Monitoring of Late Effects of Chemotherapy in Germ Cell Tumours

Authors: Sophie Heritage, Helena Sinjan, Toby Smallcombe, Thazin Wynn, Sian Pugh, Han Wong, Danish Mazhar

Department of Oncology, Cambridge University Hospitals

Background

- Testicular cancer is the commonest malignancy in men under 35 with approximately 90% of the patients being less than 55 years[1]
- Approximately 1:200 males in the UK develop testicular cancer in their lifetime[1]
- Incidence of testicular cancer is estimated to have doubled in the past 40 years particularly in western and northern Europe[1]
- Testicular germ cell tumours (GCTs) are highly chemosensitive and cisplatin-containing chemotherapy is commonly used.
- Testicular GCTs now have a 95% five[2] and ten-year[3] survival rate, leading to greater focus on survivorship and late effects monitoring.
- Long term side effects of platinum-based chemotherapy include raised BMI, hypertension, hyperlipidaemia and cardiovascular disease[4] as well as hypogonadism, nephrotoxicity and metabolic syndrome[5,6,7]
- BEP (bleomycin, etoposide, cisplatin) increases the risk of coronary artery disease and myocardial infarction[8]
- There is increased mortality due to circulatory disease in testicular cancer survivors after chemotherapy[9]
- Late effects monitoring should be done for testicular GCTs at 5 and 10 years after treatment in line with international, ESMO and regional guidelines[10]

Methodology

- Two cycle audit at tertiary centre assessing late effects monitoring for testicular germ cell tumours
- Cycle 1 – patients selected from clinician and specialist nurse clinic lists in *March to May 2022* (n=148). Electronic medical records (EMRs) retrospectively analysed for 2-year (n=100), 5-year (n=45) and 10-year (n=5) late effects monitoring.
- Cycle 2 – patients attending five-year (n=38) and ten-year (n=30) follow-up clinics between *June 2024 and February 2025* included in analysis. EMRs analysed for late effects monitoring done at this review with no retrospective review of late effects monitoring at other time-points.
- Review of electronic hospital records including clinic letters, laboratory results and GP records.
- Late effects parameters assessed: blood pressure, creatinine, lipid profile, glucose/HbA1c, LH/FSH, testosterone
- Demographic data obtained on patient age at diagnosis, tumour type and stage at diagnosis and treatment received.
- In cycle 2, data was obtained on whether any abnormalities were detected in late effects monitoring and what action was taken, whether clinics were cancelled/rescheduled/not attended, how monitoring was arranged and why monitoring was not done if applicable.

Results – Treatment

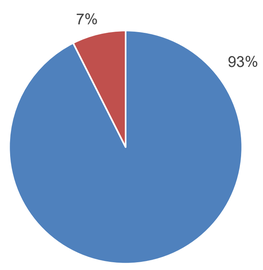
- In each cycle we assessed the percentage of patients undergoing orchidectomy and each regimen of chemotherapy. In cycle 2 we also assessed the percentage of patients having neoadjuvant compared to adjuvant chemotherapy. This included treatment for any recurrence.
- We did not record surgical treatment for any nodal or metastatic disease.

Abbreviations:

- *BEP = bleomycin, etoposide, cisplatin. BEP x3 is 3 cycles, BEP x4 is 4*
- *VIP = cisplatin, etoposide, ifosfamide*
- *AUC7 and AUC10 are different drug exposures (AUC= area under the curve)*

Fig 4a-b: Cycle 1 (n=148)

Orchidectomy *Fig 4a*



Chemotherapy *Fig 4b*

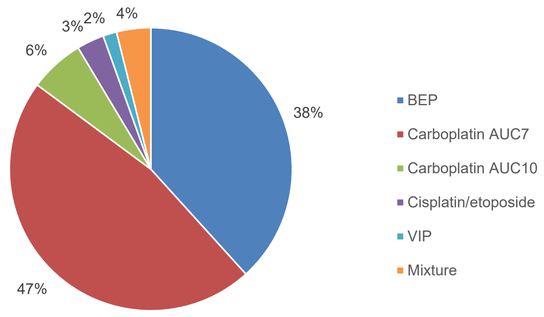
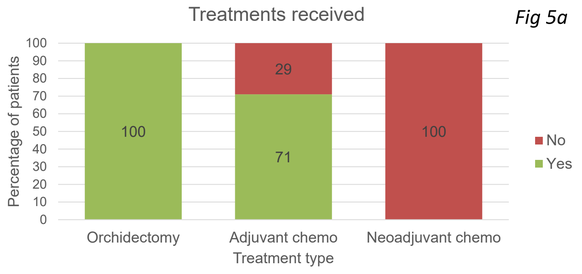


