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Delivered relative dose intensity in adolescent and young adult germ cell tumours in England: Assessment of data quality and consistency from clinical trials compared to national cancer registration data

Nicola F. Hughes[1] | Kirsten J. Cromie[2] | Richard G. Feltbower[2] | Martin G. McCabe[3] | Dan Stark[1]

[1]Leeds Institute of Medical Research, School of Medicine, University of Leeds, Leeds, UK

[2]Leeds Institute for Data Analytics, School of Medicine, University of Leeds, Leeds, UK

[3]Division of Cancer Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK

Correspondence
Nicola F. Hughes, Leeds Institute of Medical Research, School of Medicine, University of Leeds, Leeds, UK.
Email: n.f.hughes@leeds.ac.uk

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Abstract

Adolescent and young adults (AYA) with germ cell tumours (GCT) have poorer survival rates than children and many older adults with the same cancers. There are several likely contributing factors to this, including the treatment received. The prognostic benefit of intended dose intensity is well documented in GCT from trials comparing regimens. However, evidence specific to AYA is limited by poor recruitment of AYA to trials and dose delivery outside trials not being well examined. We examined the utility of cancer registration data and a clinical trials dataset to investigate the delivery of relative dose intensity (RDI) in routine National Health Service practice in England, compared to within international clinical trials. Linked data from the Cancer Outcomes and Services Dataset (COSD) and the Systemic Anti-Cancer Therapy (SACT) dataset, and data from four international clinical trials were analysed. Survival over time was described using Kaplan-Meier estimation; overall, by age category, International Germ-Cell Cancer Collaborative Group (IGCCCG) classification, stage, tumour subtype, primary site, ethnicity and deprivation. Cox regression models were used to determine the fully adjusted effect of RDI on mortality risk. The quality of both datasets was critically evaluated and clinically enhanced. RDI was found to be well maintained in all datasets with higher RDIs associated with improved survival outcomes. Real-world data demonstrated several strengths, including population coverage and inclusion of sociodemographic variables and comorbidity. It is limited in GCT however, by the poor completion of data items enabling risk classification of patients and a higher proportion of missing data.

Abbreviations: ADI, actual dose intensity; AJCC, American Joint Committee on Cancer; AUC, area under the curve; AYA, adolescent and young adult; BEP, bleomycin, etoposide and cisplatin; CBOP/BEP, vincristine, cisplatin, bleomycin, etoposide, carboplatin; COSD, Cancer Outcomes and Services dataset; CTCAE, Common Terminology Criteria for Adverse Events; DI, dose intensity; EFS, event free survival; eGFR, estimated glomerular filtration rate; EORTC, European Organisation for Research and Treatment; EP, etoposide, cisplatin; FDA, Food and Drug Administration; GCT, germ cell tumours; HES, Hospital Episode Statistics; ICD, International Classification of Diseases; IGCCC, International Germ Cell Consensus Classification; IMD, Index of Multiple Deprivation; NCRAS, National Cancer Registration and Analysis Service; NHS, National Health Service; NICE, National Institute of Clinical Excellence; ONS, Office for National Statistics; OS, overall survival; RCT, randomised controlled trials; RDI, relative dose intensity; SACT, Systemic Anticancer Therapy dataset; SDI, standard dose intensity.

KEYWORDS
chemotherapy, clinical trials, germ cell tumours, population data, survival

What's new?

Despite high survival rates for most germ cell tumour (GCT) patients, adolescents experience worse outcomes relative to children and young adults. Moreover, it is unclear whether specific treatments are more or less beneficial in terms of adolescent GCT survival. Here, the impact of relative dose intensity (RDI) on survival was examined among adolescent and young adult (AYA) patients with GCTs treated in clinical trials compared to routine practice. Maintaining chemotherapy RDI was associated with improved survival in both settings, though a stronger effect was observed in clinical trials. Further investigation could identify parameters for dose reduction in adolescent GCT patients.

1 | BACKGROUND

Germ cell tumours (GCT) are the most common malignancy in the male adolescent and young adult (AYA) cancer population, aged 15 to 39 years, constituting approximately 10% of all tumours.[1] They are often considered the success story of young onset cancers with 5-year survival rates of over 95% in localised tumours and 70% to 90% in those that have metastasised.[2] Despite this overall achievement, adolescents with GCT have worse outcomes compared to younger children and older young adults. A recent study using retrospective clinical trials data found adolescent males (11-18 years) to have a 5-year event free survival (EFS) of 72% compared to children aged 0 to 10 years (90%) and young adults aged 18 to 30 years (88%).[3] The unique biological, clinical and social needs of AYA have been well documented as contributing factors to the survival lag seen in these patients.[4] However, research focusing upon the treatment delivered has had less attention.

The cisplatin-based bleomycin, etoposide and cisplatin (BEP) chemotherapy regime[5] remains the gold standard of treatment in adult GCT. Within the adult population randomised controlled trials (RCTs) have compared regimes with high dose intensity (DI) to lower DI and found higher DI regimes to be more effective in all clinical risk groups and for each chemotherapy drug.[6,7] DI is defined as the quantity of a chemotherapy drug (eg, mg per m^2) administered per unit time (eg, weeks) and is defined by clinical trial protocols or clinical guidelines. In practice however, the desired dose intensity is not always reached due to patient toxicity requiring dose delays or reductions. A more accurate assessment is relative dose intensity (RDI), described by Hryniuk as the ratio of the DI of chemotherapy that is actually delivered, compared to the standard DI defined by trial protocol.[8,9] There are studies in other AYA cancers indicating that reduction in RDI may be associated with poorer outcomes.[10,11] Maintaining dose intensity can be problematic and costly to both the patient and health services. Short-term barriers include high levels of toxicity, which can be life threatening and require admission to high-level care. In the long term, there is the need to avoid irreversible end organ damage, which will negatively impact long-term health and quality of life. It is crucial therefore, that treatment is delivered by experienced clinical teams.[12]

Clinical trial recruitment has long been problematic for the AYA population,[13] in part due to these patients falling between the age cut offs of paediatric and adult trials. Participation rates of AYA in clinical trials is estimated at between 5% to 34% compared to over 90% in children.[14] Underrepresentation of AYA in GCT trials was evidenced by Shaikh et al. who pooled all paediatric trials from North America and the UK over the last 30 years and found only 109 male adolescent participants with metastatic GCT (3).

