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Cancer

Outcomes of Adolescent Males with Extracranial Metastatic Germ Cell Tumors. A Report from the Malignant Germ Cell Tumor International Consortium.

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1 **Title:** Outcomes of Adolescent Males with Extracranial Metastatic Germ Cell Tumors: A Report
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6 from the Malignant Germ Cell Tumor International Consortium.

7
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15
16
17 **Running Title:** Germ Cell Tumors in Adolescent Males

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3 **47 Conflict of Interest Statement:**
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6 48 Furqan Shaikh, Daniel Stark, Adriana Fonseca, Ha Dang, Caihong Xia, Mark Krailo, Farzana
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8 49 Pashankar, Thomas Olson, James C. Nichols, Mathew J. Murray, James F. Amatruda, Deborah
9

10 50 Billmire & Sara Stoneham: No Conflict to declare
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13 51 Carlos Rodriguez-Galindo: Advisory board Novimmune; A. Lindsay Frazier: Clinical Advisory
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15 52 board for Decibel Therapeutics.
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20 **54 Author Contribution Statement:**
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23 55 Furqan Shaikh: Conceptualization, methodology, data curation, formal analysis, original draft,
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25 56 writing- review and editing.
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27

28 57 Daniel Stark: Conceptualization, methodology, data acquisition writing - review and editing.
29

30 58 Adriana Fonseca: Data curation, formal analysis, original draft, and writing- review and editing.
31
32

33 59 Ha Dang: Data curation, methodology, formal analysis, writing- review and editing.
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36 60 Caihong Xia: Data curation, methodology, formal analysis, writing- review and editing.
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39 61 Mark Krailo: Conceptualization, methodology, data curation, formal analysis, writing- review
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41 62 and editing.
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43

44 63 Farzana Pashankar: Conceptualization, methodology, data acquisition writing - review and editing.
45

46 64 Carlos Rodriguez-Galindo: Conceptualization, funding acquisition, methodology, writing - review
47

48 65 and editing.
49

50 66 Thomas Olson: Conceptualization, methodology, data acquisition writing - review and editing.
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53 67 James C. Nichols: Conceptualization, methodology, data acquisition writing - review and editing.
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55 68 Mathew J. Murray: Conceptualization, methodology, data acquisition writing - review and editing.
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3 69 James F. Amatruda: Conceptualization, funding acquisition, methodology, writing - review and
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5 70 editing.

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8 71 Deborah Billmire: Conceptualization, funding acquisition, methodology, writing - review and
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10 72 editing.

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12 73 Sara Stoneham: Conceptualization, methodology, data acquisition writing - review and editing.

13
14
15 74 A. Lindsay Frazier: Conceptualization, funding acquisition, methodology, writing - review and
16
17 75 editing.

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20 76 All authors have made meaningful contributions, approved the final version of the manuscript and
21
22 77 are accountable for all aspects of the work.

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27 79 **Lay Summary:**

28
29 80 Adolescent males with metastatic germ cell tumors are frequently treated with regimens developed
30
31 81 for children. In this study, we built a large dataset of male patients with metastatic germ cell
32
33 82 tumors across different age groups to understand the outcomes of adolescent patients when
34
35 83 compared with children and young adults. Our results suggest that adolescent males with
36
37 84 metastatic germ cell tumors have worse results than children and are more similar to young adults
38
39 85 with germ cell tumors. Therefore, the treatment of adolescents with germ cell tumors, should
40
41 86 resemble young adult therapeutic approaches.

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47 88 **Précis for Table of Contents:**

48
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50 89 EFS for adolescent patients with metastatic germ cell tumors was similar to young adults but
51
52 90 significantly worse than for children. This finding highlights the importance of coordinating
53
54 91 initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

Abstract:

PURPOSE: Adolescents with extracranial metastatic germ cell tumors (GCTs) are often treated on regimens developed for children, but more closely resemble the clinical characteristics of young adult patients. We sought to determine event-free survival (EFS) for adolescents with GCTs and compared children and young adults.

PATIENTS AND METHODS: We assembled an individual patient database of eleven GCT trials: eight conducted by pediatric cooperative groups and three by an adult group. We included male patients aged 0-30 years with metastatic, non-seminomatous malignant GCTs of the testis, retroperitoneum, or mediastinum, treated with platinum-based chemotherapy. We categorized age-group as children (0 to <11 years), adolescents (11 to <18 years), or young adults (18 to <30 years old). We compared EFS and adjusted for risk-group using Cox proportional hazards analysis.

RESULTS: From a total of 2,024 individual records, 593 patients met inclusion criteria, of whom 90 were children, 109 were adolescents, and 394 were young adults. The 5-year EFS for adolescents [72 %; 95% confidence-interval (CI)=62-79%] was lower than for children (90%; CI=81-95%, p=0.003) or young adults (88%; CI=84-91%, p=0.0002). International Germ Cell Cancer Collaborative Group (IGCCCG) risk-group was associated with EFS in the adolescent age-group (p=0.0257). After adjusting for risk-group, the difference in EFS between adolescents and children remained significant (HR=0.30, p=0.001).

CONCLUSION: EFS for adolescent patients with metastatic GCTs was similar to young adults but significantly worse than for children. This finding highlights the importance of coordinating initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

Keywords: Germ cell tumors, adolescent males, outcomes, AYA, Testicular GCT.

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15 120 Supplemental material: 1 table
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17 121 **Previous presentations:**

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19 122 ASCO 2019 Annual meeting
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21 123 International Extracranial Germ Cell Tumor Conference 2019
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126 **Background**

127 Adolescents and young adults (AYAs) with cancer are a unique group of patients with
128 special characteristics.¹⁻⁴ AYAs develop a specific spectrum of cancers,⁵ require age-appropriate
129 psychosocial support, and often inhabit a medical ‘no man’s land’⁶ where they are neither the
130 specific focus of pediatric or adult worlds of oncology.⁷ This results in their care being under-
131 researched, trials under-accrued, and optimal management disputed.⁸ AYAs may sometimes be
132 subject to professional competition for patient ‘ownership’ or an individual clinical conviction that
133 the management used for one age-group is right for another.^{9, 10} But specific attention to the needs
134 of AYA cancer patients has yielded progress. In acute lymphoblastic leukemia, management has
135 evolved based upon pooling of data from different treatment approaches, with greatly improved
136 AYA outcomes in recent trials.¹¹ Similarly, Ewing sarcoma outcomes for AYAs were inferior to
137 those seen in children, until collaborative protocols overcame this difference.^{12, 13} In osteosarcoma,
138 outcomes for AYAs are also inferior to those observed in children, and pooling of clinical trial
139 data has hypothesised tractable reasons for these differences related to pharmacologic or clinical
140 factors.¹⁴ We believe similar advances can be made for AYA patients with GCTs through
141 collaborative, investigative efforts.

142
143 Extracranial germ cell tumors (GCTs) account for approximately 3-4% of cancers in
144 children, 14% of cancers in adolescents aged 15-19 years, and 18% of cancers in young adults
145 aged 20-30 years.^{15, 16} Thus, GCTs are among the few malignancies that are encountered relatively
146 commonly by both pediatric and medical oncologists. However, treatment regimens have evolved
147 separately within pediatric and adult oncology collaborative groups. The two groups use different

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3 148 staging and risk stratification systems, different numbers of cycles, and different cumulative doses
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5 149 of chemotherapy.^{17, 18}
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10 151 Historically, patients under the age of 15-18 years in North America or under 16 years in
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12 152 the United Kingdom (UK) have been treated on pediatric regimens, and most adolescents within
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14 153 these ages have been treated with the approaches developed for young children. On the other hand,
15
16 154 it can be argued that adolescents with GCTs seem to more closely resemble the characteristics of
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18 155 young adult patients with respect to clinical, biological and epidemiological characteristics.¹⁹
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20 156 Thus, there is a knowledge gap about the optimal approach to treating adolescents with GCTs. To
21
22 157 date, it is not known whether adolescents with GCTs are more effectively treated with pediatric or
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24 158 adult approaches. Compounding this matter is the observation that adolescents with GCTs are
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26 159 under-represented in clinical trials, frequently too old to meet the age inclusion criteria of pediatric
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28 160 trials and too young to meet age eligibility for adult studies.²⁰
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35 162 We sought to determine whether adolescents with GCTs experience outcomes that are
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37 163 more alike to children or to young adults, and where the dividing line between pediatric and adult
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39 164 standards of care or clinical trial inclusion criteria should be drawn. There is only limited evidence
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41 165 to help guide such discussions. This limitation stems from the heterogeneous manifestations of
42
43 166 GCTs across age-groups which precludes direct comparisons, as well as the relatively small
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45 167 sample size of individual trials which prevents adequately powered subgroup analyses. Previously,
46
47 168 Cost et al.²¹ reported on the outcomes among 20 children, 39 adolescents, and 354 adult patients
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49 169 with testicular GCTs treated at their institution. The EFS for adolescents was worse when
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51 170 compared with children and young adults, even after adjusting for stage, International Germ Cell
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3 171 Cancer Collaborative Group (IGCCCG) risk-group,¹⁷ and histology. However, this was a single
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5 172 centre analysis with a small sample size.
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10 174 The Malignant Germ Cell Tumour International Consortium (MaGIC) assembled a large
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12 175 pooled dataset of extracranial GCT patients treated across multiple clinical trials and collaborative
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14 176 groups^{20, 22}, allowing for secondary analysis of prospective trial data. For this current study, we
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16
17 177 derived a relatively homogenous subgroup of male patients with GCT across three age-groups
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19 178 (children, adolescents, and young adults) in order to compare event-free survival (EFS). A
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21
22 179 secondary objective was to determine whether the IGCCCG risk stratification system used in adult
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24 180 studies¹⁷ was predictive of outcome in pediatric or adolescent patients with GCTs.
25