Fig 5a-b: Cycle 2 patients at 5-year follow-up (n=38)

Treatments received *Fig 5a*



Chemotherapy type *Fig 5b*

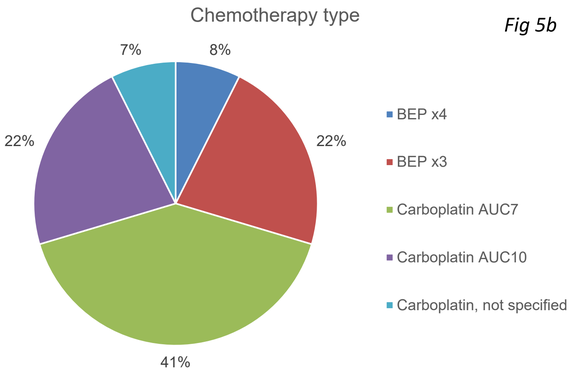
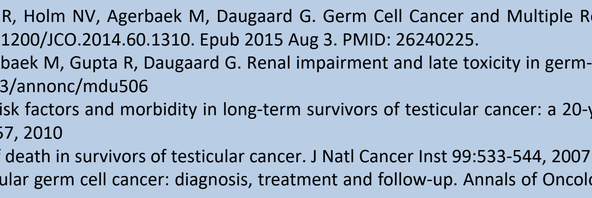
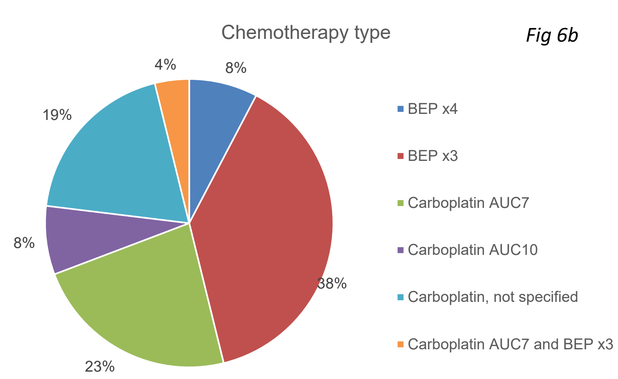


Fig 6a-b: Cycle 2 patients at 10-year follow-up (n=30)

Treatments received *Fig 6a*



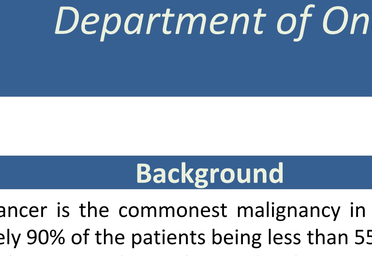
Chemotherapy type *Fig 6b*



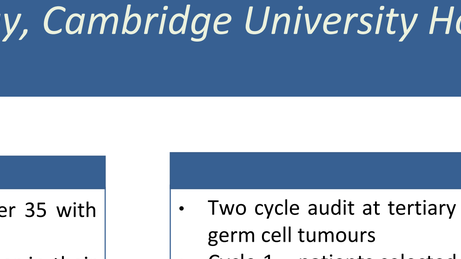
Results - Patient Demographics

Fig 1a-c: Cycle 1 patients (n=148)

Age at audit (years) *Fig 1a*



Cancer type at diagnosis *Fig 1b*



Stage at diagnosis *Fig 1c*

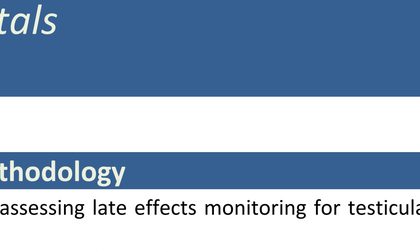
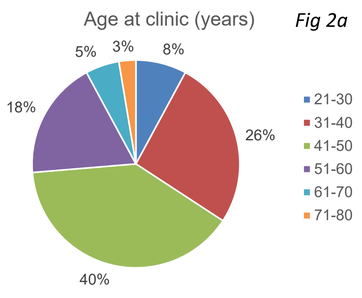
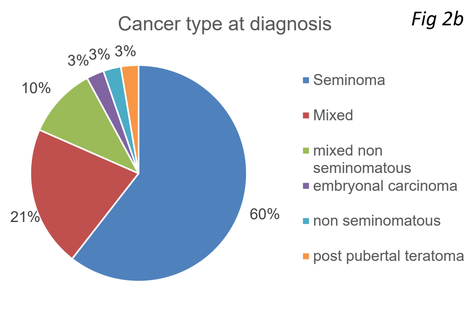


Fig 2a-c: Cycle 2 patients at 5-year follow-up (n=38)

