AYA Testis Cancer: the Unmet Challenge

Sara Stoneham [1], Matthew Murray[2], Benjamin Thomas[3], Max Williamson[4], Christopher Sweeney[5], Lindsay Frazier[6].

1. Department of Paediatrics and Child Health, University College Hospital London NHS Foundation Trust, 235 Euston Road, London.
2. Department of Pathology and Department of Paediatric Haematology and Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge.
3. Oncology Department, Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK.
4. Life Sciences Faculty, University College London.
5. Dana-Farber Cancer Institute, Department of Medical Oncology and Division of Population Sciences, Boston, MA
6. Dana-Farber/Boston Children's Cancer and Blood Disorders Center, MA, USA

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/pbc.27796.

Corresponding author: Dr Sara Stoneham, Department of Paediatrics and Child Health, 6Th Floor Central, 250 Euston Road, London NW1 2PG. Tel: +44203 4479950. Email: sara.stoneham@nhs.net.

Funding source: unfunded

Abstract: 149

Main text: 3498

Figures: 2

Key words: germ cell tumors, molecular biology, psychosocial, quality of life, tumor biology, late effects of cancer treatment, tumors, germ cell

Abbreviations: AYA – adolescent and young adult; SMN – second malignant neoplasms; CVD – cardiovascular disease; GCT- germ cell tumours; OS – overall survival; SES- socio-economic status; CCS – cancer specific survival; YST – yolk sac tumour; MMGCT -mixed malignant GCT; NSGCT-non-seminomatous GCT; mRNA – messenger RNA; RPLND - retroperitoneal lymph node dissection; TCS -testicular cancer survivors; MRD- minimal residual disease; miRNA –microRNAs; BEP - cisplatin, etoposide and bleomycin; MaGIC- the Malignant Germ Cell International Consortium.

Abstract

Testis cancer is considered a rare-incidence cancer but comprises the third most common cancer diagnosed within the AYA years (15-39y). Most testis cancer patients can anticipate a survival outcome in excess of 95%. However, there are subgroups of AYA patients where outcomes are considerably worse including younger adolescents, patients with certain histological subtypes, or from certain ethnic backgrounds. For those cured with chemotherapy, the toxicity of treatment and burden of late-effects is significant. Newer germ cell tumour - specific biomarkers may identify

patients that do not require further treatment interventions or may detect early recurrence, potentially reducing the burden of treatment required for cure. International collaboration for this rare tumour is creating the forum for trial design, where these biomarker research questions are embedded. Going forward, AYA testis cancer patients could benefit from having a more personalised treatment plan, tailored to risk, that minimises the overall burden of late-effects.

Introduction

AYA cancer patients are a unique population; presenting with age-specific cancer diagnoses, differing tolerances to conventional therapies and often differing survival outcomes. [1]

As cancer constitutes the most common cause of disease-related deaths in this age-group, health- care provision has become focused on working towards an understanding of how to provide better age-related outcomes of survival and experience of

89 care during and after treatment. [2]

90

91 Whilst there has been much progress, particularly with regard to how to create an
92 environment to accommodate the specific psychosocial needs for AYA patients,
93 there is still much to learn about how to provide optimal survival outcomes.

94

95 Testicular cancer is an excellent example of this challenge. It is the most common
96 cancer diagnosed in men under age 40 years (y). [3] Germ cell tumours (GCT) are
97 considered to be a curable cancer, with overall survival (OS) for all patients ap-
98 proaching 96%. [4] However, adolescents diagnosed with a GCT are at risk of inferior
99 outcomes when compared with either affected children or older adults. [5] More re-
100 cent reports suggest that the broader range of AYA patients (between age 15-39y)
101 do better than older men diagnosed with certain histological subtypes of testis can-
102 cer. [6] So how can we ensure we identify and provide effective therapies to accom-
103 modate these subgroups of patients who are most at risk?

104

105 The peak incidence of GCT occurs at 30y, with the natural incidence of testis cancer
106 spread across the entire AYA range. [4] There is both geographical and ethnic varia-
107 tion in incidence within AYA, with white men in developed nations being dispropor-
108 tionately affected. [7, 8] However, this largest group of patients also tends to have the
109 best outcomes. Analysis of the impact of ethnicity and socioeconomic status (SES)
110 has shown that African American and Hispanic populations have poorer cancer spe-
111 cific survival (CSS), even when corrected for SES. [8, 9] Thus, within AYA testis can-

cer, we can identify another 'at risk' subgroup. What we understand less well is why these young men are more vulnerable to adverse outcomes. Here, we will discuss whether such outcomes can be accounted for by explanations other than poor access to health care for those not insured:[10] specifically whether diagnostic delays or presence of more advanced disease at presentation; different histologic predominance or biologic behaviors can explain a survival gap.

The distribution and predominance of histologic subtypes of GCT varies with age. In children <11y the most common malignant histology is yolk sac tumor (YST). YST in children are generally exquisitely chemo-sensitive, and offer excellent outcomes after treatment, even in the face of advanced metastatic disease. [11] However, within the AYA years, mixed malignant GCT (MMGCT) becomes the most common histology. [4]. As age increases across the AYA range, there is relative increase in percentage of seminoma diagnoses represented, until ultimately seminoma overtakes MMGCT as the most common histological diagnosis (Figure 1). The 5 year CSS for either localized or metastatic MMGCT is less than for YST or seminoma in the same age-range. [4]

Pure choriocarcinoma, an aggressive non-seminomatous GCT (NSGCT) subtype which may present with a high burden of disease, remains rare. Hence, histologic subtype may in part contribute to the adolescent survival gap, but does not completely account for all of the discrepancy observed. [12]

Do AYA patients present later and have a higher burden of disease?