26 181

27 28 182 **Patients and Methods**

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30 183 At the time of this analysis, the MaGIC database included all patients enrolled in five trials
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32 184 conducted by the Children's Oncology Group (COG; INT-1016,²³ INT-0097,¹⁸ AGCT0132,²⁴
33
34 185 AGCT01P1²⁵ and P9749²⁶), three trials from the Children's Cancer and Leukemia Group (CCLG;
35
36 186 GCI,²⁷ GCII²⁸ and GCIII²⁹), and three trials from the Medical Research Council (MRC; TE09,³⁰
37
38 187 TE13³¹ and TE20³²). Each trial had received research ethics board approval from the relevant
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40 188 agencies. The project was reviewed and approved by the Institutional Review Board at the Dana-
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42 189 Farber Cancer Institute.
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49 191 From the total dataset of 2,024 patients, we selected males age 0-30 years with newly
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51 192 diagnosed, metastatic, non-seminomatous malignant GCT of the testis, retroperitoneum or
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53 193 mediastinum. The resulting subgroup of 593 patients provided a population with relatively uniform
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3 194 disease characteristics that was large enough to provide adequate numbers of patients within each
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5 195 of the three age-groups.
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10 197 In order to maintain uniform treatment intensity, we only included patients treated with
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12 198 standard regimens with outcomes known to be similar to each other. The regimens included the
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14 199 adult standard-of-care BEP (weekly bleomycin, represented henceforth by the upper case letter
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16 200 'B', and once per cycle etoposide and cisplatin), the pediatric standard-of-care PEb (cisplatin,
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18 201 etoposide and reduced bleomycin used once per cycle, represented henceforth by the lowercase
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20 202 letter 'b'), HD-PEb (high-dose cisplatin and Eb), C-PEb (cyclophosphamide and PEb), and
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22 203 pediatric JEb (carboplatin and Eb). We included pediatric JEb as it has similar outcomes to
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24 204 pediatric PEb^{29, 33}. However, adult patients treated with carboplatin regimens were excluded as
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26 205 these regimens, which notably used lower doses of carboplatin than those used in paediatric
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28 206 regimens, have been shown to be inferior to BEP in randomized trials.^{30, 34}
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35 208 We categorized 'age-group' as children (age 0 to <11 years), adolescents (11 to <18 years),
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37 209 or young adults (18 to <30 years old). The selection of age 11 years as the cut-off between children
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39 210 and adolescents was based on our earlier analysis which showed this age to be the most significant
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41 211 and discriminant prognostic cut-off among pediatric GCTs.²² We selected 18 years as the defining
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43 212 age between adolescents and young adults as it is the most frequent age of transition from pediatric
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45 213 to adult care in many centres and clinical trials. We defined 'metastatic' as lymph node metastasis
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47 214 or distant sites, classified in the MRC trials as stage II or III, in CCLG as stage II-IV, or in COG
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49 215 as stage III or IV.
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3 217 Next, we retrospectively applied the IGCCCG risk stratification, assigning each patient to
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5 218 either the good-risk, intermediate-risk, or poor-risk group.¹⁷ The IGCCCG criteria utilize
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8 219 histologic subtype, primary site, sites of metastases, and pre-chemotherapy serum levels of alpha
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10 220 fetoprotein (AFP), β subunit of human chorionic gonadotropin (β HCG), and lactate dehydrogenase
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12 221 (LDH) to determine risk-group, thus providing a composite variable of the most significant (adult)
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14 222 prognostic factors. Of note, tumor marker levels in pediatric trials measured at “diagnosis” may
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16 223 have been pre-surgical levels, rather than post-surgical levels as used by the IGCCCG.
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18 224 Furthermore, since some of the trial protocols of our pooled dataset were conducted prior to the
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20 225 IGCCCG classification, and because IGCCCG risk stratification has not traditionally been applied
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22 226 to pediatric GCT patients, we expected and encountered a high rate of missing values on the
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24 227 relevant data elements, especially LDH levels. If the particular value of a variable was not available
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26 228 to assign the IGCCCG risk group, we assumed (for the primary analysis) that the value would not
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28 229 have increased the assigned risk group (i.e., patients were assigned to the good-risk group by
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30 230 default and positive evidence was required to elevate a patient to the intermediate-risk or poor-risk
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32 231 groups) as this is analogous to what would be done in a clinical setting. A sensitivity analysis
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34 232 including only patients with complete stratifying data available was also performed.
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42 234 The primary outcome was EFS, defined as the time interval from date of diagnosis to relapse or
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44 235 progression, second malignancy, death, or date last seen (whichever occurred first). The two
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46 236 potential predictor variables of main interest were age-group and IGCCCG risk-group. We
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48 237 constructed survival curves using the Kaplan-Meier method and used the log-rank test to
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50 238 compare EFS. We examined whether the IGCCCG risk-group within each age-group was
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52 239 significantly associated with EFS. We then conducted a multivariable Cox proportional hazards
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3 240 regression analysis to determine whether age-group (with adolescent age as the reference level)
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5 241 remained independently significant when adjusting for IGCCCG risk group. Lastly, we
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7 242 conducted sensitivity analyses to determine whether the results remained the same if we
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9 243 excluded all patients a) who received carboplatin (given historic results of carboplatin studies in
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11 244 adult patients), and b) with mediastinal primary sites of disease (given that mediastinal primary
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13 245 non-seminomatous tumors are assigned to the IGCCCG poor-risk group regardless of any other
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15 246 risk factors). A P-value of ≤ 0.050 was considered as evidence of a significant difference. All
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17 247 analyses were conducted by the authors using Stata version 13.1 (College Station, TX).
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23 24 249 **Results**

25
26 250 The Consort diagram (Fig.1) shows the flow of patients in this study. From a total of 2024
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28 251 non-duplicated records in the pooled database, 593 patients met inclusion criteria, of which 191
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30 252 were from pediatric studies and 402 from adult studies. Table 1 shows the characteristics of the
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32 253 source studies, including their patient populations, regimens used, and the number of patients from
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34 254 each trial who met eligibility criteria for this study.
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39 256 The characteristics of all included patients are shown in Table 2. The mean (\pm standard
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41 257 deviation) age was 19.4 (± 8.9) years. Five-hundred and thirty patients presented with testicular
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43 258 tumors (89.4%), 44 (7.4%) with mediastinal tumors, and 19 (3.3%) with retroperitoneal primary
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45 259 tumors. There were 90 children, 109 adolescents, and 394 young adults. Among the 90 children,
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47 260 84 (93%) were less than 3 years old. Among the 109 adolescents, only four patients were between
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49 261 11 and 13 years old. Tumour marker elevation was significantly different between age-groups:
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51 262 adolescents had the highest mean serum β HCG level (24,288 IU/L) and mean LDH level (934
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53 263 U/L), while the pediatric group demonstrated the highest mean AFP elevation (29,717 ng/mL).
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3 264 While there was a significant difference in the proportion of patients with poor-risk tumors in the
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5 265 pediatric and adolescent population (46% and 47% respectively) compared with the adult
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7 266 population (6%), this likely reflected the differences in the inclusion criteria of included studies
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10 267 rather than differences in natural distribution. In the adolescent group, 95/109 (87%) patients were
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12 268 treated with pediatric protocols, of whom 85 received cisplatin-based regimes (PEb) and 10
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14 269 received carboplatin-based regimens (JEb). Fourteen of 109 (13%) adolescents were treated with
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17 270 adult-type regimens (BEP).
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21 272 Among all 593 patients, there were 91 events and 35 deaths. The overall 5-year EFS was
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23 273 85% [95% confidence intervals (CI) 82-88 %] and the overall 5-year overall survival (OS) was
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25 274 94% (95%; CI 92-96%; Fig 2A). The median follow-up time for patients who survived without an
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27 275 event was 5.9 years (range 0.1 to 14.0 years). Age-group was strongly associated with EFS
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29 276 ($p=0.0001$) (Fig 2B). The 5-year EFS for adolescents (72%; CI = 62-79 %) was lower than for
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31 277 children (90%; CI=81-95 %, $p=0.003$) and for young adults (88%; CI=84-91%, $p=0.0002$). Risk-
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33 278 group was also strongly associated with EFS ($p<0.0001$) (Fig 2C). The 5-year EFS for the good-
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35 279 risk group (89%) was higher than for the intermediate-risk group (76%) ($p=0.0003$) and poor-risk
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37 280 group (76%) ($p<0.0001$).
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44 282 Figure 3 shows the EFS curves for each age-group stratified by risk-group. Risk-group was
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46 283 not significantly associated with EFS among children ($p=0.7162$) or young adults in this cohort
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48 284 ($p=0.2703$) but was associated with EFS among adolescents ($p=0.0020$). Among the 51
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50 285 adolescents with poor-risk disease, 5-year EFS was only 57% (95% CI=42-70%), the lowest value
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52 286 observed across all subgroup analyses. In an exploratory analysis, the poor outcome in these 51
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3 287 patients was not driven by patients being treated on adult regimens (two patients, no events) or
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5 288 JEB regimens (four patients, no events). Adolescent patients treated with the pediatric regimen
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7 289 PEB had a 5- EFS of 64% (95% CI= 53-74%) compared to a 5-yr EFS of 92.9% (95%CI= 59-98%)
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9 290 in adolescent patients treated with the BEP regimen used in adult patients (log-rank $p=0.0517$).
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14 292 The Cox regression model including both age-group and risk-group (Table 3) demonstrated
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16 293 that, after adjusting for risk-group, the effect of age-group remained statistically significant
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18 294 (likelihood-ratio test for significance of age-group adjusted for risk-group $p=0.0025$). The
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20 295 difference in EFS between adolescents and children remained significant (HR=0.30., $p=0.001$),
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22 296 but the difference between adolescents and young adults was no longer significant (HR 0.66,
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24 297 $p=0.114$). The results did not change if children treated on the carboplatin based JEB regimen were
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26 298 excluded (Table 3), or if patients with mediastinal primary tumors were excluded (Table 3).
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33 300 In a sensitivity analysis, including only the 465 patients who had complete data for IGCCC
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35 301 risk stratification (78% of total sample size), the direction of results remained the same. In the
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37 302 proportional hazard analysis of these patients (Supplemental Table 1), the difference in EFS
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39 303 between adolescents and children remained significant (HR=0.21, $p=0.001$), and the difference
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41 304 between adolescents and adults was not significant (HR=0.59, $p=0.081$).
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46 306 **Discussion**