The use of routine health data for research purposes has been gathering momentum in recent years. Within the field of oncology cancer registration data holds great potential, especially when linked to other, more detailed, datasets. Given the complexities of the AYA population and the poor representation in clinical trials, we set out to explore the utility of cancer registration data to investigate the delivery of RDI in routine practice within the National Health Service (NHS) in England. Through comparison to a clinical trials dataset, we aimed to assess the quality and extent of data items available, strengths of the datasets, limitations of use and areas for improvement.

2 | METHODS

2.1 | Data sources

2.1.1 | National Cancer Registration and Analysis Service

Data from the Cancer Outcomes and Services dataset (COSD)[15] and the Systemic Anticancer Therapy dataset (SACT),[16] both held by the National Cancer Registration and Analysis Service (NCRAS) were linked to create a dataset of patients diagnosed in England with a GCT when aged 12 to 29 years. COSD holds patient details of all cancers diagnosed and resident in England, while the SACT dataset comprises chemotherapy prescribing data from all treating NHS hospital trusts in England.

Inclusion criteria were:

- Patients registered with a malignant GCT in the NCRAS dataset and diagnosed aged 12 to 29 years between first April 2014 and 31st December 2018. This period reflected the most up to date SACT data available at the time of data extraction.

- Only patients who had received first line treatment recorded in SACT were included, defined as individuals who received chemotherapy within 60 days of diagnosis.
- Patients who had received BEP (bleomycin, etoposide, cisplatin), EP (etoposide, cisplatin) and CBOP/BEP (vincristine, cisplatin, bleomycin, etoposide, carboplatin) chemotherapy, enabling comparison of bleomycin, etoposide and cisplatin delivery to that within clinical trials.
- Only male patients to improve comparability with the clinical trials dataset.

Exclusion criteria included:

- Any registration record missing both height and weight at the start of treatment.
- Patients where administration dose of drug, number of days to administration of drug or drug name were missing.
- Those who had received less than one cycle of treatment.
- Patients who had received first line carboplatin. These patients were excluded from analysis due to carboplatin dosing using area under the curve (AUC) methods. AUC requires an estimated glomerular filtration rate (eGFR) value, which was not available in the dataset.

2.1.2 | Clinical trials

Patient level data was obtained from four international European Organisation for Research and Treatment (EORTC) clinical trials: 30873, 30895, 30974 and 30983, examining mainly intermediate and poor prognosis patients (Table S1). Patients were excluded if the required data items for RDI calculation were missing. The trials combined recruited from 1987 to 2009, therefore there was no overlap in patients between the two cohorts.

2.2 | Patient and treatment related variables

The linked NCRAS data were explored and data for patient sex, age at diagnosis (years), stage, ethnicity based on categories from the 2001 Census,[17] deprivation, year of diagnosis, region where the patient was living when the tumour was diagnosed and treating speciality were extracted. Germ cell subtype was categorised using International Classification of Diseases for Oncology version 2 (ICD) morphology codes. Stage was derived from TNM imaging, TMN pathology in COSD and stage at the start of treatment in SACT, to maximise completeness. Treating specialty codes were provided in accordance with the NHS data dictionary[18] and labelled as either adult or paediatric. Population weighted quintiles of the English Index of Multiple Deprivation (IMD) 2015[19] were provided by NCRAS as the measure of socioeconomic deprivation. Vital status at the time of censoring, the number of days from diagnosis to vital status and year of death were extracted to enable survival analysis.

Where available the same data items were extracted from the clinical trials dataset with the addition of data items required for the International Germ Cell Consensus Classification (IGCCC).[20-22] This risk classification is based on age, histological subtype, primary site, site of metastases and tumour marker levels. Within the NCRAS cohort, only age, histological subtype and primary site were available to request. While the presence of lymph node and visceral metastases were given as part of the TNM pathology data this was poorly completed and did not provide information regarding the site, as required for the IGCCC. We therefore estimated the risk classification of patients in the NCRAS cohort according to the protocol treatment they commenced. Patients were classed as good risk if they had received between one and three cycles of BEP or up to four cycles of EP; intermediate risk if they received more than three cycles of BEP; and poor risk if they received CBOP/BEP chemotherapy.[2,21,22] Stage was provided according to Royal Marsden classification system in one trial and in line with the American Joint Committee on Cancer (AJCC) system in the remaining three. To provide consistency in the dataset all staging data was converted to the AJCC.

2.3 | Treatment toxicity

Data related to toxicity of treatment was explored and summarised. Toxicity data in the clinical trials dataset were given for each individual chemotherapy drug. While details relating to organ specific toxicity as per Common Terminology Criteria for Adverse Events (CTCAE) grade were available, only data relating to dose reduction, treatment delay and early cessation of treatment were extracted. This enabled comparison with the NCRAS cohort where toxicity data were limited to binary variables of regime modifications; dose reduction, treatment stopped early and treatment delay with outcomes yes, no or missing possible. Cause of death was extracted from both cohorts as a marker of toxicity, derived either from the trial follow-up data or from the Office for National Statistics (ONS)[17] death certificate data for the NCRAS cohort. Censor date for the ONS data was 28th February 2020.

2.4 | RDI calculation

The treatment variables used for RDI analysis were those providing treatment regime, drug name, numbers of days from diagnosis to administration date of chemotherapy, actual dose of drug per administration and cycle number. Patient height and weight at the start of regimen were used to calculate an individual's body surface area. Patients missing both height and weight were excluded. In instances where data on either height or weight were unavailable, these were assumed to be missing at random and imputed using predictive mean matching. This enabled calculation of the standard dose of chemotherapy a patient would have received as per the relevant protocol, without dose adjustments. Treatment data were reviewed by a clinician to ensure adequacy of data quality. Actual doses per administration were converted to standard units where required; mg/m^2 for cisplatin and etoposide, IU for bleomycin.

