission of CT of pelvis from routine follow-up may not affect clinical outcomes significantly. Furthermore, a phase III noninferiority trial, TRISST, evaluated a deintensified imaging schedule encompassing either CT or MRI and reduced frequency of scans during follow-up of seminoma.[22] Although a reduction in imaging frequency delayed diagnosis of relapse in some cases, this did not appear to affect clinical outcomes and MRI was considered both safe and cost-effective.[23]

Routine monitoring of serum tumor biomarkers during active surveillance of seminoma is inconsistent across guidelines. Although ANZUP and the European Society of Medical Oncology recommend evaluation,[1,9] US and Canadian guidelines specifically advise against monitoring of serum tumor biomarkers because of limited utility in the follow-up of individuals with stage 1 seminoma.[2,8,24] Although 21% of our cohort of individuals with relapsed seminoma had elevated tumor biomarkers at the time of relapse, biomarkers precipitated a diagnosis of relapse in only 9% and was *always* accompanied by routinely requested abnormal radiology, suggesting that biomarker evaluation added limited clinical value for this group. Furthermore, the most common pattern of elevation in seminoma was LDH, which was only mildly elevated in most instances and considered relatively nonspecific[25] and might have precipitated further unnecessary investigation or repeated evaluation. By contrast, the role of serum tumor biomarker monitoring in follow-up of NSGCT is consistent across guidelines.[1,2,7-9,24] This was supported by our observation that almost half of the individuals with NSGCT (20 of 43) had elevated biomarkers at relapse, singularly precipitating a diagnosis of relapse in 14% (6 of 43) and reclassifying the IGCCCG prognostic group in 5% (2 of 43). Notably, many individuals with NSGCT had elevated biomarkers at relapse despite being normal at the time of orchidectomy, suggesting that routine monitoring in follow-up of NSGCT remains important, even in these individuals where it may be tempting to deintensify monitoring.

As a result of this real-world analysis of Australian patients and other emerging evidence,[21-23] the ANZUP Germ Cell Tumour Subcommittee has instituted several changes to their Stage 1 Testicular Cancer Surveillance Recommendations. First, omission of CT of pelvis from routine surveillance was also considered reasonable at clinician discretion. Second, a consensus was reached to consider removal of routine 12- and 24-month imaging after orchidectomy in seminoma, mirroring the TRISST trial, while strongly recommending CT (or MRI) imaging at 6, 18, 36, and 60 months. While the deintensified scheduled evaluation in TRISST did not include the 60-month time point, the subcommittee recommended continuation given the high likelihood of discharge from follow-up at this juncture. Finally, the subcommittee recommended considering reducing serum tumor biomarker evaluation to align scheduled venepuncture for hormonal evaluation at 6, 24, and 60 months postorchidectomy in individuals with seminoma.

STRENGTHS AND LIMITATIONS

Our study has several strengths. First, to our knowledge, it represents the largest Australian data set of individuals in follow-up of testicular cancer, enrolling at geographically spread centers across the country using iTestis. In turn, we provide a comprehensive snapshot into clinical care in some Australian centers. However, as iTestis covers only a portion of Australian centers, it is possible that the clinical care observed is not representative of routine practice in Australia. Furthermore, although consecutive patients have been prospectively enrolled since iTestis's launch in 2017 and the median year of diagnosis was 2018, inclusion of individuals diagnosed before this time (and particularly those receiving follow-up beyond 5 years) might have added bias. Reassuringly, however, relapse rates for patients diagnosed before 2017 and those in extended follow-up did not differ from those diagnosed more recently, suggesting that a selection bias for high-risk testicular cancer might have been avoided. Furthermore, although the median follow-up in our cohort was 43 months, inclusion of patients with a follow-up

of <24 months might have underestimated relapse rate; however, RFS estimates using Kaplan-Meier methodology were in line with other literature.

Unfortunately, we were unable to determine adherence to the ANZUP and other Surveillance Recommendations before relapse; however, this would be important to understand in the future. There was also no centralized review of pathology and other clinical parameters.

In conclusion, testicular cancer is eminently curable, with our cohort of patients receiving treatment in Australia experiencing similar RFS compared with historical cohorts and no deaths attributable to testicular cancer or treatment. As all observed recurrences were detected at a routine surveillance visit and, almost exclusively, asymptomatic and IGCCCG good prognosis at the time of relapse, our data render further support for active surveillance as the preferred treatment pathway for most individuals. Monitoring serum tumor biomarkers for seminoma and extending CT to the pelvis in both seminoma and NSGCT may be less valuable than other elements of the Recommendations, which is reflected by forthcoming changes to the Australian Surveillance Recommendations.