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48 307 Our study describes the outcomes of adolescent males with extracranial GCTs when
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50 308 compared against children and young adults within a large pooled dataset of collaborative phase
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52 309 III clinical trials. We showed that adolescent males had the lowest 5-year EFS (72%) compared
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54 310 with both children (90%) and young adults (88%) in unadjusted analysis. After adjusting for risk-
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3 311 group, the difference between adolescents and children remained significant, but the difference
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5 312 between adolescents and young adults did not. Furthermore, we examined whether the IGCCCG
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7 313 risk-classification system could successfully discriminate outcome among children or adolescents.
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9 314 The risk-groups were associated with outcome among adolescents, but not among children. This
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11 315 showed that the IGCCCG can be usefully applied for adolescents. Children had excellent outcomes
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13 316 regardless of risk-group, further validating the results of the MaGIC risk stratification²² where all
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15 317 patients <11y belong to the same risk group.
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19 318 Our findings also pointed to the under-representation of adolescents in clinical trials. There
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21 319 were only 109 adolescent males with metastatic GCT in this entire dataset, pooled from every
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23 320 pediatric clinical trial across North America and the United Kingdom for the last thirty years.
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25 321 Considering that extracranial metastatic GCT is the most common cancer among adolescent males,
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27 322 and that 430 new testicular GCTs are diagnosed in boys aged 15-19 years in the United States each
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29 323 year,¹⁵ this remarkably small number of patient provides a stark example of the adolescent and
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31 324 young adult (AYA) ‘gap’ in cancer care, research, and outcomes.³⁵
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38 326 A strength of our study was its pooling of multiple good quality clinical trials to assemble
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40 327 the largest sample size currently possible to conduct this comparison, which any individual trial
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42 328 would not have allowed. This analysis focused on the outcomes of non-germinomatous/non-
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44 329 seminomatous GCTs in males, therefore, the results cannot be extrapolated to female patients or
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46 330 patients with pure germinomas/seminomas. One of our major limitations was the inability to
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48 331 analyse the effect of different therapeutic modalities and their individual impact on outcomes.
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50 332 Surgery is a cornerstone in the management of GCTs and the role of retroperitoneal lymph node
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52 333 dissection (RPLND) for post-chemotherapy residual lesions has been well described in the adult
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3 334 literature ³⁶⁻³⁹; this analysis was unable to account for its contribution to outcome. A potential
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5 335 weakness of the study was its moderate rate of missing data on the variables needed to assign
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7 336 IGCCCG risk-group. However, the results remained unchanged in a sensitivity analysis in which
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10 337 patients with missing data were excluded, suggesting this factor did not affect conclusions. Lastly,
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12 338 since tumor marker levels in pediatric trials measured at diagnosis may have been pre-surgical
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14 339 levels rather than post-surgical levels, it is possible that some pediatric patients may have been
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16 340 miscategorized on their IGCCCG risk group, which would have biased our risk group analyses.
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19 341 However, the direction of this bias would not be expected to weaken the results.
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24 343 Adolescents with metastatic GCT are biologically and clinically more similar to young
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26 344 adults than children¹⁹, and this study demonstrates that they are also more alike in outcomes. While
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28 345 this study could not assess the superiority of any particular treatment approach or chemotherapy
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30 346 regimen, we believe it provides enough reason to consider treating adolescent males with GCTs
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32 347 differently than young children. We suggest that adolescent males with metastatic GCTs should
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34 348 be treated with approaches that have been developed with the wider evidence-base of adult
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36 349 testicular cancer, allowing them to receive the dose intensity of weekly bleomycin⁴⁰⁻⁴⁴, the
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38 350 predictive stratification of the IGCCCG^{17, 32, 45}, and the surgical guidelines for procedures such as
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40 351 RPLND of post-chemotherapy residual tumors³⁶⁻³⁹. All of these are standards-of-care among
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42 352 medical oncologists and urologists treating adults with metastatic GCTs.
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49 354 The results of this analysis, together with our earlier work on developing a revised GCT
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51 355 risk stratification⁴⁶, has already allowed us to incorporate these lessons into the current generation
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53 356 of GCT clinical trials in the United States and the United Kingdom. The current multi-group trial
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3 357 AGCT1531 (NCT03067181) includes all standard-risk patients between age 11-25 years as a
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5 358 single study group and prescribes these standards to all Furthermore, the COG has petitioned and
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7 359 joined two clinical trials led by adult testicular cancer cooperative groups: the ANZUP P3BEP or
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9 360 COG-AGCT1532 trial of accelerated BEP for high-risk patients, and the Alliance-A031102
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11 361 TIGER trial for patients with relapsed testicular GCTs. Both these studies were originally planned
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13 362 for adult patients alone, but on the evidence presented here, their eligibility criteria were modified
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15 363 to include adolescent patients. Taken together, these three trials cover the entire spectrum of
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17 364 adolescent GCTs. The availability of the data is due to the work of the Malignant Germ Cell
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19 365 international Consortium (MaGIC) which has galvanized a remarkable collaboration of multiple
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21 366 cooperative groups across the silos of age-groups and international borders⁴⁷. Through MAGIC
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23 367 and other similar efforts, we hope to provide a path that will narrow the gap and improve outcomes
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25 368 for AYA patients with germ cell tumours.
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511 47. Olson TA, Murray MJ, Rodriguez-Galindo C, et al. Pediatric and Adolescent Extracranial
512 Germ Cell Tumors: The Road to Collaboration. *J Clin Oncol.* 2015;33: 3018-3028.
513

514 **Table 1. Characteristics of Included Clinical Trials**

Study	Patients in Source Studies	Regimens	Number in present study
TE09	598 adults with good-prognosis testicular NGGCTs (273 under 30Y)	4BEP	139
		4JEB (Carboplatin AUC 5)	0
TE13	380 adults with poor-prognosis NGGCTs (121 under 30Y)	BEP/EP	58
		BOP/VIP-B	0
TE20	812 adults with good-prognosis GCTs (230 NGGCTs under 30Y)	4BEP or 3BEP	205
GC2	137 children with MGCT	JEB (Carboplatin 600 mg/m ²)	39
GC3	138 children with MGCT	JEB (Carboplatin 600 mg/m ²)	9
POG 9048 (INT 1016)	74 children with intermediate-risk NGGCTs	4PEb	0
POG 9049 (INT 0097)	299 children with high-risk MGCTs	4PEb	43
		4HD-PEb	43
P9749	25 children with high-risk MGCT	4HD-PEb	4
AGCT01P1	19 children with high-risk NGGCT	4C-PEb	5
AGCT0132	218 children with intermediate-risk NGGCTs	3PEb	47

Abbreviations: AUC, area under the curve; b, bleomycin once per cycle; B, bleomycin once per week; C, cyclophosphamide; E, etoposide; HD-P, high dose cisplatin; I, ifosfamide; J, carboplatin; MGCT, malignant germ cell tumors; NGGCT, non-germinomatous germ cell tumors; O, vincristine; P, cisplatin; POG, Pediatric Oncology Group; V, etoposide. * includes 38 patients from GCT2 and 1 patient from GCT1

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516

517 **Table 2. Patient Characteristics**

Variable	All Pts 0 to 30y N (%)	0 to <11y N (%)	11 to <18y N (%)	18 to 30y N (%)
	N=593	N=90	N=109	N=394
Age mean (SD)	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular	530 (89%)	67 (74%)	82(75%)	381 (96.7%)
Mediastinal tumor	44 (7%)	16 (18%)	22 (20%)	6 (1.5%)
Retroperitoneal	19 (3%)	7(8%)	5(5%)	7 (1.7%)
AFP (ng/mL)				
Mean	6294	29717	6924	857
(range)	(0 -700000)	(8-700000)	(0-96000)	(0-63630)
<1000	449 (76%)	34 (38%)	57 (52%)	358 (91%)
1,000-10,000	68 (11%)	23 (26%)	25 (23%)	20 (5%)
>10,000	62 (10%)	30 (33%)	23 (21%)	9 (2%)
Missing	14 (2%)	3 (3%)	4 (4%)	7 (2%)
βHCG (IU/L)				
Mean	12358	5	24289	11592
(range)	(0-1057700)	(0-62)	(1-990000)	(0-1057700)
<5,000	435 (73%)	33 (37%)	44 (40%)	358 (91%)
5,000 – 50,000	30 (5%)	0 (0%)	12 (11%)	18 (5%)
>50,000	14 (2%)	0 (0%)	3 (3%)	11 (3%)
Missing	114 (19%)	57 (63%)	50 (46%)	7 (2%)
LDH (U/L)				
Mean	587	701	934	500
(range)	(77-5540)	(149-3631)	(77-5540)	(93-5186)
<930	318 (54%)	22 (24%)	40 (37%)	256 (65%)
930-6200	47 (8%)	7 (8%)	19 (17%)	21 (5%)
>6200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	228 (38%)	61 (68%)	50 (46%)	117 (30%)
Non-pulmonary visceral metastases	34 (6%)	9 (10%)	16 (15 %)	9 (2%)
RiskGroup				
Good	267 (45 %)	4 (4%)	14 (13%)	249 (63%)
Intermediate	82 (14%)	21 (23%)	23 (21%)	38 (10%)
Poor	116 (20%)	41 (46%)	51 (47%)	24 (6%)
Missing	128 (21%)	24 (27%)	21 (19%)	83 (21%)

Abbreviations: AFP, a-fetoprotein; B-HCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

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521 **Table 3. Univariate Kaplan-Meier and Multivariable Cox Regression Analysis of Age-Group**
 522 **and Risk-Group.**

	Univariate				Multivariate		
All Patients (N=593)							
Variable	5y EFS (%)	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age Group							
0 - <11	90	0.31	0.14-0.65	0.002	0.30	0.14 – 0.63	0.001
11 - <18	72	Reference			Reference		
18 - <30	88	0.43	0.27-0.68	0.000	0.66	0.40 – 1.11	0.114
Risk Group							
Good	89	0.42	0.26-0.67	0.000	0.42	0.24 – 0.72	0.002
Intermediate	76	0.87	0.48-1.56	0.634	0.88	0.48 – 1.60	0.663
Poor	76	Reference			Reference		
JEB patients excluded* (N=545)							
Age Group							
0 - <11	92	0.21	0.07-0.60	0.004	0.21	0.07 – 0.59	0.003
11 - <18	69	Reference			Reference		
18 - <30	88	0.38	0.24-0.60	0.000	0.62	0.36 – 1.03	0.066
Risk Group							
Good	89	0.36	0.22-0.58	0.000	0.39	0.22 – 0.68	0.001
Intermediate	75	0.77	0.42-1.42	0.401	0.81	0.44 – 1.50	0.489
Poor	73	Reference			Reference		
Mediastinal primary tumors excluded** (N=549)							
Age Group							
0 - <11	89	0.41	0.18-0.94	0.035	0.40	0.108– 0.91	0.029
11 - <18	77	Reference			Reference		
18 - <30	87	0.55	0.33-0.93	0.024	0.83	0.347– 1.47	0.506
Risk Group							
Good	89	0.43	0.25-0.75	0.003	0.40	0.22 – 0.74	0.003
Intermediate	76	0.89	0.46-1.72	0.737	0.88	0.45 – 1.71	0.693
Poor	77	Reference			Reference		

Abbreviations: CI, confidence interval; EFS, event-free survival; JEB, carboplatin/etoposide/reduced bleomycin; N, number; y, years. *48 Patients received JEB. **44 Patients with mediastinal tumours.