Localized disease is by far the most common presentation of testis cancer; approximately four-fold more common than a presentation with either regional or distant metastatic disease. [4] (Figure 2) OS from localized disease is 95%. However, in patients aged between 10-15y, <50% patients present with localized disease. Of the remaining patients in this younger age-group, up to a third of patients are diagnosed with metastatic disease; a much higher rate than in any other age group. [4] Veneroni et al found that adolescents had a longer symptom interval (SI) to diagnosis than children [13]. For adolescents with either locally or regionally advanced GCT, delays can worsen prognosis. [14] However the relationship between SI and overall survival is complex, multifactorial and must also take into account the tumour's biological behavior. [15]

Can we identify the relationship between histologic subtypes within AYA and the burden of disease at presentation?

Seminoma presents with localized disease in up to 80% of patients, across all ages. [4] In contrast, <50% of AYA diagnosed with a NSGCT have localized disease.[4] The MMGCT subtype, the most common form of NSGCT in adolescents, presents with metastatic disease three-fold more commonly than patients with seminoma. [4] Among AYAs, choriocarcinoma was the histologic type with the most advanced stage at diagnosis with up to 60% having regional or metastatic disease, but as it is rare, it has a minimal impact on overall survival outcomes. [4]

Hence, as both histology and younger AYA age at diagnosis correlate with a greater burden of disease, there is a consequent higher burden of therapy required for cure.

How does initial burden of disease, histology and patient age relate to outcome for AYA?

Overall an AYA patient with either localized disease or loco-regional disease can expect OS in excess of 95%. [4]. However, an AYA patient with distant metastatic disease can anticipate a considerably lower chance of survival, between 70-80%. [4] For those who succumb to disease, within the AYA range, the age at which death is most likely to occur is between 20-24y. This anomaly has not changed for over 20 years. [4]

Amini *et al* found that patients < 20y in the U.S., were managed more aggressively with surgery compared with the wider adult population, and received higher administration rates of adjuvant chemotherapy. [16] Conceivably, the higher surgical intervention rate and more aggressive surgery performed, is explained by the higher incidence of NSGCT relative to seminoma in this age-group and a higher burden of disease at presentation . However, AYA patients generally had less co-morbidity recorded during treatment and more often received care in high volume centers, both factors normally associated with better outcomes. [6, 17] In contrast, AYA patients diagnosed with seminoma have earlier stage disease at presentation, are treated with surveillance more frequently and have a slight OS advantage over older men.[6],

Additional factors to consider which may affect patient outcomes include the less well understood role of pharmacodynamics and pharmacokinetics. Eating disorders,

e.g. anorexia, bulimia, and obesity, all seen in the AYA age group, may have a prominent effect on drug distribution, sensitivity, efficacy, toxicity, and dosing. [18] Hence, more intervention may translate into better outcomes, but can translate into a greater burden of potential late-effects for an individual.

Can our understanding of biologic behavior of GCT across different ages guide our interventional strategies to accommodate for survival discrepancies?

GCT in pre-pubertal children generally show fundamental molecular differences to those in adult patients, despite sharing a similar histology, which suggests that basing clinical management purely on chronological age or histology alone may not provide optimal treatment strategies for AYA patients. [19]

Regarding genomic changes, gain of the short arm of chromosome 12 (12p) is an almost universal finding in adult testicular GCT patients. [20, 21] Gain of 12p was identified in 5/18 (27%) male pediatric GCTs in one study [22] and 44% in another. [23] The incidence of 12p gain increased with patient age (29% <5y; 53% 5-16y) [23]. Thus, genomic copy number imbalances distinguish GCT subgroups primarily by age, rather than by tumor site or histology [19]. However, for the AYA population, the prognostic significance of 12p gain and other genomic imbalances seen in GCTs is yet to be determined.

202 At a transcriptomic level, pediatric GCT have a distinct protein-coding (messenger
203 RNA- mRNA) gene expression program compared with adult GCTs, irrespective of
204 tumor site [24]. Furthermore, pediatric and adult tumors with comparable histology
205 (seminoma, YST) were also segregated by global mRNA expression profiles, lending
206 weight to the suggestion that the clinical management of these entities should be dif-
207 ferent [24]. Interestingly, a very small number of pediatric GCTs had 'adult' profiles
208 and *vice versa* [24]; the significance of such findings needs to be elucidated in further
209 studies, and interrogation of biospecimens from an AYA cohort will likely facilitate
210 this. An mRNA signature predictive of outcome has been reported in metastatic
211 NSGCT patients (median age 29y; range 15-60y), which added independent prog-
212 nostic accuracy to existing risk classification systems [25]. However, translation of this
213 multi-gene signature into clinical practice will be challenging and, it remains unclear
214 whether this predictive model would be applicable for pediatric or younger AYA (13-
215 24y) populations. [19, 26]
216
217 **Do AYA have suboptimal treatment strategies/cure *vs.* Quality of life for AYA –**
218 **have we got the balance right?**
219 Adult testis cancer is viewed as the success story for a curable cancer. However,
220 this cure is not without significant cost in the longer term. The burden of late effects
221 is both wide in range and significant in impact for all men requiring adjuvant treat-
222 ment. They include an increased risk of second malignant neoplasm (SMN); early
223 onset cardiovascular disease (CVD); hypogonadism; infertility; peripheral neurotoxi-

city; tinnitus and hearing loss; renal toxicity; pulmonary toxicity; fatigue; and anxiety and depression.

After mortality, fertility is the second most common concern for patients with cancer. [27] This is of particular concern for younger AYA patients diagnosed and treated for cancer at a time in life when many have not made choices around starting a family, let alone completion. The link between reduced fertility and cancer starts at diagnosis and up to to 50% of post-orchiectomy patients have been shown to have decreased sperm counts, with some patients also having low sperm motility and abnormal sperm cells. [28]

Further components of testicular cancer therapy, namely retroperitoneal lymph node dissection (RPLND), radiotherapy and chemotherapy, all come with differing fertility risks. For patients requiring chemotherapy for cure, the cumulative dose of cisplatin-based treatment is directly associated with the risk of infertility and achievement of paternity. [29, 30, 31,] Conversely, the use of carboplatin-based regimens, directly compared with cisplatin, has been shown to be associated with fourfold greater recovery to normal sperm counts. [32] The majority of AYA patients will be diagnosed with a NSGCT and will receive 'adult' BEP.