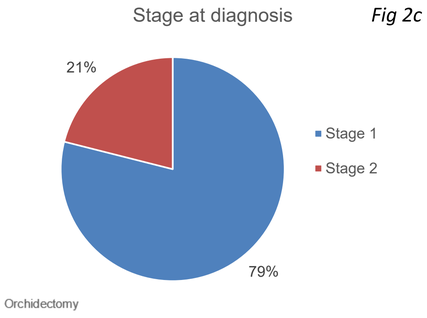
Age at clinic (years) *Fig 2a*



Cancer type at diagnosis *Fig 2b*



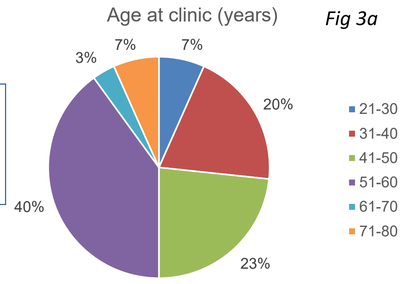
Stage at diagnosis *Fig 2c*



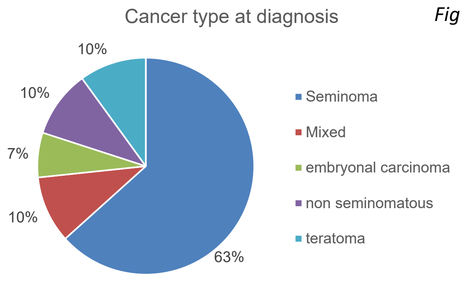
Orchidectomy

Fig 3a-c: Cycle 2 patients at 10-year follow-up (n=30)

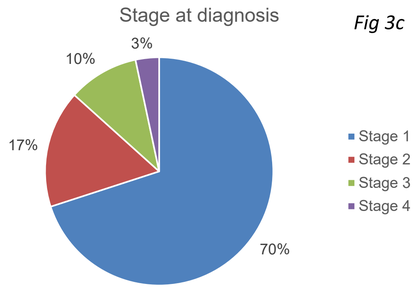
Age at clinic (years) *Fig 3a*



Cancer type at diagnosis *Fig 3b*



Stage at diagnosis *Fig 3c*



Results - Late effects monitoring

Fig 7a: Cycle 1 patients at 2,5 and 10 year follow-up

Late Effect	2yrs (%) n=100	5yrs (%) n=45	10 yrs (%) n=5
Blood pressure	41	27	60
Lipids	32	27	0
Glucose/HbA1c	32	30	80
Creatinine	66	62	80
LH/FSH	31	22	20
Testosterone	38	38	40

Fig 7b: Cycle 2 patients at 5-year follow-up (n=38)

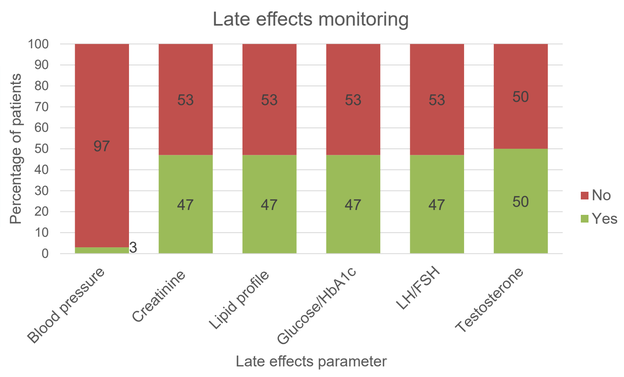
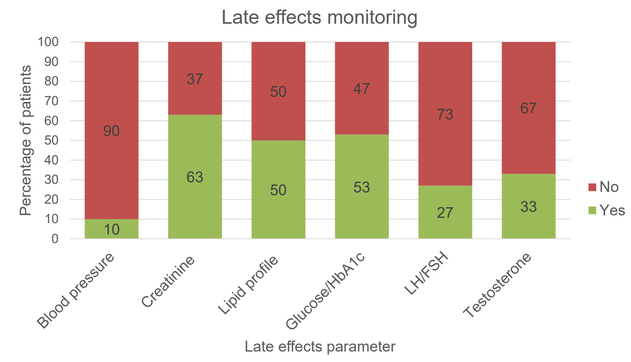


Fig 7c: Cycle 2 patients at 10-year follow-up (n=30)