The RDI of chemotherapy received by each patient was calculated by dividing the actual dose intensity (ADI) of treatment received

by the expected standard dose intensity (SDI). The ADI was the actual total dose of chemotherapy received divided by the number of weeks it was given over. The SDI was calculated by dividing the standard dose that individual should have received, assuming no toxicity, by the time over which it should have been given, as determined either by the trial protocol (Table S1) or that which is received as per standard care.[23] RDI was expressed as a decimal with 1.0 indicating that treatment had been received 100% in accordance with protocol. RDI was categorised into those that had received less than 0.75, 0.75 to 0.84, 0.85 to 0.94 and greater than 0.95. Within the literature there is variation as to what constitutes an adequate RDI. The cut offs used were chosen to align with those used in previous studies.[10,24-27] The majority of patients (93.9%) in the NCRAS cohort were treated within an adult speciality and therefore all patients were analysed in comparison to standard adult chemotherapy protocols.

2.5 | Statistical analysis

Survival over time was described using Kaplan-Meier estimation[28] at 1, 2 and 5 years. Survival rates were examined overall and by age category, IGCCG risk classification, stage, tumour subtype, primary site, ethnicity and deprivation. Cox regression models[29] were used to determine the effect of RDI as a continuous variable on mortality risk, in the two cohorts separately. The models were adjusted for confounding using the minimal sufficient adjustment set as informed by causal inference methods[30] using directed-acyclic graphs (Figure S1) within DAGitty software.[31] Only complete cases were analysed. Statistical analysis was performed using Stata 16.[32]

3 | RESULTS

3.1 | Patient characteristics

Data for 1503 GCT patients were received from NCRAS. Of these patients, 138 were excluded for missing treatment data, 107 due to missing both height and weight, 226 were excluded as they had received carboplatin first line and 73 received a first line regime other than those under investigation. There were 90 patients excluded as they had received less than one cycle of chemotherapy and 48 female patients excluded. A total of 817 patients therefore met the inclusion criteria from the NCRAS data. From the clinical trials data 799 patients were included, and nine excluded for missing treatment data. The patient characteristics of both cohorts and case numbers can be found in Table 1. The flow of patients in both datasets are shown in Figure 1.

The median age at diagnosis in the clinical trials dataset was 26.7 years (IQR, 22.5-31.4) compared to 25.0 years (IQR, 22-27) in the NCRAS cohort. The age range was 14.8 to 39.8 years in the clinical trials data and 12 to 29 years for the NCRAS cohort. Mixed was the most common histological subtype in the NCRAS cohort (47.4%) compared to nonseminoma in the clinical trials patients (72.6%). Testis was the most common primary site (85.6% and 98.3%) in the clinical trials and NCRAS cohorts, respectively.

There was a higher proportion of missing data for stage in the NCRAS cohort (45.4%) compared to the clinical trials data (1.4%). Within the clinical trials data, 11 (1.4%) patients were classified as good prognosis according to the IGCCC, 470 (58.8%) intermediate prognosis and 296 (37%) poor prognosis. 668 (81.8%) patients in the NCRAS cohort were classified as good prognosis, 108 (13.2%) as intermediate prognosis and 19 (2.3%) as poor prognosis.

Patient ethnicity and deprivation status were not recorded in the clinical trials data. In the NCRAS cohort white ethnicity was the most common group (85.2%). The highest proportion of patients fell into the least deprived fifth of the IMD (24.6%).

3.2 | Treatment toxicity and cause of death

For the analysis of toxicity, the clinical trials were treated as individual datasets and summarised in Table S2. Two clinical trials provided dose reductions, recording 67.5% and 41.3% respectively, compared to 3.1% in the NCRAS data. NCRAS data had a higher proportion of missing data for this item (23.3%) than clinical trials (0%, 1%, respectively). All four clinical trials provided treatment delay data, occurring in 20%, 6.8%, 17.8% and 13.1% of patients compared to 6.4% in NCRAS, although there was a higher level of missing data in the NCRAS cohort (39%) limiting interpretation. Treatment stopped early data was provided in trial 30 895 and reported in 19.3% of cases compared to 10.4% in the NCRAS cohort; levels of missing data were 3% and 14.9%, respectively.

Thirty-five patients (4.3%) died in the NCRAS cohort with a cause of death provided on ONS death certificate for 33 (94%) patients. Of these, 89% (n = 24) were recorded as being directly related to malignancy, and one death from complication post procedure. Three patients died of accidental causes. There were 6 causes of death attributed to toxicity including neutropenic sepsis (n = 2), pneumonia (n = 3) and liver failure (n = 1). Only three deaths occurred within 30 days of the last recorded chemotherapy, all of which were recorded as being cancer related. There were 151 (18.9%) deaths in the clinical trials dataset; malignant disease was recorded as the cause of death for 78.8%, toxicity for 13.9% and other for 4.7%.

3.3 | Achieved RDI and survival analysis

Comparison of median achieved RDIs (Table 2) showed high RDIs were delivered in both the clinical trials and NCRAS cohorts for each drug (bleomycin: clinical trials 0.97 (IQR: 0.85-1.0) vs NCRAS 1.02 (IQR: 0.90-1.06), cisplatin: clinical trials 0.98 (IQR: 0.93-1.0) vs NCRAS 1.01 (IQR: 0.92-1.08), etoposide: clinical trials 0.96 (IQR: 0.88-1.0) vs NCRAS 1.00 (IQR: 0.89-1.06). Within the clinical trials cohort a higher proportion of patients received an RDI of 0.85 to 0.94 (Figure 2) in comparison to the NCRAS cohort for all drugs (bleomycin; 53.2% vs 11.2%, etoposide; 53.4% vs 13.9%, cisplatin 60.3% vs 10.6%). A lower

TABLE 1 Germ cell patient characteristics within the clinical trials and NCRAS datasets.