Up to a third of patients with NSGCT metastatic disease may require consideration of a RPLND following chemotherapy. RPLND is associated with significant potential morbidity, both in the peri-operative period and in the long-term. In the post-chemotherapy setting, the gold standard for surgery remains a bilateral template dis-

247 section via an open approach. [33] If the retroperitoneal postganglionic sympathetic
248 nerves are damaged intra-operatively, this surgical procedure carries the risk of in-
249 ducing retrograde ejaculation in up to 9% of patients. [34]
250 Radiotherapy (RT) has played an important adjuvant role in advanced stage semi-
251 noma therapy for many years, and for most patients, there is recovery of normal
252 spermatogenesis within 24 months of end of treatment [30,35] . In long-term follow-up,
253 when compared with a surgery-only cohort, there appears to be no significant impact
254 on spermatogenesis. [30, 35] Thus overall, RT is less likely to be implicated in any loss
255 of fertility for AYA patients, as fewer AYA patients will require RT.
256
257 Hypogonadism contributes to the risk of infertility. Causes of hypogonadism include
258 orchiectomy itself, chemotherapy, radiotherapy and any underlying testicular dys-
259 genesis syndrome. The additional side effects of hypogonadism include reduced
260 sexual functioning, depression, fatigue, loss of muscle mass and osteoporosis. Fur-
261 thermore, the known association between the metabolic syndrome and CVD as a
262 direct result of hypogonadism adds substantially to the burden of late-effects. [36]
263
264 The risk of early onset CVD is of particular concern. The relative risk of CVD in pa-
265 tients treated with chemotherapy is 1.4-7.1 fold higher compared with the general
266 population or those patients undergoing surgery alone. [36, 37, 38] Hypogonadism, to-
267 gether with chemotherapy-induced vascular injury and chemotherapy-related dis-
268 turbance of metabolic homeostasis, combine [39] to increase CVD mortality risk. In a

population based study, Fung *et al* described patients appearing to be at most risk within the first year off treatment, with a calculated 5.3-fold risk of mortality. [40]

SMN constitutes a significant cause of morbidity and mortality. Post-chemotherapy, there is an increased risk of both solid and leukemic SMNs. Kollmansberger *et al* reported that the 5 year cumulative incidence of secondary leukemia after a cumulative etoposide dose of <2000mg/m^2 and >2000mg/m^2 was approximately 0.5% and 2.0%, respectively. [41] Similarly, when Fung *et al* reviewed the risk of solid tumor SMN, a 1.4-fold increase risk for those who had received chemotherapy compared with those who underwent surgery alone was identified. [42] Therefore, not only the choice of chemotherapy drugs, but also the dosing of these drugs, appears to be important.

Long-term renal dysfunction has been directly associated with cumulative dosing of cisplatin. [43] Up to 40% of testicular cancer survivors (TCS) experience symptoms of peripheral neuropathy during and/or after chemotherapy. [44, 45] Non-fatal pulmonary toxicity has been reported between 7-21% of TCS. [46, 47] Risk factors for restrictive lung disease included cisplatin dose and increasing age, after adjusting for bleomycin, etoposide and vinblastine exposure. [48] For TCS treated with chemotherapy, there was a higher mortality rate from all respiratory diseases when compared with the general population. [49]

Ototoxicity secondary to cisplatin may also have a significant impact on quality-of-life. [50, 51] Bokemeyer *et al* reported symptomatic ototoxicity in 20% of testicular cancer survivors. [52] Tinnitus was the most reported symptom in 59% patients, but

23% reported both tinnitus and hearing loss together. Dose was important, with 50% of patients receiving >400mg/m^2 cisplatin experiencing persistent ototoxicity. [52]

One of the late effects TCS find most distressing is fatigue; it is often the most frequently reported concern in long-term follow-up. [53] The prevalence of depression in up to 20% of TCS has been reported widely [54, 55, 56, and 57] with anxiety significantly associated with younger age at diagnosis. [55] AYA patients are already known to be more likely to suffer psychological problems after a cancer diagnosis and greater difficulty in retaining employment or maintaining education. [58, 58, 60]

Many AYAs with cancer report that their cancer makes them feel 'abnormal'. [61] TCS describe difficulty both with romantic partnerships and support. [62] Anxieties around body image and masculinity arise when changes in appearance (e.g. scarring, loss of hair/body parts etc.) result in diminishment of sexual attractiveness. [61, 62] Bellizzi *et al*, in the AYA HOPE study, showed that over 50% of TCS reported they felt like 'damaged goods' due to surgical scars and loss of a testicle and had concerns about their ability to have children. [60, 61, 62]

Although a cancer diagnosis may be disruptive to normal social maturation for an AYA patient [63, 64], TCS considered that those who had not experienced testicular cancer could not understand how the experience had shaped their life views on maturing and growing up. They considered the experience provided them with a unique, but different, outlook on life, marriage and parenthood compared with their peers. [61] Hence for a common cancer in this AYA age range, for patients with many life years ahead, the burden of late-effects can be profound.

What can we do to reduce burden of therapy? Personalizing the treatment plan.

A better understanding of the absolute need for surgery, radiotherapy and intensity of chemotherapy regimens could mitigate against some late-effects. Minimal residual disease (MRD) testing by highly sensitive PCR techniques has been transformative for patients with ALL; allowing a more elegant risk stratification to inform the burden of therapy. [65]

The emergence of microRNAs (miRNA) as a biomarker of disease could potentially help risk-stratify the burden of therapy required for cure in a way analogous to MRD for ALL patients i.e. allowing understanding of 'molecular remission' and no requirement for any further treatment intervention. MiRNAs are short, non-coding RNAs that modulate protein-coding gene expression, through interactions with specific binding sites in the 3' untranslated regions of messenger RNAs. [66]. MiRNAs are dysregulated in cancer, acting either as oncogenes or tumor suppressor genes. [67] In GCTs, the most striking finding was universal miR-371~373 and miR-302/367 cluster over-expression in all malignant tumors, regardless of patient age (pediatric/AYA/adult), histologic subtype (YST/ seminoma) or anatomic site (gonadal/extragonadal). [66] Expression levels of just the eight main miRNAs from these two clusters accurately separated >100 malignant GCTs from non-malignant samples, suggesting that these miRNAs could offer high sensitivity and specificity as malignant GCT biomarkers [66].