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B.T. and A.K. contributed equally to this work.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/OP.23.00191.

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Financial support: Ben Tran
Administrative support: Ben Tran, Francis Parnis, Ian D. Davis, Margaret McJannett
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Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We would like to acknowledge the contributions of the following individuals who assisted us in developing and maintaining the iTestis testicular cancer registry: Kristina Zlatic, Sophie O'Haire, Javier Haurat, Maureen Turner, Arsha Anton, Mingxia Wang, Joshua Li, Andrew Jensen, Claudia Corrente, Olivia Baenziger, Gillian Yeo, Jenny Liu, Matthew Taylor, Connor Allen, Anisija Gillian, Elizabeth Liow, Michael Harold, and Maria Edmonds alongside other team members at the Walter and Eliza Hall Institute of Medical Research, Biogrid Australia and ANZUP.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Patterns of Relapse in Australian Patients With Clinical Stage 1 Testicular Cancer: Utility of the Australian and New Zealand Urogenital and Prostate Surveillance Recommendations

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No other potential conflicts of interest were reported.

APPENDIX

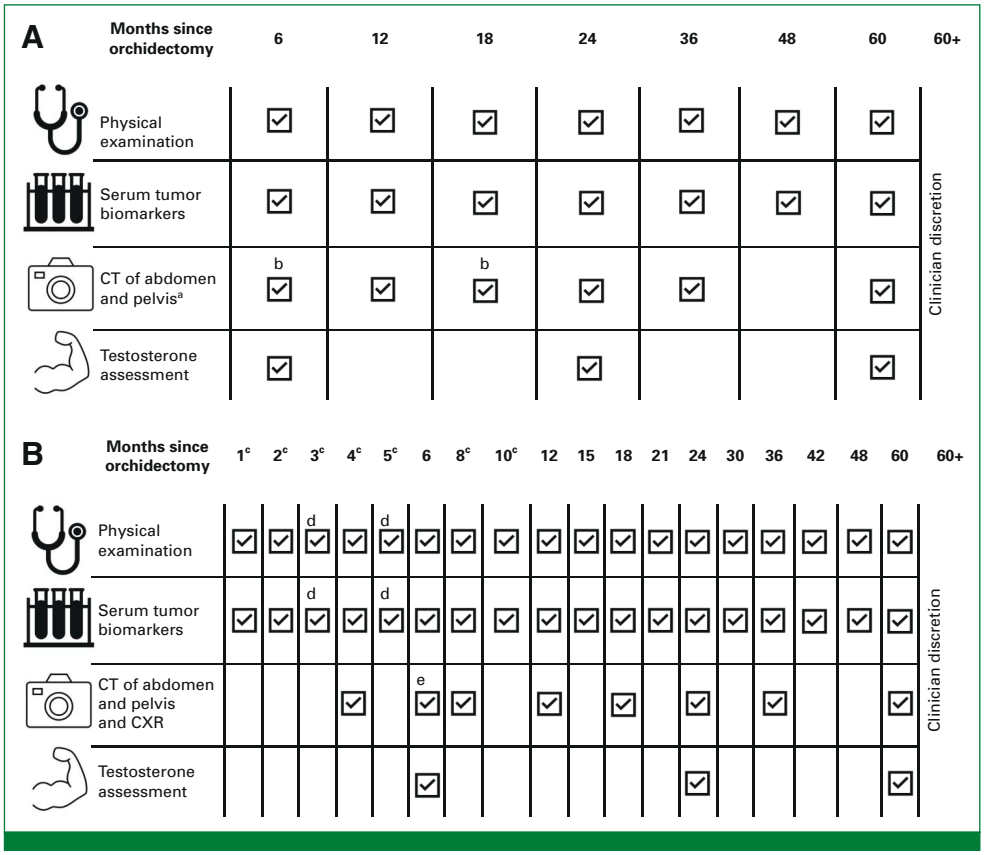

FIG A1. The ANZUP Cancer Trials Group surveillance recommendations for clinical stage 1 testicular cancer after orchidectomy with or without adjuvant chemotherapy for (A) seminoma and (B) non-seminoma. [a]An abdominal MRI is an acceptable alternative if interpreted by a radiologist experienced in MRI surveillance for testis cancer. [b]Only required if adjuvant treatment is not given. [c]Assessments at months 1-5 postorchidectomy and at month 8/10 only required in patients not receiving adjuvant chemotherapy. [d]Only recommended if lymphovascular invasion is present in the orchidectomy specimen. [e]Only required at 6 months postorchidectomy in individuals who receive adjuvant chemotherapy; alternatively, individuals not receiving adjuvant chemotherapy should be evaluated at 4 and 8 months. Routine radiologic assessment after 12 months does not differ between these groups. ANZUP, Australian and New Zealand Urogenital and Prostate; CT, computerized tomography; CXR, chest x-ray. Adapted from ANZUP Surveillance Recommendations.[9]

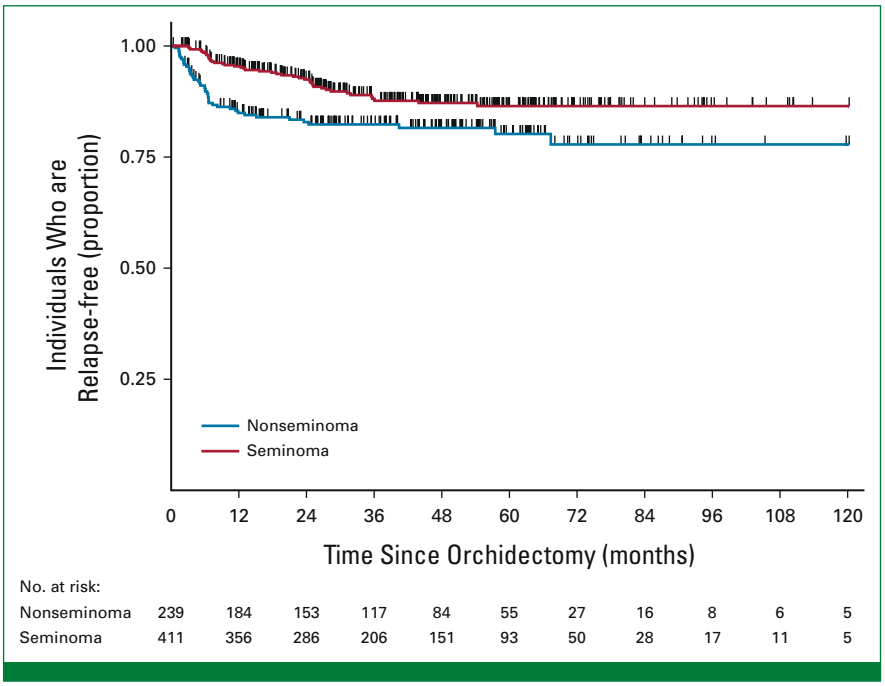

FIG A2. Metastatic relapse-free survival by histologic subtype using the Kaplan-Meier method.

TABLE A1. Statistical Analysis of Clinical Factors Predicting the Use of Adjuvant Chemotherapy and Relapse