		Clinical trials, n (%)	NCRAS, n (%)
Total number patients		799	817
Total number of deaths		151 (18.9)	35 (4.3)
Age at diagnosis (years)	17 or under	31 (3.9)	33 (4.0)
	18-23	228 (28.5)	282 (34.6)
	24-29	268 (33.5)	502 (61.4)
	30 or over	272 (34.1)	
Tumour subtype	Seminoma	27 (3.4)	75 (9.2)
	Nonseminoma	580 (72.6)	260 (31.8)
	Yolk Sac		13
	Embryonal		164
	Choriocarcinoma		13
	Teratoma		70
	Mixed	113 (14.1)	387 (47.4)
	Other		95 (11.6)
	Unknown/missing	79 (9.9)	-
Stage[a]	1	1 (0.1)	78 (9.5)
	2	139 (17.4)	175 (21.4)
	3	648 (81.1)	46 (5.6)
	4	0 (0)	147 (18.0)
	Missing	11 (1.4)	371 (45.4)
IGCCC risk classification[b,c]	Good	11 (1.4)	668 (81.8)
	Intermediate	470 (58.8)	108 (13.2)
	Poor	296 (37)	19 (2.3)
	Not possible	22 (2.8)	22 (2.7)
Primary site	Abdomen/retroperitoneal	40 (5)	4 (0.5)
	Testis	684 (85.6)	803 (98.3)
	Mediastinal	39 (4.9)	10 (1.2)
	Other	22 (2.8)	-
	Missing	14 (1.8)	0
Site metastatic disease			
Lymph nodes			
Mediastinal			
	Yes	218 (27.3)	[d]
	No	566 (70.8)	[d]
Supraclavicular	Missing	15 (1.9)	[d]
	Yes		
	No	125 (15.6)	[d]
	Missing	660 (82.6)	[d]
Abdominal		14 (1.8)	[d]
	Yes		
	No	444 (55.6)	[d]
	Missing	341 (42.7)	[d]
		14 (1.7)	[d]
	Yes		
Visceral	No		
Lung	Missing		

TABLE 1 (Continued)

		Clinical trials, n (%)	NCRAS, n (%)
	Yes	479 (60)	[d]
	No	314 (39.3)	[d]
	Missing	6 (0.7)	[d]
Other		74 (9.3)	[d]
		708 (88.7)	[d]
		16 (2)	[d]
Tumour markers	HCG (IU/L)		
	<5000	492 (61.6)	[d]
	≥5000 and ≤50 000	192 (24)	[d]
	>50 000	115 (14.4)	[d]
	AFP (ng/mL)		
	<1000	2 (0.2)	[d]
	≥1000 and ≤10 000	59 (7.4)	[d]
	>10 000	738 (92.4)	[d]
	LDH		
	<1.5 × ULN	237 (29.7)	[d]
	≥1.5 × ULN ≤10 × ULN	416 (52.1)	[d]
	>10 × ULN	146 (18.3)	[d]
Ethnicity	White/White Irish	[d]	696 (85.2)
	Other	[d]	117 (14.3)
	Missing	[d]	4 (0.5)
Socioeconomic status	1	[d]	139 (17)
(IMD quintile)[e]	2	[d]	133 (16.3)
	3	[d]	164 (20.1)
	4	[d]	180 (22)
	5	[d]	201 (24.6)

[a]Different staging systems applied in trials and NCRAS data.
[b]International Germ-Cell Cancer Consensus Classification.[20]
[c]Coded according to treatment received as in methods.
[d]Data item not available.
[e]English Index of Multiple Deprivation (IMD) 2015.[19]

proportion of patients in the clinical trials cohort however received a RDI greater than 0.95, compared to the NCRAS cohort (bleomycin; 27.6% vs 70.2%, etoposide; 27.6% vs 66.%, cisplatin 32% vs 70.3%).

Median survival time for those that died in the clinical trials cohort was 0.95 years (IQR: 0.50-1.62 years) with an overall median follow up time of 4.85 years (IQR: 3.75-6.5 years). In the NCRAS cohort median survival time for those that died was 1.14 years (IQR, 0.62-1.62 years), with an overall median follow up time of 4 years (IQR: 2-5 years).

Overall survival (OS) was lower in the clinical trials dataset (1 year 90% and 5 year 80%) compared to NCRAS (1 year 98% and 5 year 95%) (Table 3). In the clinical trials dataset those aged 30 years or over had the lowest 5-year survival (78%) followed by 18- to 23-year-olds (80%). In the NCRAS cohort 5-year survival was highest in those 17 years and under (97%) with no difference seen in patients aged 18 to 23 (95%) or 24- to 29-year-olds (95%). These differences are demonstrated in the Kaplan-Meier survival estimates (Figure S2). When age was categorised into under 18 years and over 18 years, to enable comparison with the literature, 5-year survival was higher for those under 18 years compared to those over 18 years in both the NCRAS cohort; (97% vs 95%) and in the clinical trials data; (84% vs 81%) (Table S3).

Poorer survival rates were seen at all time points with an increase in IGCCC risk category within the NCRAS patients (1 year; good 99%, intermediate 96%, poor 84%, 2 years; good 98%, intermediate 92%, poor 68%, 5 years; good 97%, intermediate 92%, poor 51%). These findings were also seen in the clinical trials patients (Figure S2), providing some validation for the clinical estimation of risk grouping we applied.

There was a trend of lower survival estimates associated with increasing stage in the NCRAS data at 1 year (stage 1; 100%, stage 2; 99%, Stage 3; 98%, stage 4; 98%) and 5 years (stage 1; 99%, stage 2; 98%, Stage 3; 94%, stage 4; 89%).