Serum miRNAs have also been shown to be useful longitudinally for early sensitive detection of malignant recurrence in stage I disease and disease-monitoring following initiation of chemotherapy. [68] Serum miRNA testing and validation in prospective clinical trials (e.g. the Children's Oncology Group's trial AGCT1531) is now under way, heralding an opportunity for non-invasive monitoring and reduced use of serial CT scans with consequent radiation exposure during treatment and follow-up. [69]

The potential methods of decreasing the morbidity of surgery in the future are likely to involve a decrease in the extent of surgical dissection, and the increased utilization of minimally invasive approaches, particularly robot-assisted RPLND. These methods are of particular significance in the AYA population. European and North American studies in high volume centers have shown that the use of modified unilateral templates for selected cases did not result in any recurrences within the field of a bilateral template dissection and did not compromise oncological outcomes, exemplifying that when RPLND is a fundamentally important for cure, referral to high volume centres with experienced uro-oncology surgeons is paramount.[70, 71] Robotic RPLND in the post-chemotherapy setting is increasingly utilized. Small series have shown significant decreases in peri-operative morbidity, rates of retrograde ejaculation and hospital length of stay without compromise of oncological outcomes although long-term follow-up is not yet present. [72, 73, 74]

For those AYA patients where chemotherapy remains essential for cure, we have a responsibility to develop less toxic but equally effective treatment regimens. Adult BEP chemotherapy (cisplatin, etoposide and bleomycin) remains the gold standard

360 treatment. [75] Carboplatin is a platinum agent that has not been demonstrated to
361 have the same long-term toxicity profile as cisplatin. Historically, carboplatin regi-
362 mens have been tested against cisplatin in the hope that carboplatin may provide
363 equally effective survival outcomes but with less morbidity. [76, 77, 78] These trials had
364 concluded it was less effective than cisplatin. Recent reviews comparing these and
365 other cisplatin and carboplatin outcomes, suggests we should re-consider its use
366 across all ages, as inadequate dosing and frequency of delivery could account for
367 the discrepancy in outcomes documented in the era before the use of stem-cell fac-
368 tor support. [79, 80] Pharmacogenomics studies may further help finesse decision mak-
369 ing.
370
371
372 **How do we achieve this?**
373 As a result of the above, the international GCT community needs to continue to ad-
374 vocate for all GCT patients, but in particular for AYA patients with testicular cancer
375 where arguably much more remains unknown and unresolved. MaGIC (the Malig-
376 nant Germ Cell International Consortium; https://www.magicconsortium.com/) is an
377 international collaboration comprising clinicians and scientists from pediatric, medi-
378 cal, gynecological, clinical oncology and allied disciplines. International platforms
379 such as MaGIC can begin to address geographic and ethnic variation in outcomes
380 and ensure biology is embedded in new trial development. This strategy should allow
381 us to locate these vulnerable subgroups of patients, reduce the burden of therapy
382 and engage the groups of patients that are most at risk of late-effects in tailored re-

search programs. More locally, discussion of teenage GCT patients should always take place in a disease-specific multidisciplinary meeting with combined medical and paediatric oncology representation. This will facilitate sharing of expertise, promote enrolment into international trials open to AYA patients and adherence to national guidance to support safe delivery of care and minimize treatment related mortality.

Conclusion

The incidence of testicular cancer is increasing across all ages within the AYA spectrum (13-39y). Compared with older adult patients, AYA patients present with a higher burden of disease and with more NSGCT histologies which require more intensive treatment for cure; this inevitably translates into an increased burden of late effects. By contrast, for men aged >40y, the prevalence remains stable. Thus, for those patients with the most life years left to live, the numbers of patients requiring the most morbid treatment are increasing.

The identified miRNA signature, applicable across all patient ages, offers the potential for a universal test for diagnosis and disease-monitoring. Although the genomic and protein-coding gene molecular differences observed between pediatric and adult GCTs [19] may well be triggered by puberty, most, but not all, AYA GCT are likely to be 'adult' tumors biologically, the lack of focus on this cohort to date makes this largely an assumption. Consequently, clinical management based simply on chronological patient

age may well be suboptimal. Future research focused on AYAs, particularly the younger AYA group (13-24y), may alleviate these challenges and facilitate more personalized clinical management including removal of disparities in access to health care as an issue. Moreover, such work may also allow more accurate prognostic risk groups to be defined and assist the development of novel therapies that have increased efficacy in poor-prognosis tumors and/or cause less long-term toxicity in good-prognosis patients. All this will be best achieved within a collaborative, international forum.

Conflict of Interest Statement:

1. Dr Lindsay Frazier - clinical advisory board, Decibel Advisory Board.

Acknowledgments:

St Baldrick's Foundation

References:

1. Bleyer A, 'Adolescent and Young Adult oncology: the first A,' Paediatric Hematology and Oncology, Vol.24, no.5, pp. 325-336, 2007.

2. Schmidt C, 'Lack of progress in teen and young adult cancers concerns researchers, prompts study, 'Journal of the National Cancer Institute, vol. 98, no.24, pp. 1760-1763, 2006.

3. Barr RD, Ries LA, Lewis DR, Harlan LC, Keegan TH, Pollock BH, Bleyer WA; US National Cancer Institute Science of Adolescent and Young Adult Oncology Epidemiology Working Group. Incidence and incidence trends of the most frequent cancers in adolescent and young adult Americans, including "nonmalignant/noninvasive" tumors. Cancer. 2016 Apr 1;122(7):1000-8.

4. Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER 18 Regs Research Data + Hurricane Katrina Impacted Louisiana Cases, Nov 2017 Sub (2000-2015) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2016 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission.

5. Cost NG, Lubahn JD, Adibi M, Romman A, Wickiser JE, Raj GV, Sagalowsky AI, Margulis V. A comparison of pediatric, adolescent, and adult testicular germ cell malignancy. Pediatr Blood Cancer. 2014 Mar;61 (3):446-51.