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3 528 **FIGURE LEGENDS**
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7 530 Figure 1. CONSORT diagram describing flow of patients through the study
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11 533 Figure 2. A) Event-free survival (EFS) and overall survival (OS) for all patients (N=593)

12 534 B) EFS by risk-group; C) EFS by age-group
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14 535

15 536

16 537 Figure 3. A) EFS for children (age 0 to <11 years) by risk-group; B) EFS for adolescents (age 11

17 538 to <18 years) by risk-group; C) EFS for young adults (age 18 to <30 years) by risk-group.
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1 **Title:** Outcomes of Adolescent Males with Extracranial Metastatic Germ Cell Tumors:- A Report
2 from the Malignant Germ Cell Tumor International Consortium.

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3 **47 Conflict of Interest Statement:**
4
5

6 48 Furqan Shaikh, Daniel Stark, Adriana Fonseca, Ha Dang, Caihong Xia, Mark Krailo, Farzana
7

8 49 Pashankar, Thomas Olson, James C. Nichols, Mathew J. Murray, James F. Amatruda, Deborah
9

10 50 Billmire & Sara Stoneham: No Conflict to declare
11
12

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14

15 52 board for Decibel Therapeutics.
16
17

18 53
19

20 **54 Author Contribution Statement:**
21
22

23 55 Furqan Shaikh: Conceptualization, methodology, data curation, formal analysis, original draft,
24

25 56 writing- review and editing.
26
27

28 57 Daniel Stark: Conceptualization, methodology, data acquisition writing - review and editing.
29

30 58 Adriana Fonseca: Data curation, formal analysis, original draft, and writing- review and editing.
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32

33 59 Ha Dang: Data curation, methodology, formal analysis, writing- review and editing.
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13
14
15 74 A. Lindsay Frazier: Conceptualization, funding acquisition, methodology, writing - review and
16
17 75 editing.

18
19
20 76 All authors have made meaningful contributions, approved the final version of the manuscript and
21
22 77 are accountable for all aspects of the work.

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27 79 **Lay Summary:**

28
29 80 Adolescent males with metastatic germ cell tumors are frequently treated with regimens developed
30
31 81 for children. In this study, we built a large dataset of male patients with metastatic germ cell
32
33 82 tumors across different age groups to understand the outcomes of adolescent patients when
34
35 83 compared with children and young adults. Our results suggest that adolescent males with
36
37 84 metastatic germ cell tumors have worse results than children and are more similar to young adults
38
39 85 with germ cell tumors. Therefore, the treatment of adolescents with germ cell tumors, should
40
41 86 resemble young adult therapeutic approaches.

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47 88 **Précis for Table of Contents:**

48
49
50 89 EFS for adolescent patients with metastatic germ cell tumors was similar to young adults but
51
52 90 significantly worse than for children. This finding highlights the importance of coordinating
53
54 91 initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

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2
3 **92 Abstract:**
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5 **93 PURPOSE:** Adolescents with extracranial metastatic germ cell tumors (GCTs) are often treated on
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8 **94** regimens developed for children, but more closely resemble the clinical characteristics of young
9
10 **95** adult patients. We sought to determine event-free survival (EFS) for adolescents with GCTs and
11
12 **96** compared children and young adults.

13
14 **97 PATIENTS AND METHODS:** We assembled an individual patient database of eleven GCT trials:
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16
17 **98** eight conducted by pediatric cooperative groups and three by an adult group. We included male
18
19 **99** patients aged 0-30 years with metastatic, non-seminomatous malignant GCTs of the testis,
20
21 **100** retroperitoneum, or mediastinum, treated with platinum-based chemotherapy. We categorized age-
22
23 **101** group as children (0 to <11 years), adolescents (11 to <18 years), or young adults (18 to <30 years
24
25 **102** old). We compared EFS and adjusted for risk-group using Cox proportional hazards analysis.

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27
28 **103 RESULTS:** From a total of 2,024 individual records, 593 patients met inclusion criteria, of whom
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30
31 **104** 90 were children, 109 were adolescents, and 394 were young adults. The 5-year EFS for
32
33 **105** adolescents [72 %; 95% confidence-interval (CI)=62-79%] was lower than for children (90%;
34
35 **106** CI=81-95%, p=0.003) or young adults (88%; CI=84-91%, p=0.0002). International Germ Cell
36
37 **107** Cancer Collaborative Group (IGCCCG) risk-group was associated with EFS in the adolescent age-
38
39 **108** group (p=0.0257). After adjusting for risk-group, the difference in EFS between adolescents and
40
41 **109** children remained significant (HR=0.30, p=0.001).

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45 **110**
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47 **111 CONCLUSION:** EFS for adolescent patients with metastatic GCTs was similar to young adults
48
49 **112** but significantly worse than for children. This finding highlights the importance of coordinating
50
51 **113** initiatives across clinical trial organizations to improve outcomes for adolescents and young adults.

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53
54 **114 Keywords:** Germ cell tumors, adolescent males, outcomes, AYA, Testicular GCT.
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124

125

126 **Background**

127 Adolescents and young adults (AYAs) with cancer are a unique group of patients with
128 special characteristics.¹⁻⁴ AYAs develop a specific spectrum of cancers,⁵ require age-appropriate
129 psychosocial support, and often inhabit a medical ‘no man’s land’⁶ where they are neither the
130 specific focus of pediatric or adult worlds of oncology.⁷ This results in their care being under-
131 researched, trials under-accrued, and optimal management disputed.⁸ AYAs may sometimes be
132 subject to professional competition for patient ‘ownership’ or an individual clinical conviction that
133 the management used for one age-group is right for another.^{9, 10} But specific attention to the needs
134 of AYA cancer patients has yielded progress. In acute lymphoblastic leukemia, management has
135 evolved based upon pooling of data from different treatment approaches, with greatly improved
136 AYA outcomes in recent trials.¹¹ Similarly, Ewing sarcoma outcomes for AYAs were inferior to
137 those seen in children, until collaborative protocols overcame this difference.^{12, 13} In osteosarcoma,
138 outcomes for AYAs are also inferior to those observed in children, and pooling of clinical trial
139 data has hypothesised tractable reasons for these differences related to pharmacologic or clinical
140 factors.¹⁴ We believe similar advances can be made for AYA patients with GCTs through
141 collaborative, investigative efforts.

142
143 Extracranial germ cell tumors (GCTs) account for approximately 3-4% of cancers in
144 children, 14% of cancers in adolescents aged 15-19 years, and 18% of cancers in young adults
145 aged 20-30 years.^{15, 16} Thus, GCTs are among the few malignancies that are encountered relatively
146 commonly by both pediatric and medical oncologists. However, treatment regimens have evolved
147 separately within pediatric and adult oncology collaborative groups. The two groups use different

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3 148 staging and risk stratification systems, different numbers of cycles, and different cumulative doses
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5 149 of chemotherapy.^{17, 18}
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10 151 Historically, patients under the age of 15-18 years in North America or under 16 years in
11
12 152 the United Kingdom (UK) have been treated on pediatric regimens, and most adolescents within
13
14 153 these ages have been treated with the approaches developed for young children. On the other hand,
15
16 154 it can be argued that adolescents with GCTs seem to more closely resemble the characteristics of
17
18 155 young adult patients with respect to clinical, biological and epidemiological characteristics.¹⁹
19
20 156 Thus, there is a knowledge gap about the optimal approach to treating adolescents with GCTs. To
21
22 157 date, it is not known whether adolescents with GCTs are more effectively treated with pediatric or
23
24 158 adult approaches. Compounding this matter is the observation that adolescents with GCTs are
25
26 159 under-represented in clinical trials, frequently too old to meet the age inclusion criteria of pediatric
27
28 160 trials and too young to meet age eligibility for adult studies.²⁰
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35 162 We sought to determine whether adolescents with GCTs experience outcomes that are
36
37 163 more alike to children or to young adults, and where the dividing line between pediatric and adult
38
39 164 standards of care or clinical trial inclusion criteria should be drawn. There is only limited evidence
40
41 165 to help guide such discussions. This limitation stems from the heterogeneous manifestations of
42
43 166 GCTs across age-groups which precludes direct comparisons, as well as the relatively small
44
45 167 sample size of individual trials which prevents adequately powered subgroup analyses. Previously,
46
47 168 Cost et al.²¹ reported on the outcomes among 20 children, 39 adolescents, and 354 adult patients
48
49 169 with testicular GCTs treated at their institution. The EFS for adolescents was worse when
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51 170 compared with children and young adults, even after adjusting for stage, International Germ Cell
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3 171 Cancer Collaborative Group (IGCCCG) risk-group,¹⁷ and histology. However, this was a single
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5 172 centre analysis with a small sample size.
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9
10 174 The Malignant Germ Cell Tumour International Consortium (MaGIC) assembled a large
11
12 175 pooled dataset of extracranial GCT patients treated across multiple clinical trials and collaborative
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14 176 groups^{20, 22}, allowing for secondary analysis of prospective trial data. For this current study, we
15
16 177 derived a relatively homogenous subgroup of male patients with GCT across three age-groups
17
18 178 (children, adolescents, and young adults) in order to compare event-free survival (EFS). A
19
20 179 secondary objective was to determine whether the IGCCCG risk stratification system used in adult
21
22 180 studies¹⁷ was predictive of outcome in pediatric or adolescent patients with GCTs.
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26 181