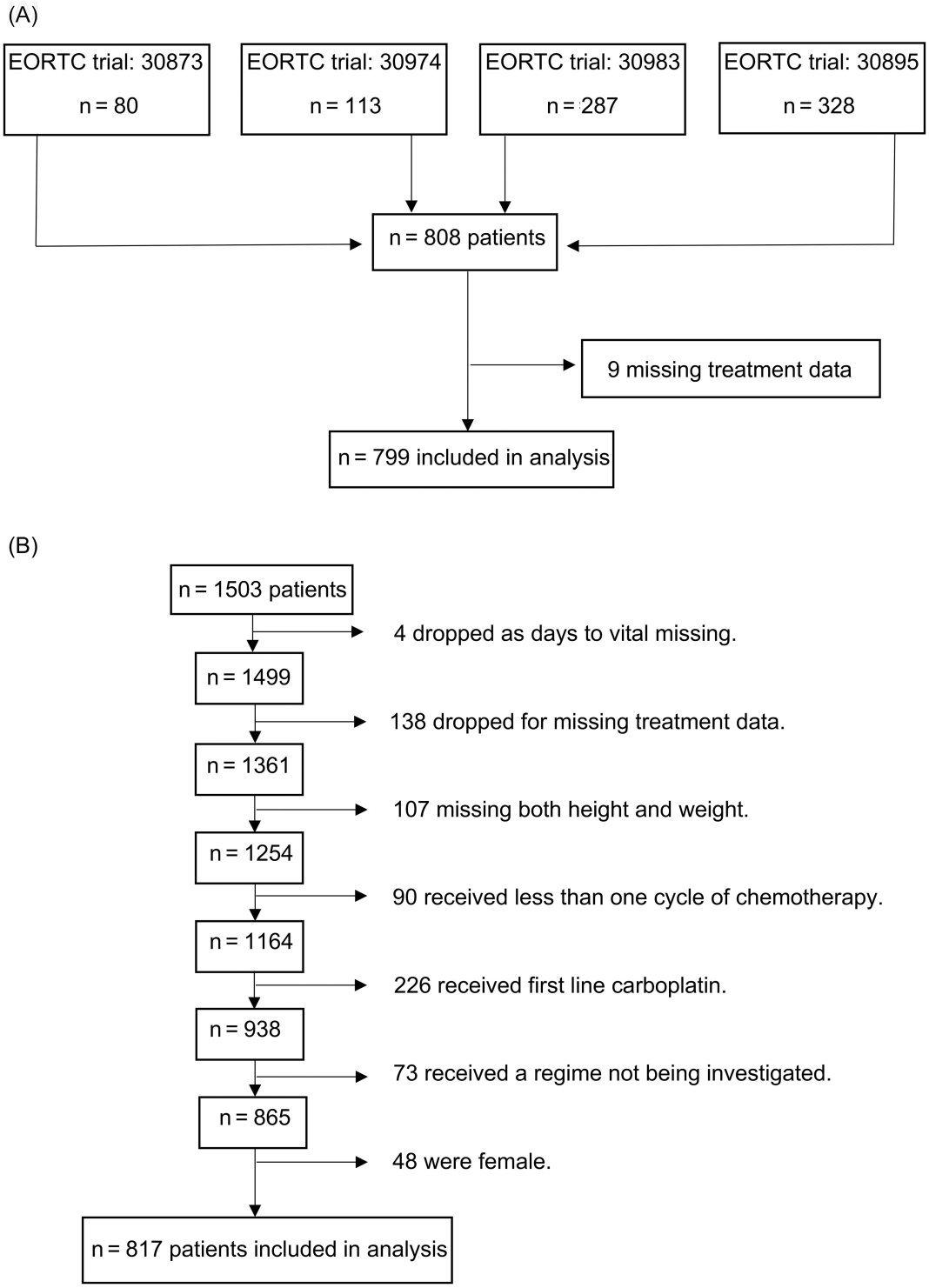

FIGURE 1 Consort diagram demonstrating patient flow in the clinical trials cohort (A) the NCRAS cohort (B).

	Clinical trials		NCRAS	
	Median RDI achieved	IQR (25%-75%)	Median RDI achieved	IQR (25%, 75%)
Bleomycin	0.97	0.85-1.0	1.02	0.90-1.06
Cisplatin	0.98	0.93-1.0	1.01	0.92-1.08
Etoposide	0.96	0.88-1.0	1.00	0.89-1.06

TABLE 2 The median achieved relative dose intensity and associated interquartile range (IQR) within the clinical trials and National Cancer Registration and Analysis Service datasets.