6. Stokes W, Amini A, Maroni PD, Kessler ER, Stokes C, Cost CR, Greffe BS, Garrington TP, Liu AK, Cost NG. Patterns of care and survival outcomes for adolescent and young adult patients with testicular seminoma in the United States: A National Cancer Database analysis. J Pediatr Urol. 2017 Aug;13(4):386

7. Znaor A, Lortet-Tieulent J, Laversanne M, Jemal A, Bray F. International testicular cancer incidence trends: generational transitions in 38 countries 1900-1990. Cancer Causes Control. 2015 Jan;26(1):151-8.

8. Chien FL, Schwartz SM, Johnson RH. Increase in testicular germ cell tumor incidence among Hispanic adolescents and young adults in the United States. Cancer. 2014 Sep 1;120(17):2728-34. doi: 10.1002/cncr.28684.

9. Biggs ML, Schwartz SM. Differences in testis cancer survival by race and ethnicity: a population-based study, 1973-1999 (United States). Cancer Causes Control. 2004 Jun;15(5):437-44

10. . Markt SC, Lago-Hernandez CA, Miller RE, Mahal BA, Bernard B, Albiges L, Frazier LA, Beard CJ, Wright AA, Sweeney CJ. Insurance status and disparities in disease presentation, treatment, and outcomes for men with germ cell tumors. Cancer. 2016 Oct 15;122(20):3127-3135.

11. Faure Conter C, Xia C, Gershenson D, Hurteau J, Covens A, Pashankar F, Krailo M, Billmire D, Patte C, Fresneau B, Shaikh F, Stoneham S, Nicholson J, Murray M, Frazier AL. Ovarian Yolk Sac Tumors; Does Age Matter? Int J Gynecol Cancer. 2018 Jan;28(1):77-84

12. DeRouen MC, Mujahid M, Srinivas S, Keegan TH. Disparities in Adolescent and Young Adult Survival After Testicular Cancer Vary by Histologic Subtype: A Population-Based Study in California 1988-2010.,J Adolesc Young Adult Oncol. 2016 Mar;5(1):31-40. doi: 10.1089/jayao.2015.0041. Epub 2015 Nov 18.

13. Veneroni L, Mariani L, Lo Vullo S et al . Symptom interval in pediatric patients with solid tumors: adolescents are at greater risk of late diagnosis. Pediatr Blood Cancer. 2013 Apr;60(4):605-10. doi: 10.1002/pbc.24312

14. Ferrari A, Lo Vullo S, Giardiello D, Veneroni L et al The Sooner the Better? How Symptom Interval Correlates With Outcome in Children and Adolescents With Solid Tumors: Regression Tree Analysis of the Findings of a Prospective Study. Pediatr Blood Cancer. 2016 Mar;63(3):479-85. doi: 10.1002/pbc.25833

15. Barr RD. "Delays" in diagnosis: a misleading concept, yet providing opportunities for advancing clinical care. J Pediatr Hematol Oncol. 2014 Apr;36(3):169-72. doi: 10.1097/MPH

16. Amini A, Waxweiler TV, Maroni PD, Kessler ER, Cost CR, Greffe BS, Garrington TP, Liu AK, Cost NG. Survival outcomes of adolescent and adult patients with non-seminomatous testicular germ-cell tumors: A population-based study. J Pediatr Urol. 2016 Dec; 12(6):405.

17. Albritton KH, Coccia P. Influencing referral of adolescents and young adults with cancer to sites with higher rates of trial enrollment. Pediatrics. 2014 Jun;133 Suppl 3:S104-8. doi: 10.1542/peds.2014-0122E

18. Veal GJ, Hartford CM, Stewart CF. Clinical pharmacology in the adolescent oncology patient. J Clin Oncol. 2010 Nov 10;28(32):4790-9.

19. Collinson K, Murray MJ, Orsi NM, et al. Age-related biological features of germ cell tumors. Genes Chromosomes Cancer 2014:53(3):215-227.

20. Atkin NB, Baker MC. Specific chromosome change, i(12p), in testicular tumours? Lancet 1982:2(8311):1349.

21. Atkin NB, Baker MC. i(12p): specific chromosomal marker in seminoma and malignant teratoma of the testis? Cancer Genet Cytogenet 1983:10(2):199-204.

22. Bussey KJ, Lawce HJ, Himoe E, et al. Chromosomes 1 and 12 abnormalities in pediatric germ cell tumors by interphase fluorescence in situ hybridization. Cancer Genetics and Cytogenetics 2001:125(2):112-118.

23. Palmer RD, Foster NA, Vowler SL, et al. Malignant germ cell tumours of childhood: new associations of genomic imbalance. Br J Cancer 2007:96(4):667-676.

24. Palmer RD, Barbosa-Morais NL, Gooding EL, et al. Pediatric malignant germ cell tumors show characteristic transcriptome profiles. Cancer research 2008:68(11):4239-4247.

25. Korkola JE, Houldsworth J, Feldman DR, et al. Identification and validation of a gene expression signature that predicts outcome in adult men with germ cell tumors. Journal of clinical oncology : official journal of the American Society of\ Clinical Oncology 2009:27(31):5240-5247.

26. Chen KS, Fustino NJ, Shukla AA, et al. EGF Receptor and mTORC1 Are Novel Therapeutic Targets in Nonseminomatous Germ Cell Tumors. Mol Cancer Ther. 2018 May;17(5):1079-1089.

27. Loscalzo MJ, and Clark KL. 'The Psychosocial context of cancer related infertility,' Cancer Treatment and Research, vol. 138, pp. 180-190, 2007.

28. Fossa SD, Abyholm T, and Aakvaag A. 'Spermatogenesis and hormonal status after orchiectomy for cancer and before supplementary treatment, 'European Urology, vol. 10, no. 3 pp. 173-177, 1984.

29. Brydoy, M, Fossa SD, Klepp O, et al., 'Paternity following treatment for testicular cancer,' Journal of the National Cancer Institute, vol. 97, no.21, pp.1580-1588, 2005.