Additional Results

- **Abnormalities detected and actions taken:** high triglycerides (*9 patients 'p'*), high HbA1c (*4p*), high FSH/LH (*8p*), low FSH/LH (*1p),* high testosterone *(2p),* low testosterone (*2p),* high creatinine (*1p).* This resulted in endocrinology referral for 2 patients and lipid clinic referral for 1 patient. Verbal advice or recommendations to the GP were frequently documented outcomes.
- **Missed/rescheduled clinic attendance:** 1 patient did not attend, 3 patients did not attend the initial appointment leading to clinic rescheduling and 2 patients asked to reschedule appointments.
- **How bloods were arranged:** blood pack but location unclear (25p), blood pack at the hospital (12p), blood pack at the local blood service (5p), GP (2p), unclear (12p), another hospital (1p).
- **Reasons for monitoring not being done:** unclear (17p), orders placed but not yet done (6p), done earlier than scheduled (4p), non-attendance (1p), outdated guidelines (3p)

Conclusions and Future Directions

- Between cycle 1 and 2 clearer guidelines were introduced for clinic letters to GPs with revised follow-up protocols. Blood packs were introduced and given to patients to be done at their GP/hospital/locally, with results sent back to the oncologists. Results of cycle 1 were also presented to clinicians for education.
- Different methodology for cycle 1 and 2 makes comparison challenging given a stricter criteria was used for cycle 2 to ensure parameters were being checked with the purpose of late effects monitoring. This likely impacts creatinine and blood pressure which are routinely monitored during unrelated admissions.
- Blood pressure (BP) is the least well monitored in cycle 2 which may be attributed to more remote follow-up or failure to record BP measurements taken by the patient or in primary care.
- There is suboptimal late effects monitoring despite implementations since cycle 1, but some areas show improvement. Creatinine measurement is worse.
- Whilst face to face clinics may be useful, there is likely to be increasing use of remote follow-up in the future, so follow-up protocols need to be more rigorous to ensure late effects tests and assessments are completed e.g. through the GP, though patient compliance may still be an issue.
- Specialist teams need to place greater importance on late effects monitoring. Relapse is rare at 5 and 10 years so the main focus should arguably be on toxicity and late effects monitoring from 5 years onwards.
- Further patient and GP education is needed on late treatment effects.

References

1. Gurney JK, Florio AA, Znaor A, *et al*. International trends in the incidence of testicular cancer: lessons from 35 years and 41 countries. *Eur Urol*. 2019;76(5):615-623.
2. Haugnes HS, Bosl GJ, Boer H, Gietema JA, Brydøy M, Oldenburg J, Dahl AA, Bremnes RM, Fosså SD. Long-term and late effects of germ cell testicular cancer treatment and implications for follow-up. J Clin Oncol. 2012 Oct 20;30(30):3752-63. doi: 10.1200/JCO.2012.43.4431. Epub 2012 Sep 24. PMID: 23008318.
3. Jovanovski A, Zugna D, Di Cuonzo D, Lista P, Ciuffreda L, Merletti F, Rosato R, Richiardi L. Quality of life among germ-cell testicular cancer survivors: The effect of time since cancer diagnosis. PLoS One. 2021 Oct 6;16(10):e0258257. doi: 10.1371/journal.pone.0258257. PMID: 34614027; PMCID: PMC8494333.
4. Willemse PM, Burggraaf J, Hamdy NA, *et al*. Prevalence of the metabolic syndrome and cardiovascular disease risk in chemotherapy-treated testicular germ cell tumour survivors. *Br J Cancer*. 2013; 109(1):60-7.
5. M. Bandak, N. Jorgensen, A. Juul et al., Testosterone deficiency in testicular cancer survivors - a systematic review and meta-analysis. Andrology, vol. 4, no. 3, pp. 382–388, 2016.
6. Lauritsen J, Kier MG, Mortensen MS, Bandak M, Gupta R, Holm NV, Agerbaek M, Daugaard G. Germ Cell Cancer and Multiple Relapses: Toxicity and Survival. J Clin Oncol. 2015 Oct 1;33(28):3116-23. doi: 10.1200/JCO.2014.60.1310. Epub 2015 Aug 3. PMID: 26240225.
7. Lauritsen J, Mortensen MS, Kier MG, Christensen IJ, Agerbaek M, Gupta R, Daugaard G. Renal impairment and late toxicity in germ-cell cancer survivors. Annals of Oncology. 2015 Jan; 26(1):173-178. doi: 10.1093/annonc/mdu506
8. H. S. Haugnes, T. Wethal, N. Aass et al., Cardiovascular risk factors and morbidity in long-term survivors of testicular cancer: a 20-year follow-up study. Journal of Clinical Oncology, vol. 28, no. 30, pp. 4649–4657, 2010
9. Fossa SD, Gilbert E, Dores GM, et al: Noncancer causes of death in survivors of testicular cancer. J Natl Cancer Inst 99:533-544, 2007.
10. Honecker, F. et al. ESMO Consensus Conference on testicular germ cell cancer: diagnosis, treatment and follow-up. Annals of Oncology. 2018 Aug; 29(8): 1658-1686