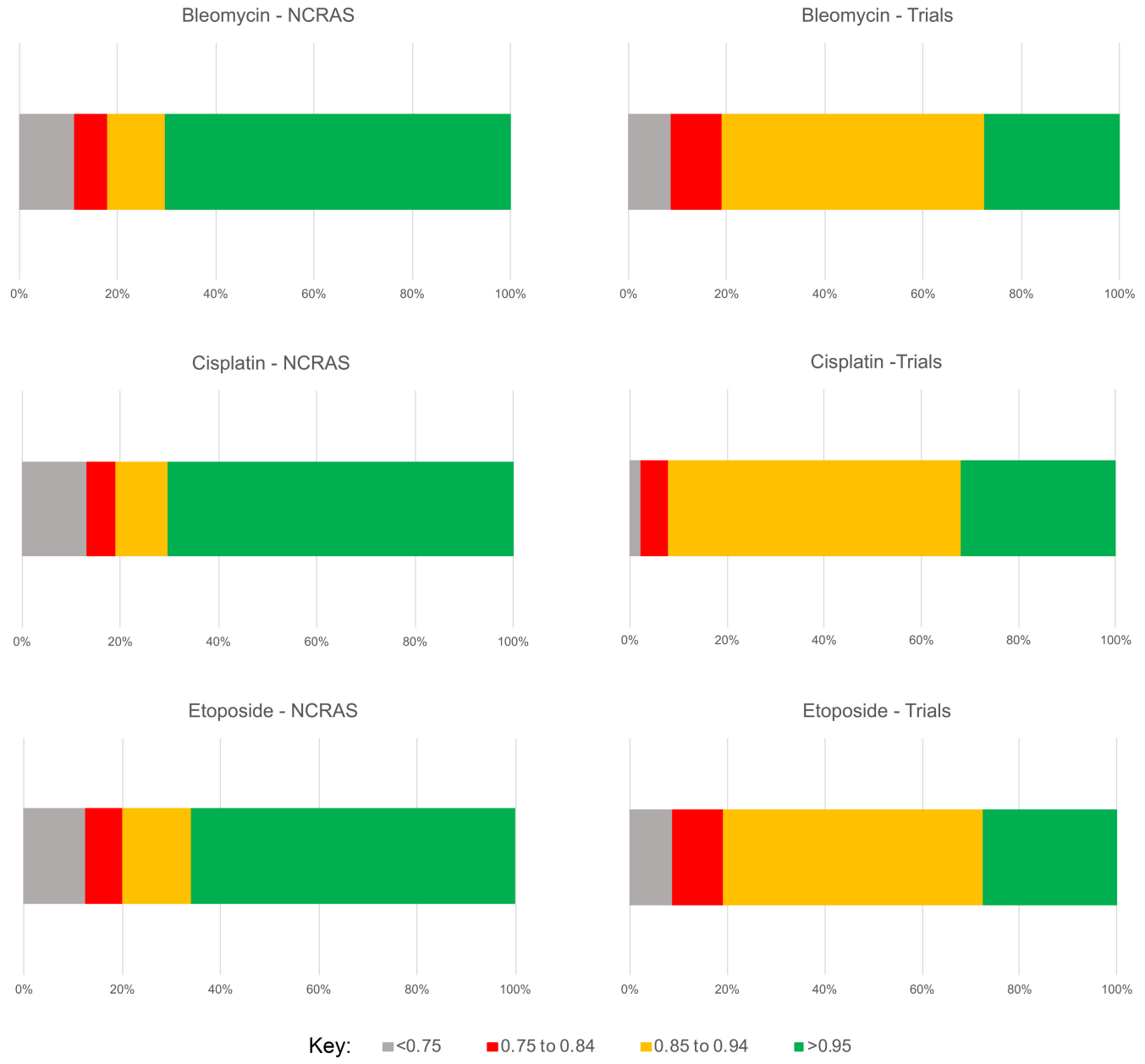

FIGURE 2 Bar charts demonstrating the proportion of patient achieving each category of relative dose intensity.

Ethnicity and socioeconomic status data were only available within the NCRAS cohort. Evidence was seen of lower survival in patients of Asian ethnicity (1 year 96% and 5 years 86%). No clear effects were seen by level of deprivation.

Multivariable regression showed that increasing RDI was associated with a lower risk of death (Table 4) in both datasets. In the clinical trial dataset those patients who received higher RDI had a lower risk of death for; bleomycin (HR: 0.21, 95% CI 0.08-0.54), cisplatin (HR: 0.09, 95% CI 0.02-0.44) and etoposide (HR: 0.18, 95% CI 0.06-0.55). In the NCRAS cohort the same pattern was noted with a similar effect for bleomycin; (HR: 0.26, 95% CI 0.07-1.04) but less strongly for cisplatin (HR: 0.87, 95% CI 0.44-1.72) and etoposide (HR: 0.88, 95% CI 0.33-2.34). This pattern remained when only the intermediate and poor risk patient subsets were analysed in the NCRAS dataset, enabling comparison with the trials data; the association strengthened for etoposide (HR: 0.75, 95% CI 0.18-3.20), weakened for bleomycin (HR: 0.57, 95% CI 0.13-2.49) and remained unchanged for cisplatin (HR: 0.86, 95% CI 0.35-2.13). Further sensitivity analyses can be found in Table S4.

4 | DISCUSSION

This is the first study to compare prescribing practice and data quality within clinical trials and routine care with regards to RDI in GCT and evaluate the impact on survival outcomes. While other population-

TABLE 3 Kaplan-Meier 1, 2 and 5-year survival estimates presented for clinical trials and National Cancer Registration and Analysis Service cohorts, both overall and by clinical and demographic variables.

	Clinical trials % (95% CI)			NCRAS % (95% CI)		
	1 year	2 years	5 years	1 year	2 years	5 years
Overall	90 (88-92)	84 (81-86)	80 (77-83)	98 (97-99)	96 (95-97)	95 (93-96)
Age category at diagnosis (years)						
17 or under	97 (79-100)	97 (79-100)	84 (61-94)	100	97 (80-100)	97 (80-100)
18-23	88 (82-92)	82 (76-87)	80 (73-85)	98 (95-99)	95 (91-97)	95 (91-97)
24-29	91 (88-94)	85 (80-89)	83 (78-87)	98 (96-99)	97 (95-98)	95 (92-97)
30 or over	89 (85-92)	82 (77-86)	78 (73-83)	–	–	–
IGCCC risk						
Good	100	100	–	99 (98-100)	98 (97-99)	97 (95-98)
Intermediate	95 (93-97)	92 (89-94)	89 (86-92)	96 (90-99)	92 (85-96)	92 (85-96)
Poor	82 (77-86)	71 (66-76)	67 (60-72)	84 (59-95)	68 (42-84)	51 (17-77)
Stage						
1	100	100	100	100	99 (91-100)	99 (91-100)
2	99 (94-100)	96 (90-98)	95 (89-97)	99 (96-100)	98 (95-99)	98 (95-99)
3	88 (85-90)	81 (77-84)	77 (73-80)	98 (86-100)	96 (86-100)	94 (78-99)
4	–	–	–	98 (94-99)	91 (85-95)	89 (82-94)
Tumour subtype						
Seminoma	93 (74-98)	85 (65-94)	77 (55-89)	100	99 (91-100)	99 (91-100)
Nonseminoma	91 (88-93)	84 (81-87)	81 (77-84)	97 (94-99)	96 (93-98)	95 (91-97)
Mixed	78 (51-91)	72 (46-88)	72 (46-88)	99 (98-100)	98 (96-99)	98 (96-99)
Other	–	–	–	95 (88-98)	85 (76-91)	78 (63-88)
Unknown/missing	77 (64-86)	70 (57-80)	68 (54-78)	–	–	–
Primary site						
Abdomen/retroperitoneal	85 (70-93)	77 (61-88)	75 (58-85)	75 (13-96)	75 (13-96)	–
Testis	93 (91-95)	87 (84-89)	84 (81-87)	99 (97-99)	97 (95-98)	95 (93-97)
Mediastinal	57 (39-71)	45 (29-60)	37 (21-54)	80 (41-95)	64 (23-87)	–
Other	73 (49-87)	57 (34-75)	–	–	–	–
Missing	100	100	100	100	100	–
Ethnicity[a]						
White	–	–	–	98 (97-99)	97 (95-98)	95 (93-97)
Mixed	–	–	–	100	100	–
Asian	–	–	–	96 (85-99)	86 (72-94)	86 (72-94)
Black	–	–	–	100	100	–
Other	–	–	–	98 (88-100)	98 (88-100)	98 (88-100)
Deprivation quintile[a,b,c]						
1—least deprived	–	–	–	98 (93-99)	96 (91-98)	96 (91-98)
2	–	–	–	99 (94-100)	96 (91-98)	94 (87-97)
3	–	–	–	96 (91-98)	96 (91-98)	96 (91-98)
4	–	–	–	100	98 (95-99)	96 (90-99)
5—most deprived	–	–	–	99 (95-100)	95 (91-97)	93 (88-96)

[a]Ethnicity and deprivation quintile were not provided for the clinical trials cohort.
[b]Deprivation indicator is the English Index of Multiple Deprivation (IMD) 2015.[19]
[c]International Germ-Cell Cancer Consensus Classification.[20]

based studies have looked at treatment delivered[33-35] few have calculated the actual DI delivered using population level data. We have found that chemotherapy RDI is being maintained in patients within NHS care in England at similar levels to those seen in clinical trials and other single centre studies, but with greater variation.[35] This is a positive reflection of the specialist network of AYA centres in England put

TABLE 4 Hazard ratios (HRs) and 95% confidence intervals (CIs) from Cox regression models presenting the association between RDI received and risk of death in germ cell tumour patients within the clinical trials and National Cancer Registration and Analysis Service cohort.