30. Brydoy, M, Fossa SD, Klepp O, et al. 'Paternity and testicular function among testicular cancer survivors treated with two to four cycles of cisplatin -based chemotherapy, ' European Urology, vol. 58, no.1, pp. 134-140, 2010

31. Brydoy, M, Fossa SD, Klepp O, et al. "Sperm counts and endocrinological markers of spermatogenesis in long-term survivors of testicular cancer,' British Journal of Cancer, vol. 107, no.11, pp. 1833-1839, 2012.

32. Lampe H, Horwich A, Norman A, et al., Fertility after chemotherapy for testicular germ cell cancers, ' Journal of Clinical Oncology, vol. 15, no.1, pp. 239-245, 1997.

33. Large MC, Sheinfeld J, Eggener SE, Retroperitoneal lymph node dissection: reassessment of modified templates. BJU Int 2009; 104: 1369-75.

34. Beck SD, Bey AL, Birhle R, et al., 'Ejaculatory status and fertility rates after primary retroperitoneal lymph node dissection, 'Journal of urology, vol. 184, no.5, pp. 2078-2080, 2010.

35. Gandino L, Sgro P, Lombardo F, et al., "Effect of chemo- or radiotherapy on sperm parameters of testicular cancer patients,' Human Reproduction, vol. 21, no. 11, pp. 2882-2889, 2006.

36. Christensen JF, Bandak M, Campbell A et al. 'Treatment-related cardiovascular late effects and exercise training countermeasures in testicular germ cell cancer survivorship',Acta Oncologica, vol. 54, no.5, pp.592-599.

37. Meinardi MT, Gietema JA, van der Graaf WT et al., 'Cardiovascular morbidity in long-term survivors of metastatic testicular cancer, ' Journal of Clinical Oncology, vol. 18, no.8, pp. 17245-1732, 2000.

38. Haughnes HS, Wethal T, Aass N, 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.

39. Huddart, RA, Norman A, Shahidi M, et al., "Cardiovascular disease as a long-term complication of treatment for testicular cancer,' Journal of Clinical Oncology, vol. 21, no. 21, no. 8, pp. 1513-1523, 2003.

40. Fung C, Fossa SD, Milano MT et al., 'Cardiovascular disease mortality after chemotherapy or surgery for testicular non-seminoma: a population -based study, ' Journal of Clinical Oncology, vol. 33, no. 28, pp. 3105-3115, 2015.

41. Kollmannsberger C, Hartmann JT, Kanz L, et al., 'Therapy-related malignancies following treatment of germ cell cancer, ' International Journal of Cancer, vol. 83, no.6, pp. 860-863, 1999.

42. Fung c, Fosa SD, Milano MT et al., 'Solid tumours after chemotherapy or surgery for testicular non-seminoma: a population -based study,' Journal of Clinical Oncology, vol. 31, no. 30, pp. 3807-3814, 2013.

659 43. Fossa SD, Aass N, Winderen M, et al., 'Long-term renal function after treat-
660 ment for malignant germ-cell tumours. Annals of Oncology vol. 13, no. 2, pp. 222-
661 228, 2002.
662
663 44. Glendenning JL, Barbachano Y, Norman AR et al., 'Long-term neurologic and
664 peripheral vascular toxicity after chemotherapy treatment of testicular cancer, '
665 Cancer vol. 116, no. 10, pp. 2322-2331, 2010.
666 Brydoy M., Oldernburg J, klepp O et al., 'Observational study of prevalence of long-
667 term raynaud-like phenomena and neurological side effects in testicular cancer sur-
668 vivors, ' Journal of the National Cancer Institute, vol. 101, no.24, pp. 1682-1695,
669 2009.
670 45. O'Sullivan JM, Huddart RA, Norman AR, et al., 'Predicting the risk of bleomy-
671 cin lung toxicity in patients with germ cell tumours Annals Oncology, vol. 14, no.1,
672 pp. 91-96, 2003.
673
674 46. Dearnaley DP, Horwich A, A'Hern R et al., 'Combination chemotherapy with
675 bleomycin, etoposide, and cisplatin (BEP) for metastatic teratomas: long-term fol-
676 low-up. European Journal of Cancer, vol. 27, no. 6, pp. 684-691, 19991
677
678
679
680

681 47. Haughnes HS, Aaass N, Fossa SD, et al., 'Pulmonary function in long-term
682 survivors of testicular cancer,' Journal of Clinical Oncology, vol. 27, no. 17, pp.
683 2779-2786, 2009
684
685 48. Fossa SD, Gilbrt E, Dores GM et al., 'Non-cancer cases of death in survivors
686 of testicular cancer. Journal of National Cancer Institute, vol. 99, no. 7, pp. 533-
687 544, 2007.
688
689 49. Hyams AV, Hay-McCutcheon M, Scogin F, 'Hearing and quality of life in older
690 adults. Journal Clinical Psychology, J une 2018..
691
692 50. Matkin, ND, Wilcox MS, 'Considerations in the education of children with hear-
693 ing loss,' Paediatric Clinics of North America vol. 46, no.1, pp. 143-152, 1999.
694 51.
695
696 52. Bokemeyer C, Berger CC, Hartmann JT, et al., 'Analysis of risk factors for
697 cisplatin-induced ototoxicity in patients with testicular cancer. British Journal Can-
698 cer, vol. 77, no.8, pp. 1355-1362, 1998..
699
700 53. Oechsle K, Hartmann M, Mehnert A et al., 'Symptom Burden in long-term
701 germ cell tumour survivors,' Support Cancer Care, vol. 24, no.5, pp. 2243-2250,
702 2016.
703