27 28 182 **Patients and Methods**

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30 183 At the time of this analysis, the MaGIC database included all patients enrolled in five trials
31
32 184 conducted by the Children's Oncology Group (COG; INT-1016,²³ INT-0097,¹⁸ AGCT0132,²⁴
33
34 185 AGCT01P1²⁵ and P9749²⁶), three trials from the Children's Cancer and Leukemia Group (CCLG;
35
36 186 GCI,²⁷ GCII²⁸ and GCIII²⁹), and three trials from the Medical Research Council (MRC; TE09,³⁰
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38 187 TE13³¹ and TE20³²). Each trial had received research ethics board approval from the relevant
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40 188 agencies. The project was reviewed and approved by the Institutional Review Board at the Dana-
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42 189 Farber Cancer Institute.
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48 191 From the total dataset of 2,024 patients, we selected males age 0-30 years with newly
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50 192 diagnosed, metastatic, non-seminomatous malignant GCT of the testis, retroperitoneum or
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52 193 mediastinum. The resulting subgroup of 593 patients provided a population with relatively uniform
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3 194 disease characteristics that was large enough to provide adequate numbers of patients within each
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5 195 of the three age-groups.
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10 197 In order to maintain uniform treatment intensity, we only included patients treated with
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12 198 standard regimens with outcomes known to be similar to each other. The regimens included the
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14 199 adult standard-of-care BEP (weekly bleomycin, represented henceforth by the upper case letter
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16 200 'B', and once per cycle etoposide and cisplatin), the pediatric standard-of-care PEb (cisplatin,
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18 201 etoposide and reduced bleomycin used once per cycle, represented henceforth by the lowercase
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20 202 letter 'b'), HD-PEb (high-dose cisplatin and Eb), C-PEb (cyclophosphamide and PEb), and
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22 203 pediatric JEb (carboplatin and Eb). We included pediatric JEb as it has similar outcomes to
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24 204 pediatric PEb^{29, 33}. However, adult patients treated with carboplatin regimens were excluded as
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26 205 these regimens, which notably used lower doses of carboplatin than those used in paediatric
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28 206 regimens, have been shown to be inferior to BEP in randomized trials.^{30, 34}
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34
35 208 We categorized 'age-group' as children (age 0 to <11 years), adolescents (11 to <18 years),
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37 209 or young adults (18 to <30 years old). The selection of age 11 years as the cut-off between children
38
39 210 and adolescents was based on our earlier analysis which showed this age to be the most significant
40
41 211 and discriminant prognostic cut-off among pediatric GCTs.²² We selected 18 years as the defining
42
43 212 age between adolescents and young adults as it is the most frequent age of transition from pediatric
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45 213 to adult care in many centres and clinical trials. We defined 'metastatic' as lymph node metastasis
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47 214 or distant sites, classified in the MRC trials as stage II or III, in CCLG as stage II-IV, or in COG
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49 215 as stage III or IV.
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3 217 Next, we retrospectively applied the IGCCCG risk stratification, assigning each patient to
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5 218 either the good-risk, intermediate-risk, or poor-risk group.¹⁷ The IGCCCG criteria utilize
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7 219 histologic subtype, primary site, sites of metastases, and pre-chemotherapy serum levels of alpha
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9 220 fetoprotein (AFP), β subunit of human chorionic gonadotropin (β HCG), and lactate dehydrogenase
10
11 221 (LDH) to determine risk-group, thus providing a composite variable of the most significant (adult)
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13 222 prognostic factors. Of note, tumor marker levels in pediatric trials measured at “diagnosis” may
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15 223 have been pre-surgical levels, rather than post-surgical levels as used by the IGCCCG.
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17 224 Furthermore, sSince some of the trial protocols of our pooled dataset were conducted prior to the
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19 225 IGCCCG classification, and because IGCCCG risk stratification has not traditionally been applied
20
21 226 to pediatric GCT patients, we expected and encountered a high rate of missing values on the
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23 227 relevant data elements, especially LDH levels. If the particular value of a variable was not
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25 228 available to assign the IGCCCG risk group, we assumed (for the primary analysis) that the value
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27 229 would not have increased the assigned risk group (i.e., patients were assigned to the good-risk
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29 230 group by default and positive evidence was required to elevate a patient to the intermediate-risk or
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31 231 poor-risk groups) as this is analogous to what would be done in a clinical setting. A sensitivity
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33 232 analysis including only patients with complete stratifying data available was also performed.
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37 234 The primary outcome was EFS, defined as the time interval from date of diagnosis to relapse or
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39 235 progression, second malignancy, death, or date last seen (whichever occurred first). The two
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41 236 potential predictor variables of main interest were age-group and IGCCCG risk-group. We
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43 237 constructed survival curves using the Kaplan-Meier method and used the log-rank test to
44
45 238 compare EFS. We examined whether the IGCCCG risk-group within each age-group was
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47 239 significantly associated with EFS. We then conducted a multivariable Cox proportional hazards
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3 240 regression analysis to determine whether age-group (with adolescent age as the reference level)
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5 241 remained independently significant when adjusting for IGCCCG risk group. Lastly, we
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7 242 conducted sensitivity analyses to determine whether the results remained the same if we
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9 243 excluded all patients a) who received carboplatin (given historic results of carboplatin studies in
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11 244 adult patients), and b) with mediastinal primary sites of disease (given that mediastinal primary
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13 245 non-seminomatous tumors are assigned to the IGCCCG poor-risk group regardless of any other
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15 246 risk factors). A P-value of ≤ 0.050 was considered as evidence of a significant difference. All
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19 247 analyses were conducted by the authors using Stata version 13.1 (College Station, TX).
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23 24 249 **Results**

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26 250 The Consort diagram (Fig.1) shows the flow of patients in this study. From a total of 2024
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28 251 non-duplicated records in the pooled database, 593 patients met inclusion criteria, of which 191
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30 252 were from pediatric studies and 402 from adult studies. Table 1 shows the characteristics of the
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32 253 source studies, including their patient populations, regimens used, and the number of patients from
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34 254 each trial who met eligibility criteria for this study.
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39 256 The characteristics of all included patients are shown in Table 2. The mean (\pm standard
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41 257 deviation) age was 19.4 (± 8.9) years. Five hundred and thirty patients presented with testicular
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43 258 tumors (89.4%), 44 (7.4%) with mediastinal tumors, and 19 (3.3%) with retroperitoneal primary
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45 259 tumors. There were 90 children, 109 adolescents, and 394 young adults. Among the 90 children,
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47 260 84 (93%) were less than 3 years old. Among the 109 adolescents, only four patients were between
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49 261 11 and 13 years old. Tumour marker elevation was significantly different between age-groups:
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51 262 adolescents had the highest mean serum β HCG level (24,288 IU/L) and mean LDH level (934
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53 263 U/L), while the pediatric group demonstrated the highest mean AFP elevation (29,717 ng/mL).
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3 264 While there was a significant difference in the proportion of patients with poor-risk tumors in the
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5 265 pediatric and adolescent population (46% and 47% respectively) compared with the adult
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7 266 population (6%), this likely reflected the differences in the inclusion criteria of included studies
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10 267 rather than differences in natural distribution. In the adolescent group, 95/109 (87%) patients were
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12 268 treated with pediatric protocols, of whom 35 received cisplatin-based regimens (PEb) and 10
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14 269 received carboplatin-based regimens (IEb). Fourteen of 109 (13%) adolescents were treated with
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16 270 adult-type regimens (EB).

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21 272 Among all 593 patients, there were 91 events and 35 deaths. The overall 5-year EFS was
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23 273 85% [95% confidence intervals (CI) 82-88 %] and the overall 5-year overall survival (OS) was
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25 274 94% (95%; CI 92-96%; Fig 2A). The median follow-up time for patients who survived without an
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27 275 event was 5.9 years (range 0.1 to 14.0 years). Age-group was strongly associated with EFS
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29 276 ($p=0.0001$) (Fig 2B). The 5-year EFS for adolescents (72%; CI = 62-79 %) was lower than for
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31 277 children (90%; CI=81-95 %, $p=0.003$) and for young adults (88%; CI=84-91%, $p=0.0002$). Risk-
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33 278 group was also strongly associated with EFS ($p<0.0001$) (Fig 2C). The 5-year EFS for the good-
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35 279 risk group (89%) was higher than for the intermediate-risk group (76%) ($p=0.0003$) and poor-risk
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37 280 group (76%) ($p<0.0001$).
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44 282 Figure 3 shows the EFS curves for each age-group stratified by risk-group. Risk-group was
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46 283 not significantly associated with EFS among children ($p=0.7162$) or young adults in this cohort
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48 284 ($p=0.2703$) but was associated with EFS among adolescents ($p=0.0020$). Among the 51
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50 285 adolescents with poor-risk disease, 5-year EFS was only 57% (95% CI=42-70%), the lowest value
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52 286 observed across all subgroup analyses. In an exploratory analysis, the poor outcome in these 51
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3 287 patients was not driven by patients being treated on adult regimens (two patients, no events) or
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5 288 JEB regimens (four patients, no events). Adolescent patients treated with the pediatric regimen
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8 289 EB had a 5-yr EFS of 64% (95% CI= 53-74%) compared to a 5-yr EFS of 92.9% (95% CI= 59-98%)
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10 290 in adolescent patients treated with the BEP regimen used in adult patients (log-rank p=0.0517).
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15 292 The Cox regression model including both age-group and risk-group (Table 3) demonstrated
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17 293 that, after adjusting for risk-group, the effect of age-group remained statistically significant
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19 294 (likelihood-ratio test for significance of age-group adjusted for risk-group p=0.0025). The
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21 295 difference in EFS between adolescents and children remained significant (HR=0.30., p=0.001),
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23 296 but the difference between adolescents and young adults was no longer significant (HR 0.66,
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25 297 p=0.114). The results did not change if children treated on the carboplatin based JEB regimen were
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27 298 excluded (Table 3), or if patients with mediastinal primary tumors were excluded (Table 3).
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33 300 In a sensitivity analysis, including only the 465 patients who had complete data for IGCCC
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35 301 risk stratification (78% of total sample size), the direction of results remained the same. In the
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37 302 proportional hazard analysis of these patients (Supplemental Table 1), the difference in EFS
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39 303 between adolescents and children remained significant (HR=0.21, p=0.001), and the difference
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41 304 between adolescents and adults was not significant (HR=0.59, p=0.081).
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46 306 **Discussion**