	Seminoma (n = 411)						Nonseminoma (n = 239)					
Clinical Factors Predicting the Use of Adjuvant Chemotherapy												
Clinical Factor	Adjuvant Chemotherapy (n = 106)	No Adjuvant Treatment (n = 304[a])	Univariable OR (95% CI)	Univariable *P*	Multivariable OR (95% CI)	Multivariable *P*	Adjuvant Chemotherapy (n = 36)	No Adjuvant Treatment (n = 203)	Univariable OR (95% CI)	Univariable *P*	Multivariable OR (95% CI)	Multivariable *P*
Tumor >4 cm, No. (%)	43 (41)	93 (31)	**1.9 (1.2 to 2.5)**	**.01**	1.6 (1.0 to 2.7)	**.05**	10 (9)	64 (21)	1.1 (0.4 to 1.8)	.84	NA	NA
Presence of rete testis invasion, No. (%)	39 (37)	66 (22)	**2.2 (1.4 to 3.6)**	**.001**	2.1 (1.3 to 3.5)	**.004**	7 (19)	44 (22)	1 (0.4 to 2.5)	.99	NA	NA
Presence of embryonal carcinoma, No. (%)	NA	NA	NA	NA	NA	NA	27 (75)	149 (73)	1.7 (0.6 to 5.1)	.34	NA	NA
Presence of lymphovascular invasion, No. (%)	12 (11)	37 (12)	1 (0.5 to 1.9)	.92	NA	NA	17 (47)	68 (33)	2 (1.0 to 4.3)	.07	NA	NA
Serum tumor markers elevated at diagnosis, No. (%)	21 (20)	78 (26)	0.7 (0.4 to 1.2)	.16	NA	NA	15 (42)	113 (56)	0.5 (0.2 to 1.1)	.09	NA	NA
Clinicopathologic Features by Relapse Status												
	No Relapse (n = 368)	Relapse (n = 43)	Univariable OR (95% CI)	Univariable *P*	Multivariable OR (95% CI)	Multivariable *P*	No Relapse (n = 196)	Relapse (n = 43)	Univariable OR (95% CI)	Univariable *P*	Multivariable OR (95% CI)	Multivariable *P*
Age, years, median (range)	36 (20-74)	34 (14-54)	NA	NA	NA	NA	29 (17-71)	29 (19-73)	NA	NA	NA	NA
Histopathologic details												
pT stage, No. (%)												
1	282 (77)	33 (77)	NA	NA	NA	NA	115 (59)	22 (51)	NA	NA	NA	NA
2	62 (17)	7 (16)	NA	NA	NA	NA	66 (34)	19 (44)	NA	NA	NA	NA
3	4 (1)	1 (2)	NA	NA	NA	NA	1 (1)	2 (5)	NA	NA	NA	NA
4	3 (1)	0 (0)	NA	NA	NA	NA	0 (0)	0 (0)	NA	NA	NA	NA
Unknown	17 (5)	2 (5)	NA	NA	NA	NA	14 (7)	0 (0)	NA	NA	NA	NA
Tumor >4 cm, No. (%)	119 (32)	17 (40)	1.3 (0.7 to 2.5)	.46	NA	NA	59 (30)	15 (35)	1.1 (0.6 to 2.3)	.75	NA	NA
Tumor type present, n (%)												
Embryonal carcinoma	NA	NA	NA	NA	NA	NA	138 (70)	38 (89)	**3.2 (1.2 to 8.5)**	**.02**	**4.7 (0 to 21.3)**	**.04**
Teratoma (mature/immature)	NA	NA	NA	NA	NA	NA	97 (50)	17 (40)	0.7 (0.3 to 1.3)	.24	NA	NA
Yolk sac tumor	NA	NA	NA	NA	NA	NA	101 (51)	18 (42)	0.6 (0.3 to 1.1)	.12	NA	NA
Choriocarcinoma	NA	NA	NA	NA	NA	NA	19 (10)	2 (5)	0.4 (0.1 to 1.9)	.26	NA	NA
Seminoma	368 (100)	43 (100)	NA	NA	NA	NA	71 (36)	17 (40)	1 (0.5 to 2)	.93	NA	NA
Lymphovascular invasion, No. (%)	44 (12)	5 (12)	0.99 (0.4 to 2.7)	.98	NA	NA	65 (33)	20 (47)	1.7 (0.9 to 3.4)	.13	NA	NA
Rete testis invasion, No. (%)	92 (25)	13 (30)	1.4 (0.7 to 2.8)	.38	NA	NA	33 (17)	18 (42)	**3.3 (1.6 to 6.7)**	**.001**	**2.9 (1.4 to 6.2)**	**.01**
Intratubular germ cell neoplasia, No. (%)	168 (46)	22 (51)	1.4 (0.7 to 2.7)	.38	NA	NA	96 (49)	25 (56)	1.4 (0.7 to 3)	.33	NA	NA
Spermatic cord invasion, No. (%)	5 (1)	1 (2)	1.7 (0.2 to 15.3)	.63	NA	NA	2 (1)	2 (5)	4.4 (0.6 to 32.2)	.14	NA	NA
Tunica albuginea invasion, No. (%)	43 (12)	5 (12)	1.0 (0.4 to 2.7)	1	NA	NA	18 (9)	9 (21)	**2.5 (1.0 to 6.2)**	**.04**	2.2 (0.8 to 5.8)	.12
Tunica vaginalis invasion, No. (%)	9 (2)	0 (0)	0.4 (0.02 to 7.5)[a]	.58	NA	NA	0 (0)	1 (2)	13.4 (0.5 to 335.2)[a]	.11	NA	NA

(continued on following page)