Clinical trials						NCRAS (all risk categories)						NCRAS (intermediate and poor prognosis only)					
Chemotherapy drug	Adjusted[a]			Unadjusted		Chemotherapy drug	Adjusted[b]			Unadjusted		Chemotherapy drug	Adjusted[b]			Unadjusted	
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Bleomycin (n = 652)	0.21	0.08-0.54	.00	0.13	0.05-0.31	.00	Bleomycin (n = 769)	0.26	0.07-1.04	.06	0.27	0.07-1.04	.06	Bleomycin (n = 154)	0.57	0.13-2.49	.46	0.65	0.16-2.64	.55
Cisplatin (n = 739)	0.09	0.02-0.44	.00	0.06	0.01-0.31	.00	Cisplatin (n = 794)	0.87	0.44-1.72	.69	0.86	0.44-1.69	.67	Cisplatin (n = 145)	0.86	0.35-2.13	.75	0.75	0.28-1.99	.56
Etoposide (n = 730)	0.18	0.06-0.55	.00	0.17	0.05-0.59	.00	Etoposide (n = 798)	0.88	0.33-2.34	.80	0.88	0.34-2.26	.79	Etoposide (n = 144)	0.75	0.18-3.20	.70	0.68	0.16-3.00	.62

[a]Adjusted for age and IGCCCG classification.
[b]Adjusted for age, dose adjusted for comorbidity, ethnicity, deprivation quintile, sex and region treatment received in.

in place in response to the publication of 'Guidance on Improving Outcomes in Children and Young People with Cancer' by the National Institute of Clinical Excellence (NICE) in 2005.[36] Our results show some variation in treatment received. Fewer patients received an RDI over 0.95 in clinical trials compared to routine practice. This may reflect dose reductions being driven by strict trial protocols as opposed to clinical experience alone and is supported by a greater number of treatment modifications being recorded in the clinical trials cohort compared to the NCRAS cohort. It may also be the result of clinical trials excluding patients due to comorbidities (Table S1). A higher overall proportion of patients received an RDI of over 0.75 in clinical trials. One possible reason for this is that support given when participating in clinical trials may enable patients to tolerate higher dose intensities.[37] In addition, within the busy NHS setting, treatment timings may need to be altered according to the availability of resources. Although we tried to identify and exclude patients with missing treatment data in the analysis, the possibility of incomplete treatment data should also be considered as a cause of the higher proportion of patients receiving an RDI of less the 0.75 in the NCRAS cohort. The historical nature of some of the trials should be noted with the earliest trial included starting in 1987. The BEP protocol has changed little over this time with limited effect on efficacy[38] however G-CSF achieved United States Food and Drug Administration (FDA) approval in 1991 which could explain some of the variations seen between the two cohorts. While we are satisfied that the clinical trials dataset provides a valid comparison to the real-world data caution is required when making comparisons to historical trials.[39] In keeping with other research findings,[6,7] an association of maintaining dose intensity with survival was demonstrated for all drugs in both patient cohorts. The hazard ratios were suggestive of a stronger association in the clinical trials cohort, compared to those in the NCRAS cohort, most of these patients received an RDI in the category of 0.85 to 0.94 (Figure 2). A similar population-based study found patients to have 5-year OS rates of 95% despite 44% receiving dose modifications,[34] it may therefore be that RDIs within this range have the greatest survival benefit.

A strength of our study is our utilisation of data linkage between COSD and SACT data to create a detailed treatment dataset for AYA patients. While the utility of SACT data in the research of adult solid tumours has been demonstrated[40] poorer ascertainment of the treatment data in children, teenagers and young adults (CTYA) is a known limitation.[16,41] This is the first published research we know of to detail the analysis possible with SACT data alongside structured clinical interpretation. In addition, we have demonstrated the many strengths that the NCRAS data holds for research purposes. Firstly, the availability and completeness of sociodemographic details provides the ability to investigate health inequalities in the AYA population, such as ethnicity as we have shown. Not only is this data lacking in the clinical trials data but is also limited by difficulties in the recruitment of certain patient subgroups to trials.[13] Cancer registration data also enables the impact of comorbidities, often excluded from trial participation, on treatment delivered to be assessed. Within NCRAS data, a comorbidity adjustment indicator indicates whether coexisting comorbidities

were considered for dose or regime. This, along with ECOG performance status, provides data on how patients ineligible for a trial are treated. Further linkage to Hospital Episode Statistics (HES) admissions and primary care data can extend this in future[42] and although outside the scope of his paper, will be beneficial for research in the increasing number of older patients developing GCT. A further strength of the NCRAS data is that cause of death data is captured directly from the ONS,[17] providing almost complete ascertainment, which is not always possible in clinical trials due to loss to follow-up.