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48 307 Our study describes the outcomes of adolescent males with extracranial GCTs when
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50 308 compared against children and young adults within a large pooled dataset of collaborative phase
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52 309 III clinical trials. We showed that adolescent males had the lowest 5-year EFS (72%) compared
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54 310 with both children (90%) and young adults (88%) in unadjusted analysis. After adjusting for risk-
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3 311 group, the difference between adolescents and children remained significant, but the difference
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5 312 between adolescents and young adults did not. Furthermore, we examined whether the IGCCCG
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7 313 risk-classification system could successfully discriminate outcome among children or adolescents.
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9 314 The risk-groups were associated with outcome among adolescents, but not among children. This
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11 315 showed that the IGCCCG can be usefully applied for adolescents. Children had excellent outcomes
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13 316 regardless of risk-group, further validating the results of the MaGIC risk stratification²² where all
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15 317 patients <11y belong to the same risk group.
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19 318 Our findings also pointed to the under-representation of adolescents in clinical trials. There
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21 319 were only 109 adolescent males with metastatic GCT in this entire dataset, pooled from every
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23 320 pediatric clinical trial across North America and the United Kingdom for the last thirty years.
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25 321 Considering that extracranial metastatic GCT is the most common cancer among adolescent males,
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27 322 and that 430 new testicular GCTs are diagnosed in boys aged 15-19 years in the United States each
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29 323 year,¹⁵ this remarkably small number of patient provides a stark example of the adolescent and
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31 324 young adult (AYA) ‘gap’ in cancer care, research, and outcomes.³⁵
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37 326 A strength of our study was its pooling of multiple good quality clinical trials to assemble
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39 327 the largest sample size currently possible to conduct this comparison, which any individual trial
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41 328 would not have allowed. This analysis focused on the outcomes of non-germinomatous/non-
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43 329 seminomatous GCTs in males, therefore, the results cannot be extrapolated to female patients or
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45 330 patients with pure germinomas/seminomas. One of our major limitations was the inability to
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47 331 analyse the effect of different therapeutic modalities and their individual impact on outcomes.
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49 332 Surgery is a cornerstone in the management of GCTs and the role of retroperitoneal lymph node
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51 333 dissection (RPLND) for post-chemotherapy residual lesions has been well described in the adult
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3 334 literature ³⁶⁻³⁹; this analysis was unable to account for its contribution to outcome. A potential
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5 335 weakness of the study was its moderate rate of missing data on the variables needed to assign
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7 336 IGCCCG risk-group. However, the results remained unchanged in a sensitivity analysis in which
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10 337 patients with missing data were excluded, suggesting this factor did not affect conclusions. Lastly,
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12 338 since tumor marker levels in pediatric trials measured at diagnosis may have been pre-surgical
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14 339 levels rather than post-surgical levels, it is possible that some pediatric patients may have been
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16 340 miscategorized on their IGCCCG risk group, which would have biased our risk group analyses.
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19 341 However, the direction of this bias would not be expected to weaken the results.
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24 343 Adolescents with metastatic GCT are biologically and clinically more similar to young
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26 344 adults than children¹⁹, and this study demonstrates that they are also more alike in outcomes. While
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28 345 this study could not assess the superiority of any particular treatment approach or chemotherapy
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30 346 regimen, we believe it provides enough reason to consider treating adolescent males with GCTs
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32 347 differently than young children. We suggest that adolescent males with metastatic GCTs should
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34 348 be treated with approaches that have been developed with the wider evidence-base of adult
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36 349 testicular cancer, allowing them to receive the dose intensity of weekly bleomycin⁴⁰⁻⁴⁴, the
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38 350 predictive stratification of the IGCCCG^{17, 32, 45}, and the surgical guidelines for procedures such as
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40 351 RPLND of post-chemotherapy residual tumors³⁶⁻³⁹. All of these are standards-of-care among
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42 352 medical oncologists and urologists treating adults with metastatic GCTs.
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49 354 The results of this analysis, together with our earlier work on developing a revised GCT
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51 355 risk stratification⁴⁶, has already allowed us to incorporate these lessons into the current generation
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53 356 of GCT clinical trials in the United States and the United Kingdom. The current multi-group trial
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3 357 AGCT1531 (NCT03067181) includes all standard-risk patients between age 11-25 years as a
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5 358 single study group and prescribes these standards to all Furthermore, the COG has petitioned and
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7 359 joined two clinical trials led by adult testicular cancer cooperative groups: the ANZUP P3BEP or
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9 360 COG-AGCT1532 trial of accelerated BEP for high-risk patients, and the Alliance-A031102
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11 361 TIGER trial for patients with relapsed testicular GCTs. Both these studies were originally planned
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13 362 for adult patients alone, but on the evidence presented here, their eligibility criteria were modified
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15 363 to include adolescent patients. Taken together, these three trials cover the entire spectrum of
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17 364 adolescent GCTs. The availability of the data is due to the work of the Malignant Germ Cell
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19 365 international Consortium (MaGIC) which has galvanized a remarkable collaboration of multiple
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21 366 cooperative groups across the silos of age-groups and international borders⁴⁷. Through MAGIC
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23 367 and other similar efforts, we hope to provide a path that will narrow the gap and improve outcomes
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25 368 for AYA patients with germ cell tumours.
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514 **Table 1. Characteristics of Included Clinical Trials**

Study	Patients in Source Studies	Regimens	Number in present study
TE09	598 adults with good-prognosis testicular NGGCTs (273 under 30Y)	4BEP	139
		4JEB (Carboplatin AUC 5)	0
TE13	380 adults with poor-prognosis NGGCTs (121 under 30Y)	BEP/EP	58
		BOP/VIP-B	0
TE20	812 adults with good-prognosis GCTs (230 NGGCTs under 30Y)	4BEP or 3BEP	205
GC2	137 children with MGCT	JEb (Carboplatin 600 mg/m ²)	39
GC3	138 children with MGCT	JEb (Carboplatin 600 mg/m ²)	9
POG 9048 (INT 1016)	74 children with intermediate-risk NGGCTs	4PEb	0
POG 9049 (INT 0097)	299 children with high-risk MGCTs	4PEb	43
		4HD-PEb	43
P9749	25 children with high-risk MGCT	4HD-PEb	4
AGCT01P1	19 children with high-risk NGGCT	4C-PEb	5
AGCT0132	218 children with intermediate-risk NGGCTs	3PEb	47

Abbreviations: AUC, area under the curve; b, bleomycin once per cycle; B, bleomycin once per week; C, cyclophosphamide; E, etoposide; HD-P, high dose cisplatin; I, ifosfamide; J, carboplatin; MGCT, malignant germ cell tumors; NGGCT, non-germinomatous germ cell tumors; O, vincristine; P, cisplatin; POG, Pediatric Oncology Group; V, etoposide. * includes 38 patients from GCT2 and 1 patient from GCT1

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517 **Table 2. Patient Characteristics**

Variable	All Pts 0 to 30y N (%)	0 to <11y N (%)	11 to <18y N (%)	18 to 30y N (%)
	N=593	N=90	N=109	N=394
Age mean (SD)	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular	530 (89%)	67 (74%)	82(75%)	381 (96.7%)
Mediastinal tumor	44 (7%)	16 (18%)	22 (20%)	6 (1.5%)
Retroperitoneal	19 (3%)	7(8%)	5(5%)	7 (1.7%)
AFP (ng/mL)				
Mean	6294	29717	6924	857
(range)	(0 -700000)	(8-700000)	(0-96000)	(0-63630)
<1000	449 (76%)	34 (38%)	57 (52%)	358 (91%)
1,000-10,000	68 (11%)	23 (26%)	25 (23%)	20 (5%)
>10,000	62 (10%)	30 (33%)	23 (21%)	9 (2%)
Missing	14 (2%)	3 (3%)	4 (4%)	7 (2%)
βHCG (IU/L)				
Mean	12358	5	24289	11592
(range)	(0-1057700)	(0-62)	(1-990000)	(0-1057700)
<5,000	435 (73%)	33 (37%)	44 (40%)	358 (91%)
5,000 – 50,000	30 (5%)	0 (0%)	12 (11%)	18 (5%)
>50,000	14 (2%)	0 (0%)	3 (3%)	11 (3%)
Missing	114 (19%)	57 (63%)	50 (46%)	7 (2%)
LDH (U/L)				
Mean	587	701	934	500
(range)	(77-5540)	(149-3631)	(77-5540)	(93-5186)
<930	318 (54%)	22 (24%)	40 (37%)	256 (65%)
930-6200	47 (8%)	7 (8%)	19 (17%)	21 (5%)
>6200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	228 (38%)	61 (68%)	50 (46%)	117 (30%)
Non-pulmonary visceral metastases	34 (6%)	9 (10%)	16 (15 %)	9 (2%)
RiskGroup				
Good	267 (45 %)	4 (4%)	14 (13%)	249 (63%)
Intermediate	82 (14%)	21 (23%)	23 (21%)	38 (10%)
Poor	116 (20%)	41 (46%)	51 (47%)	24 (6%)
Missing	128 (21%)	24 (27%)	21 (19%)	83 (21%)

Abbreviations: AFP, a-fetoprotein; B-HCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

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521 **Table 3. Univariate Kaplan-Meier and Multivariable Cox Regression Analysis of Age-Group**
 522 **and Risk-Group.**

	Univariate				Multivariate		
All Patients (N=593)							
Variable	5y EFS (%)	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age Group							
0 - <11	90	0.31	0.14-0.65	0.002	0.30	0.14 – 0.63	0.001
11 - <18	72	Reference			Reference		
18 - <30	88	0.43	0.27-0.68	0.000	0.66	0.40 – 1.11	0.114
Risk Group							
Good	89	0.42	0.26-0.67	0.000	0.42	0.24 – 0.72	0.002
Intermediate	76	0.87	0.48-1.56	0.634	0.88	0.48 – 1.60	0.663
Poor	76	Reference			Reference		
JEB patients excluded* (N=545)							
Age Group							
0 - <11	92	0.21	0.07-0.60	0.004	0.21	0.07 – 0.59	0.003
11 - <18	69	Reference			Reference		
18 - <30	88	0.38	0.24-0.60	0.000	0.62	0.36 – 1.03	0.066
Risk Group							
Good	89	0.36	0.22-0.58	0.000	0.39	0.22 – 0.68	0.001
Intermediate	75	0.77	0.42-1.42	0.401	0.81	0.44 – 1.50	0.489
Poor	73	Reference			Reference		
Mediastinal primary tumors excluded** (N=549)							
Age Group							
0 - <11	89	0.41	0.18-0.94	0.035	0.40	0.108– 0.91	0.029
11 - <18	77	Reference			Reference		
18 - <30	87	0.55	0.33-0.93	0.024	0.83	0.347– 1.47	0.506
Risk Group							
Good	89	0.43	0.25-0.75	0.003	0.40	0.22 – 0.74	0.003
Intermediate	76	0.89	0.46-1.72	0.737	0.88	0.45 – 1.71	0.693
Poor	77	Reference			Reference		

Abbreviations: CI, confidence interval; EFS, event-free survival; JEB, carboplatin/etoposide/reduced bleomycin; N, number; y, years. *48 Patients- received JEB. **44 Patients with mediastinal tumours.