704 54. Dahl AA, Haaland CF, Mykletun A et al., “Study of anxiety disorder and de-
705 pression in long-term survivors of testicular cancer, ‘ Journal of Clinical Oncology,
706 vol. 23, no.10, pp. 2389-2395, 2005.
707
708 55. Vehling S, Mehnert A, Hartmann M, et al., ‘Anxiety and depression in long-
709 term testicular germ cell tumour survivors,’ General Hospital Psychiatry, vol. 38,
710 pp. 21-25, 2016.
711
712 56. Shinn EH, Basen-Engquist K, Thornton B et al., ‘Health behaviors and de-
713 pressive symptoms in testicular cancer survivors, ‘Urology, vol. 69, no. 4, pp. 748-
714 753, 2007.
715
716 57. Smith AB, Butow P, Olver I et al., ‘The prevalence, severity, and correlates of
717 psychological distress and impaired health-related quality of life following treat-
718 ment for testicular cancer: a survivorship study, ‘ Journal of cancer survivorship,
719 vol. 10, no.2, pp. 223-233, 2016.
720
721 58. Parsons HM, Harlan LC, Lynch CF et al., Impact of cancer on work and edu-
722 cation among adolescent and young adult cancer survivors, Journal of Clinical On-
723 cology, vol. 30 no. pp. 2393-2400, 2012
724

59. Smith AW, Bellizzi KM, Keegan TH et al., 'Health- related quality of life of adolescent and young adult cancer patients in the United states: the AYA HOPE study, Frontiers in Oncology, vol. 3, no.75, pp.

60. Bellizzi KM, Smith A, Schmidt S, et al. Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) Study Collaborative Group. Positive and negative psychosocial impact of being diagnosed with cancer as an adolescent or young adult. Cancer. 2012; 118:5155–5162.

61. Carpentier MY, Fortenberry JD, Ott MA, Brames MJ, Einhorn LH. Perceptions of masculinity and self-image in adolescent and young adult testicular cancer survivors: implications for romantic and sexual relationships. Psycho-oncology. 2011; 20:738–745. [PubMed: 20878864]

62. Love B, Thompson CM, Knapp J. The need to be Superman: the psychosocial support challenges of young men affected by cancer. Oncol Nurs Forum. 2014; 41:E21–E27. [PubMed: 24368249]

63. Grinyer A. The biographical impact of teenage and adolescent cancer. Chronic Illn. 2007; 3:265– 277.

64. Psychology Interactive. [July 2, 2015] Social development: why it is important and how to impact it. http://www.edpsycinteractive.org/papers/socdev.pdf.

65. Nunes V, Cazzaniga G, Biondi A An update on PCR use for minimal residual disease monitoring in acute lymphoblastic leukemia. Expert Rev Mol Diagn. 2017 Nov;17(11):953-963. doi: 10.1080/14737159.2017.1377073. Epub 2017 Sep 21.

66. Palmer RD, Murray MJ, Saini HK, et al. Malignant germ cell tumors display common microRNA profiles resulting in global changes in expression of messenger RNA targets. Cancer research 2010:70(7):2911-2923.

67. Shenouda S, Alahari S. MicroRNA function in cancer: oncogene or a tumor suppressor? Cancer Metastasis Rev 2009:28(3-4):369-378.

68. Murray MJ, Halsall DJ, Hook CE, et al. Identification of microRNAs From the miR-371~373 and miR-302 clusters as potential serum biomarkers of malignant germ cell tumors. American Journal Clinical Pathology 2011:135(1):119-125.

69. Murray MJ, Bell E, Raby KL, et al. A pipeline to quantify serum and cerebrospinal fluid microRNAs for diagnosis and detection of relapse in paediatric malignant germ-cell tumours. Br J Cancer 2016:114(2):151-162

70. Cho JS, Kaimakliotis, Cary C, Masterson TA, Beck S, Foster R. Modifed retroperitoneal lymph node dissection for post-chemotherapy residual tumour: a long-term update. BJU Int 2001; 120(1): 104-108.

71. Heidenreich A, Pfister D, Witthuhn R, Thüer D, Albers P. Postchemotherapy retroperitoneal lymph node dissection in advanced testicular cancer: radical or modified template resection. Eur Urol. 2009; 55(1):217-24

72. Stepanian S, Patel M, Porter J. Robot-assisted Laparoscopic Retroperitoneal Lymph Node Dissection for Testicular Cancer: Evolution of the Technique. Eur Urol 2016, 70:661-227.

73. Cheney SM, Andrews PE, Leibovich BC, Castle EP. Robot-assisted retroperitoneal lymph node dissection: technique and initial case series of 18 patients. BJU Int 2015; 115:114–20.

74. Thomas BC, Lee EWYL, Coret HM. Robotic retroperitoneal lymph node dissection for non-seminomatous germ cell tumour in a centralised post-chemotherapy surgical practice. BJU Int 2018; 121 (S1): 27.

75. Einhorn LH, Williams SD. Combination chemotherapy with cis-dichlorodiammineplatinum(II) and adriamycin for testicular cancer refractory to vinblastine plus bleomycin. Cancer Treat Rep. 1978 Sep;62(9):1351-3.

76. Bokemeyer C, Kohrmann O, Tischler J, et al. A randomized trial of cisplatin, etoposide and bleomycin (PEB) versus carboplatin, etoposide and bleomycin

(CEB) for patients with ‘good-risk’ metastatic non-seminomatous germ cell tumors. Ann Oncol 1996;7:1015–102.