TABLE A1. Statistical Analysis of Clinical Factors Predicting the Use of Adjuvant Chemotherapy and Relapse (continued)

Clinicopathologic Features by Relapse Status												
	No Relapse (n = 368)	Relapse (n = 43)	Univariable OR (95% CI)	Univariable *P*	Multivariable OR (95% CI)	Multivariable *P*	No Relapse (n = 196)	Relapse (n = 43)	Univariable OR (95% CI)	Univariable *P*	Multivariable OR (95% CI)	Multivariable *P*
Serum tumor markers at diagnosis, No. (%)												
Elevated	86 (23)	13 (30)	0.3 (0.7 to 3.1)	.26	NA	NA	106 (54)	22 (51)	1 (0.5 to 2.2)	.93	NA	NA
Normal	232 (61)	23 (53)			NA	NA	65 (33)	13 (30)			NA	NA
Adjuvant treatment, No. (%)												
Chemotherapy												
All	104 (27)	2 (5)	**0.1 (0.03 to 0.5)**	**.004**	NA	NA	36 (15)	0 (0)	**0.1 (0 to 0.84)**[b]	**.04**	NA	NA
Carboplatin	103 (28)	2 (5)			NA	NA	1 (3)	NA			NA	NA
BEP	0 (0)	0 (0)			NA	NA	29 (15)	NA			NA	NA
EP	0 (0)	0 (0)			NA	NA	5 (3)	NA			NA	NA
Other	1 (<1)	0 (0)			NA	NA	1 (<1)	NA			NA	NA
Radiotherapy	1 (<1)	0 (0)			NA	NA	0 (0)	0 (0)			NA	NA
Active surveillance only	263 (69)	41 (95)			NA	NA	160 (82)	43 (100)			NA	NA

NOTE. Bold indicates $P < 0.05$.

Abbreviations: BEP, bleomycin/etoposide/cisplatin; EP, etoposide/cisplatin; OR, odds ratio; pT, pathologic tumor stage.

[a]Excluding the individual who received adjuvant radiotherapy.

[b]Calculated using continuity correction; multivariable analysis was not performed, even where covariate was statistically significant in univariable analysis.

TABLE A2. Serum Tumor Biomarker Elevation at Relapse

Serum Tumor Biomarker			Seminoma (n = 43)	Nonseminoma (n = 43)
Serum tumor biomarkers at relapse, No. (%)	Elevated	All	9 (21)	28 (65)
		Elevated at original diagnosis	3 (7)[a]	14 (32)
		Normal at original diagnosis	5 (12)	11 (26)
		Markers unknown at original diagnosis	1 (2)	3 (7)
	Normal	All	30 (70)	12 (28)
		Elevated at original diagnosis	10 (23)	6 (14)
		Normal at original diagnosis	10 (23)	6 (14)
		Markers unknown at original diagnosis	10 (23)	0 (0)
	Unknown or not evaluated at relapse		4 (9)	5 (11)
Pattern of serum tumor biomarker elevation, No. (%)	bHCG only		0 (0)	5 (18)
	AFP only		2 (22)[b]	3 (11)
	LDH only		5 (56)	2 (7)
	bHCG and AFP		0 (0)	13 (46)
	bHCG and LDH		2 (22)	3 (11)
	AFP and LDH		0 (0)	1 (4)
	bHCG, AFP and LDH		0 (0)	1 (4)
Degree of marker elevation	bHCG	No. with elevation, No. (%)	2 (22)	22 (79)
		Median value, IU/L (range)	126 (9-242)	28 (5-239)
		Median factor of elevation > ULN (range)	63 (5-121)	10 (1-92)
	AFP	No. with elevation, No. (%)	2 (22)[b]	18 (64)
		Median value, μg/L (range)	18 (10-26)	33 (10-393)
		Median factor of elevation > ULN (range)	2 (1-2)	3 (1-33)
	LDH	No. with elevation, No. (%)	5 (56)	7 (25)
		Median value, U/L (range)	338 (266-1,216)	282 (254-682)
		Median factor of elevation > ULN (range)	1 (1-3)	1 (1-2)

Abbreviations: AFP, alpha-fetoprotein; bHCG, beta-human chorionic gonadotrophin; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]Inclusive of one individual with chronic, mild elevation of AFP, felt to be consistent with pure seminoma on review of case notes at participating institution.
[b]Inclusive of two individuals with chronic, mild elevation of AFP, clinically not significant per participating institution.