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3 528 **FIGURE LEGENDS**
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7 530 Figure 1. CONSORT diagram describing flow of patients through the study
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11 533 Figure 2. A) Event-free survival (EFS) and overall survival (OS) for all patients (N=593)

12 534 B) EFS by risk-group; C) EFS by age-group

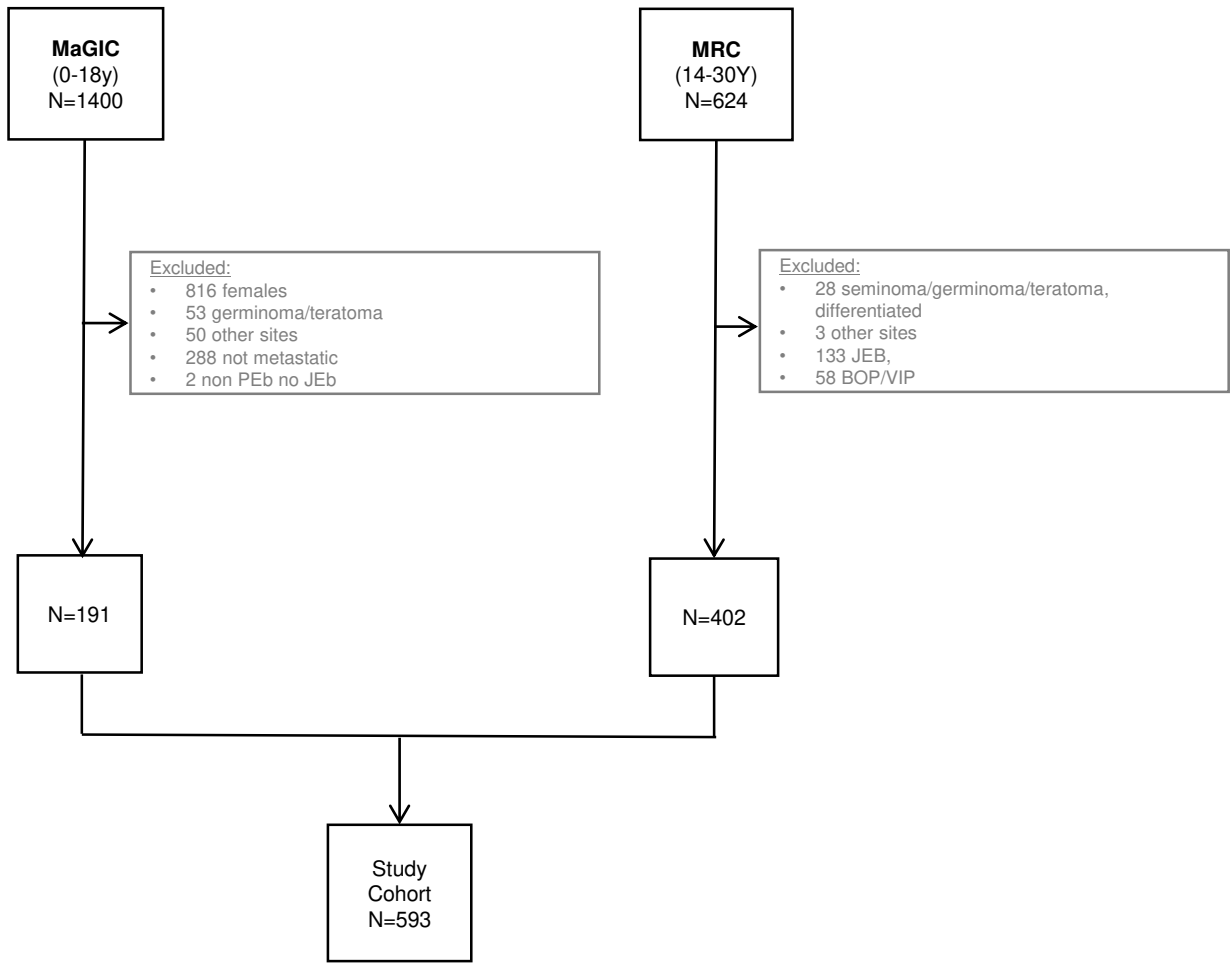
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16 537 Figure 3. A) EFS for children (age 0 to <11 years) by risk-group; B) EFS for adolescents (age 11

17 538 to <18 years) by risk-group; C) EFS for young adults (age 18 to <30 years) by risk-group.
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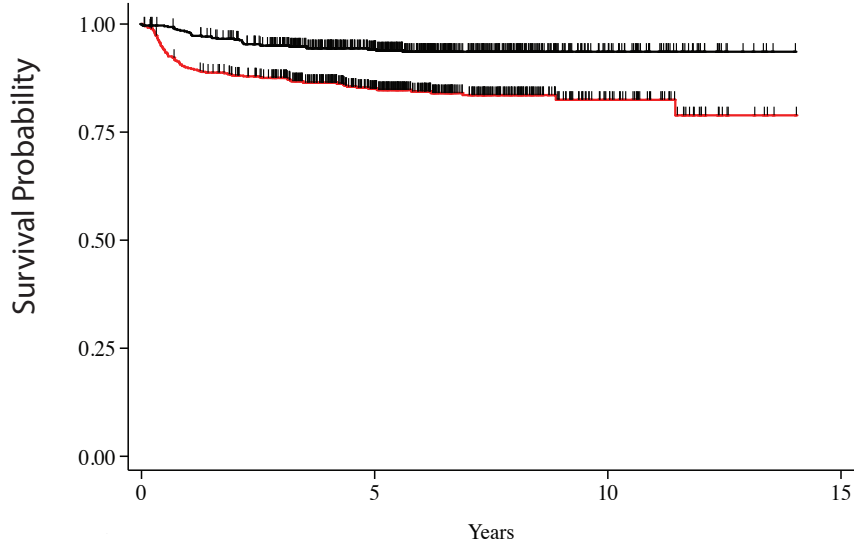
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MRC: Medical Research Council

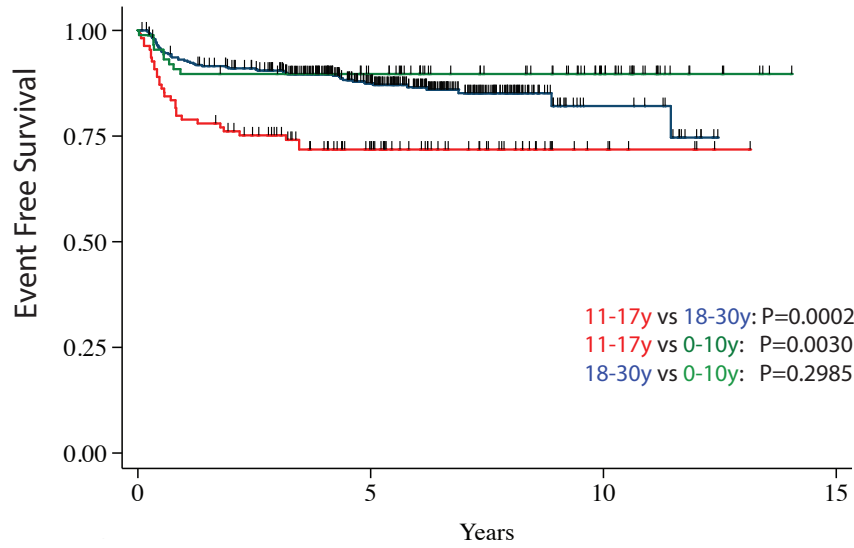
Figure 2.

A.



EFS	593	331	49	0
OS	593	365	58	0

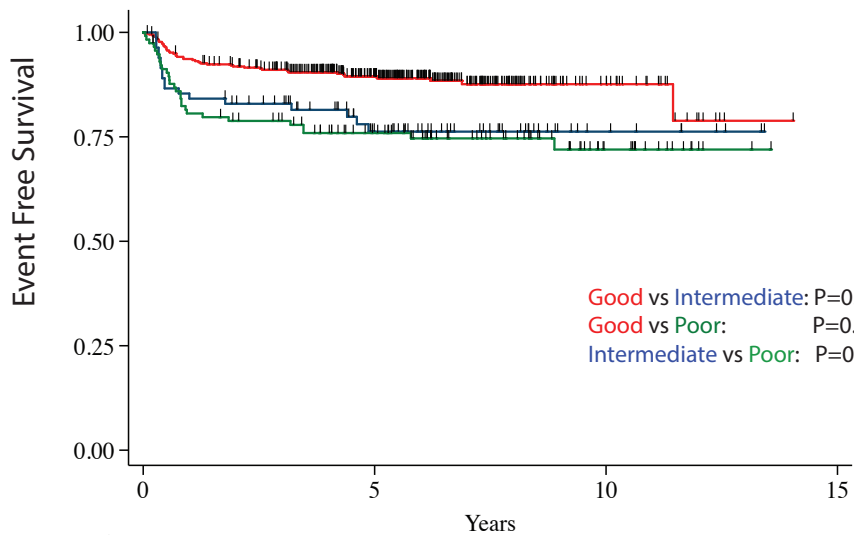
B.