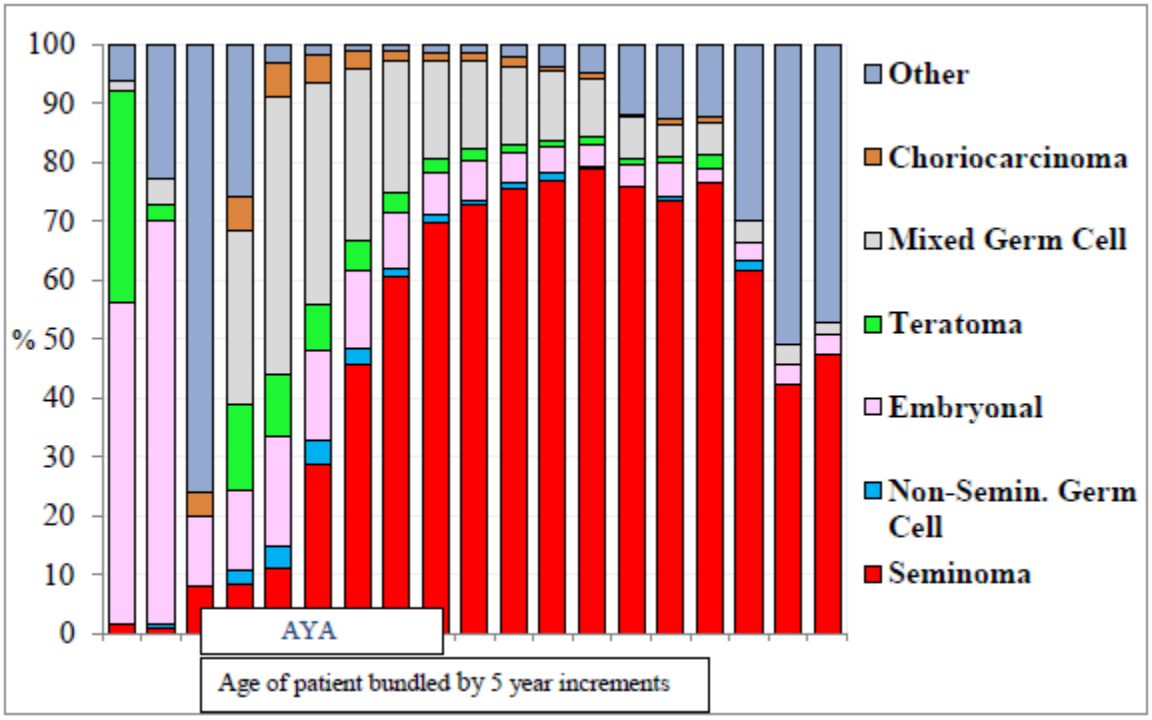
77. Horwich A, Sleijfer DT, Fossa SD, et al. Randomized trial of bleomycin, etoposide, and cisplatin compared with bleomycin, etoposide, and carboplatin in good-prognosis metastatic nonseminomatous germ cell cancer: A multi-institutional Medical Research Council/European Organization for Research and Treatment of Cancer Trial. J Clin Oncol 1997;15:1844–1852.

78. Bajorin DF, Sarosdy MF, Pfister DG, et al. Randomized trial of etoposide and cisplatin versus etoposide and carboplatin in patients with good-risk germ cell tumors: A multi-institutional study. J Clin Oncol 1993; 11:598–606.

79. Shaikh F, Nathan PC, Hale J, et al..Is there a role for carboplatin in the treatment of malignant germ cell tumors? A systematic review of adult and pediatric trials. Pediatr Blood Cancer. 2013 Apr;60(4):587-92.

80. Frazier AL, Stoneham S, Rodriguez-Galindo C, Et al. Comparison of carboplatin versus cisplatin in the treatment of paediatric extracranial malignant germ cell tumours: A report of the Malignant Germ Cell International Consortium. Eur J Cancer. 2018 Jul; 98:30-37.

817



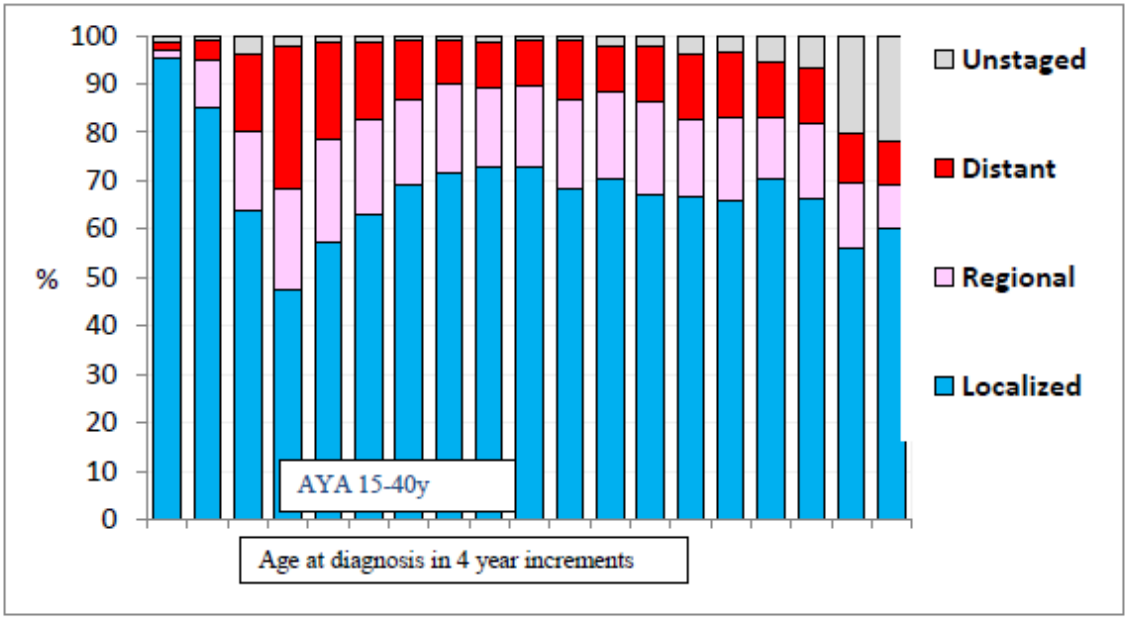
818

819 FIGURE 1 Histology Distribution of Testis Cancer, 2000-2011, SEER18, by Age

820

821

822



823

824 FIGURE 2 Distribution of Stage of Testis Cancer, SEER 18, 2000-2011, by Age

825

Author/s:
Stoneham, S; Murray, M; Thomas, B; Williamson, M; Sweeney, C; Frazier, L

Title:
AYA testis cancer: The unmet challenge.

Date:
2019-08

Citation:
Stoneham, S., Murray, M., Thomas, B., Williamson, M., Sweeney, C. & Frazier, L. (2019). AYA testis cancer: The unmet challenge.. Pediatr Blood Cancer, 66 (8), pp.e27796-. https://doi.org/10.1002/pbc.27796.