Our study has some weaknesses, which we considered in our interpretation. The two datasets differ in some areas, notably the greater proportion of good prognosis patients in the NCRAS cohort. This is the result of comparing a population dataset (NCRAS) to more focused clinical trials datasets and is a likely reason for the better survival outcomes seen in the real-world dataset. We found that the available NCRAS data has limitations for use in AYA-specific cancers, particularly in relation to data for risk stratification. Only histological subtype and primary site are available for request from the NCRAS dataset, limiting IGCCC risk classification. While further required data items, such as lymphovascular invasion, are present in COSD, completion rates are low. Stage also had a high proportion of missingness in the NRCAS data. This may be because clinicians use IGCCC classification, not stage, to make decisions. We compared the completeness of stage in GCT patients with that of FIGO staging in cervical cancer patients of the same age and found a missingness of 46.2% compared to 4.8%, highlighting the difference in comparison to a common carcinoma in adulthood where stage more directly determines treatment. We have demonstrated how the lack of risk stratification data can, in part, be overcome with clinical interpretation but acknowledge that this remains imperfect. Standard treatment for intermediate and poor prognostic adult testicular cancer remains four cycles of BEP chemotherapy.[23] It was not possible to separate out these patients from the NCRAS data using our algorithm, therefore some poor prognosis patients will have been misclassified as intermediate. In our cohort the number of patients categorised as good risk was 81.3% compared to that in the literature of 45%.[3] It is therefore likely that some patients classified as good risk are in fact intermediate or poor prognostic risk patients who did not complete four cycles of chemotherapy. The immaturity of SACT data, which became available from 2014 onwards, means only a limited period of follow-up of patients is available. This restricts the survival analysis possible where initial survival rates are high, resulting in high right censoring rates for this early data (in our case a censor rate of 95.6%). We attempted to compare the survival rates of the NCRAS cohort with both the clinical trials data and the findings by Shaikh et al. and found the NCRAS 5-year survival to be much higher (Table S3), likely due to both the censoring, a higher proportion of good prognosis patients and the data being more contemporary. Toxicity data in the NCRAS cohort was limited to binary outcomes at regimen level. While this could be enhanced by calculating the percentage dose reduction using the available data items it would still lack the detail provided in clinical trials which provides insight into the barriers faced in delivering each chemotherapy agent.

We have identified a number of areas for further work. Requesting the data in accordance with data minimisation practice meant that we could not investigate the impact of treatment setting on received RDI in the population data, as treatment centre identities were pseudonymised. This is an important area for future consideration as variations may exist between specialist and nonspecialist AYA centres. The latter less likely to have been involved in clinical trials and to have experience of treating patients with rare presentations. Decisions around dose modifications may therefore be different, with specialised AYA cancer services able to provide greater supportive care, maintaining survival in poor risk cases.[43,44] This is supported by the work by Collete which found GCT patients treated in centres that entered fewer than five patients in clinical trials had poorer survival outcomes.[45] In this data those aged over 18 years had the poorest 5-year survival rates. The potential for pharmacokinetic differences across the AYA age range to influence chemotherapy efficacy has been described.[46] Exploration of the potential benefits that therapeutic drug monitoring and individualised dosing may bring to AYA warrants further investigation. A stronger association between survival benefit and RDI was seen in the clinical trials dataset, where most patients received an RDI of 0.85 to 0.94 compared to over 0.95 in the NCRAS data. We reported recorded cause of death as a marker of toxicity; 17% of deaths within the NCRAS data were likely due to toxicity and 14.3% in the clinical trials. Given the high proportion of good prognosis patients in the NCRAS cohort, it could be considered whether improvements might be gained from trials of lower dose-intensity approaches in these patients. Dose reduction to reduce toxicity and maintain survival may not be feasible in intermediate and poor prognosis disease but analyses such as these can inform the design of future dose de-escalation trials in cohorts such as the good prognosis GCT patients.[47]

AYA cancers are important but rare, so small patient numbers can restrict the analysis of datasets and the meaningfulness of findings produced. Here we have analysed a substantial population level dataset of 817 patients taken from one country over a 4-year period, limited from 1503 by our own inclusion criteria. This is comparable to the 799 patients achieved from four international clinical trials. While we appreciate that GCT is within the most common tumour types in AYA, the use of population-based registries to enhance research in this field holds great possibility. Several global initiatives are embracing this including the MaGIC consortium[48] for GCTs who are amalgamating data sets trials into 'data commons'. The STRONG-AYA[49] initiative is a European Union funded consortium using new data analysis initiatives such as federated data analysis to compare outcomes for AYA with cancer. Although the limited follow up time restricted the survival analysis possible in our study, with time follow up duration available will become a strength of the NCRAS dataset, greater than possible in clinical trials. Linkage to other datasets such as HES could enable the long-term toxicity

of treatments, both within trials and routine practice, to be monitored. There are potential mutual benefits to be gained from the linkage of clinical trials and NCRAS data. The former gaining through better sociodemographic data and longer follow up, the latter by more detailed stage, dose and toxicity data. For this to be effective adequate resources, capacity and training are required to improve data completeness. In addition, patient consent needs to be obtained in clinical trials to enable linkage of data for research purposes in order to help overcome the information governance legislation currently preventing this.[50]

5 | CONCLUSION

We have demonstrated that delivered dose intensity is associated with improved survival in routine NHS care of AYA with GCT. Careful cleaning, interpretation and analysis maximised the utility of the linked SACT and COSD data, enabling high level analysis, albeit limited in GCT by data completeness for robust risk classification and staging. The ultimate potential of this data can only be harnessed by improving completeness and overcoming existing barriers to data sharing.

AUTHOR CONTRIBUTIONS

The study was conceived by Nicola Hughes, Dan Stark and Richard Feltbower. Nicola Hughes performed the analysis with statistical support from Kirsten Cromie. Nicola Hughes, Dan Stark, Richard Feltbower, Kirsten Cromie and Martin McCabe contributed to the interpretation of the analysis. Nicola Hughes drafted the article with contributions from all other authors. All authors have read and approved the final manuscript for publication. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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CONFLICT OF INTEREST STATEMENT

Dan Stark holds programmatic research grant funding from the Teenage Cancer Trust. The other authors have no conflict to disclose.

DATA AVAILABILITY STATEMENT

The NCRAS dataset consists of patient-level information collected by the NHS. These data are collated, maintained and quality assured by the NCRAS team, part of NHS digital.

The data that support the findings of our study are available from the authors, following permission from NHS digital and the EORTC.

ETHICS STATEMENT

Ethical approval for our study was obtained from the Yorkshire and The Humber- Bradford Leeds Research Ethics Committee (REC reference 19/YH/0121).

ORCID

Nicola F. Hughes https://orcid.org/0000-0003-2956-1760
Richard G. Feltbower https://orcid.org/0000-0002-1728-9408
Martin G. McCabe https://orcid.org/0000-0002-5138-0707

TWITTER

Nicola F. Hughes *nfhughes1*

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SUPPORTING INFORMATION

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