11-17y vs 18-30y: P=0.0002
 11-17y vs 0-10y: P=0.0030
 18-30y vs 0-10y: P=0.2985

11-17Y	109	48	7	0
18-30Y	394	219	15	0
0-10Y	90	64	27	0

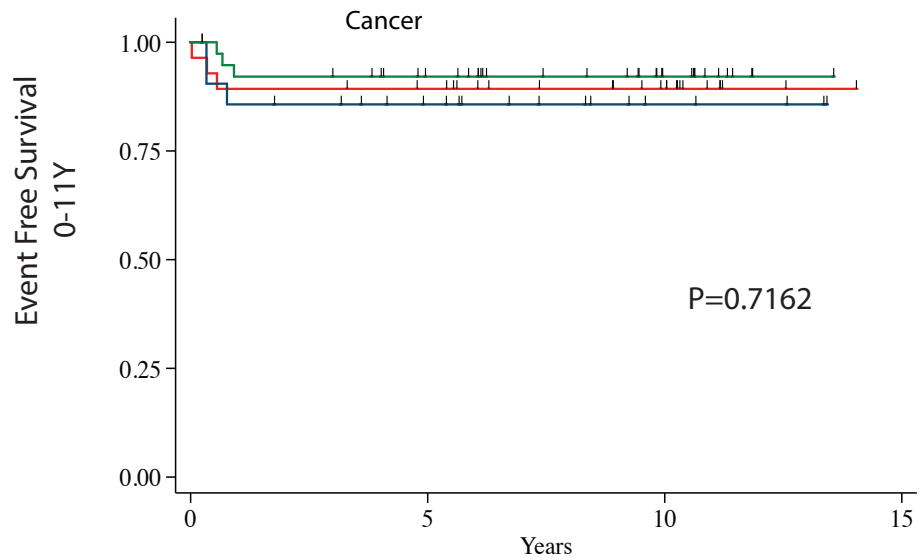
C.



Good vs Intermediate: P=0.0085
 Good vs Poor: P=0.0002
 Intermediate vs Poor: P=0.6458

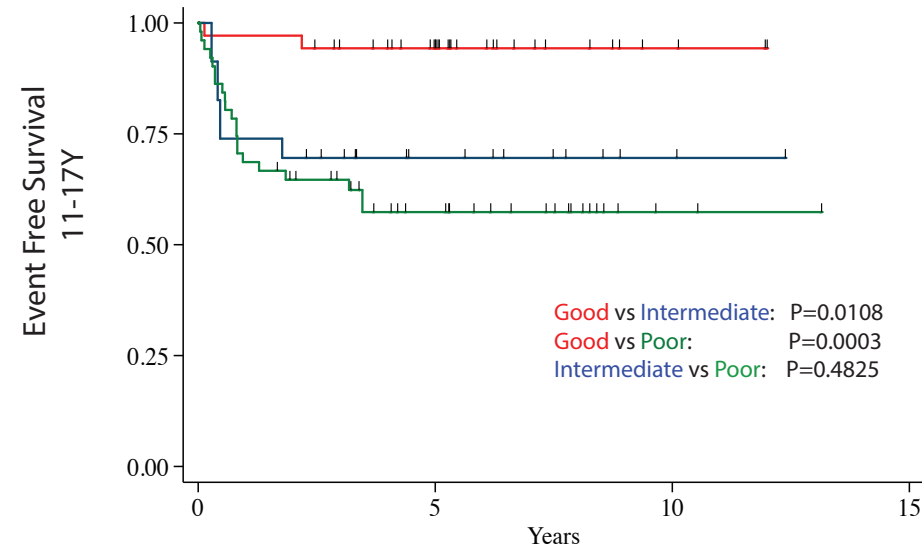
Good	395	226	25	0
Intermediate	82	40	8	0
Poor	116	65	16	0

A.



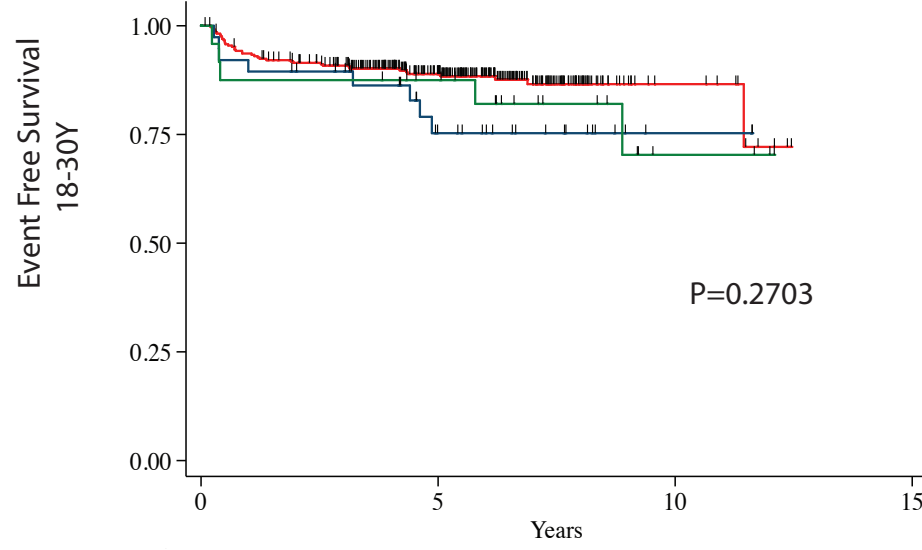
Good	28	23	12	0
Intermediate	21	13	4	0
Poor	41	28	11	0

B.



Good	35	20	3	0
Intermediate	23	9	2	0
Poor	51	19	2	0

C.



Good	332	183	10	0
Intermediate	38	18	2	0
Poor	24	18	3	0

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Study	Patients in Source Studies	Regimens	Number included in present study
TE09	598 adults with good-prognosis testicular NGGCTs (273 under 30Y)	4BEP 4JEB (Carboplatin AUC 5)	139 0
TE13	380 adults with poor-prognosis NGGCTs (121 under 30Y)	BEP/EP BOP/VIP-B	58 0
TE20	812 adults with good-prognosis GCTs (230 NGGCTs under 30Y)	4BEP or 3BEP	205
GC2	137 children with MGCT	JEb (Carboplatin 600 mg/m ²)	39 (+1 from GC1)
GC3	138 children with MGCT	JEb (Carboplatin 600 mg/m ²)	9
POG 9048 (INT 1016)	74 children with intermediate-risk NGGCTs	4PEb	0
POG 9049 (INT 0097)	299 children with high-risk MGCTs	4PEb 4HD-PEb	43 43
P9749	25 children with high-risk MGCT	4HD-PEb	4
AGCT01P1	19 children with high-risk NGGCT	4C-PEb	5
AGCT0132	218 children with intermediate-risk NGGCTs	3PEb	47

Abbreviations: AUC, area under the curve; b, bleomycin once per cycle; B, bleomycin once per week; C, cyclophosphamide; E, etoposide; HD-P, high dose cisplatin; I ifosfamide; J, carboplatin; MGCT, malignant germ cell tumors; NGGCT, non-germinomatous germ cell tumors; O, vincristine; P, cisplatin; POG, Pediatric Oncology Group; V, etoposide.

Variable	All Pts 0 to 30y N (%)	0 to <11y N (%)	11 to <18y N (%)	18 to 30y N (%)
	N=593	N=90	N=109	N=394
Age mean (SD)	19.4 (8.9)	1.9 (1.9)	14.7 (1.5)	24.8 (3.6)
Testicular	530 (89%)	67 (74%)	82(75%)	381 (96.7%)
Mediastinal tumor	44 (7%)	16 (18%)	22 (20%)	6 (1.5%)
Retroperitoneal	19 (3%)	7(8%)	5(5%)	7 (1.7%)
AFP (ng/mL)				
Mean	6294	29717	6924	857
(range)	(0 -700000)	(8-700000)	(0-96000)	(0-63630)
<1000	449 (76%)	34 (38%)	57 (52%)	358 (91%)
1,000-10,000	68 (11%)	23 (26%)	25 (23%)	20 (5%)
>10,000	62 (10%)	30 (33%)	23 (21%)	9 (2%)
Missing	14 (2%)	3 (3%)	4 (4%)	7 (2%)
βHCG (IU/L)				
Mean	12358	5	24289	11592
(range)	(0-1057700)	(0-62)	(1-990000)	(0-1057700)
<5,000	435 (73%)	33 (37%)	44 (40%)	358 (91%)
5,000 – 50,000	30 (5%)	0 (0%)	12 (11%)	18 (5%)
>50,000	14 (2%)	0 (0%)	3 (3%)	11 (3%)
Missing	114 (19%)	57 (63%)	50 (46%)	7 (2%)
LDH (U/L)				
Mean	587	701	934	500
(range)	(77-5540)	(149-3631)	(77-5540)	(93-5186)
<930	318 (54%)	22 (24%)	40 (37%)	256 (65%)
930-6200	47 (8%)	7 (8%)	19 (17%)	21 (5%)
>6200	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	228 (38%)	61 (68%)	50 (46%)	117 (30%)
Non-pulmonary visceral metastases	34 (6%)	9 (10%)	16 (15 %)	9 (2%)
RiskGroup				
Good	267 (45 %)	4 (4%)	14 (13%)	249 (63%)
Intermediate	82 (14%)	21 (23%)	23 (21%)	38 (10%)
Poor	116 (20%)	41 (46%)	51 (47%)	24 (6%)
Missing	128 (21%)	24 (27%)	21 (19%)	83 (21%)

Abbreviations: AFP, a-fetoprotein; B-HCG, beta subunit of human chorionic gonadotropin; LDH, lactate dehydrogenase.

	Univariate				Multivariate		
All Patient (N=593)							
Variable	5y EFS (%)	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age Group							
0 - <11	90	0.31	0.14-0.65	0.002	0.30	0.14 – 0.63	0.001
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Intermediate	76	0.89	0.46-1.72	0.737	0.88	0.45 – 1.71	0.693
Poor	77	Reference			Reference		

Abbreviations: CI, confidence interval; EFS, event-free survival; JEb, carboplatin/etoposide/reduced bleomycin; N, number; y, years. *48 Patients received JEb. **44 Patients with mediastinal tumours.

Univariate				Multivariate		
All Patient with non-missing IGCCCG (N=465)						
Variable	Hazard Ratio	95% CI	P value	Hazard Ratio	95% CI	P value
Age Group						
0 - <11	0.31	0.14-0.65	0.000	0.21	0.09 – 0.52	0.001
11 - <18	Reference			Reference		
18 - <30	0.43	0.14-0.65	0.002	0.59	0.32 – 1.07	0.081
Risk Group						
Good	0.29	0.17-0.51	0.000	0.29	0.15 – 0.58	<0.001
Intermediate	0.87	0.48-1.57	0.646	0.89	0.49 – 1.63	0.706
Poor	Reference			Reference		