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Review

Survival of non-seminomatous germ cell cancer patients according to the IGCC classification: An update based on meta-analysis

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ABSTRACT

The International Germ Cell Consensus (IGCC) Classification distinguishes patients with non-seminomatous germ cell tumours (NSGCT) with a good, intermediate or poor prognosis, with a reported 5-year overall survival of 92%, 80% and 48%, respectively. Since the IGCC classification was based on patients treated between 1975 and 1990, we aimed to investigate whether survival has improved for more recently treated patients. We did a systematic search of the literature and included studies on survival of patients with NSGCT, treated after 1989 and classified according to the IGCC classification. Survival estimates of selected studies were pooled using meta-analytic techniques. We included 10 papers, describing 1775 patients with NSGCT with good ($n = 1087$), intermediate ($n = 232$), or poor ($n = 456$) prognosis. Pooled 5-year survival estimates were 94%, 83% and 71%, respectively. Since the publication of the IGCC classification, there was a small increase in survival for good and intermediate prognosis patients, and a large increase in survival for patients with a poor prognosis. This increase is most likely due to both more effective treatment strategies and more experience in treating NSGCT patients.

1. Introduction

Testicular germ cell tumours (seminomatous and non-seminomatous) are the most common cancers among young adult men. Since the 1970s the overall long-term cure rate of patients with germ cell tumours has increased to over 80%, mainly due to the use of cisplatin-based chemotherapy that can cure advanced disease.[1–4] Due to the high overall cure rate, interest has shifted to reducing treatment related toxicity for patients with a good prognosis.[5] However, a small group of patients with a poor prognosis remains who might profit from alternative, more severe treatment strategies.[6–8]

The coexistence of classifications differing in type, complexity and ability to separate good from poor prognosis, has complicated international collaboration in randomised trials and making comparison of non-randomised studies impossible. Therefore, the International Germ Cell Consensus (IGCC) Classification was developed, based on individual patient data from previously conducted studies, which has now been widely adopted.[9] The IGCC classification identifies good, intermediate and poor prognosis groups using the following variables: primary site, presence of non-pulmonary visceral metastases (NPVM) and levels of the tumour markers alpha-fetoprotein (AFP), human chorionic gonadotrophin

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Table 1 – International Germ Cell Consensus Classification for nonseminomatous germ cell tumours

Good prognosis
Testis/retroperitoneal primary site
and
No non-pulmonary visceral metastases
and
AFP good and HCG good and LDH good
5 year PFS 89%
5 year OS 92%
Intermediate prognosis
Testis/retroperitoneal primary site
and
No non-pulmonary visceral metastases
and
AFP intermediate or HCG intermediate or LDH intermediate
5 year PFS 75%
5 year OS 80%
Poor prognosis
Mediastinal primary site
or
non-pulmonary visceral metastases
or
AFP poor or HCG poor or LDH poor
5 year PFS 41%
5 year OS 48%

Tumour markers α-fetoprotein (AFP)/human chorionic gonadotrophin (HCG)/lactic dehydrogenase (LDH): Good-AFP < 1000 ng/ml, HCG < 5000 iu/l, LDH < 1.5 × upper limit of normal; Intermediate-AFP 1000–10,000 ng/ml, HCG 5000–50,000 ng/ml, LDH 1.5–10 × *N*; Poor-AFP > 10,000 ng/ml, HCG > 50,000 iu/l, LDH > 10 × *N*.

(HCG) and lactic dehydrogenase (LDH) (Table 1). According to the IGCC classification 56%, 28% and 16% of patients with non-seminomatous germ cell cancer were allocated to the good, intermediate and poor prognosis groups, with a 5-year overall survival of 92%, 80% and 48%, respectively.[9] The IGCC classification is currently the standard for selecting patients for randomised controlled trials (RCTs)[5,10,11] and for the analysis of observational studies, such as Phase I/II trials and hospital series. In observational studies, direct comparison with patients receiving standard treatment is not possible and, therefore, results are usually compared with the survival estimates reported by the IGCC classification.

The IGCC classification is based on patients treated between 1975 and 1990. Survival might be better for more recently treated patients with non-seminomatous germ cell tumours (NSGCT). There are some indications that indeed survival has improved. Sonneveld and colleagues reported a 10-year disease specific survival of 94%, 87% and 66% for good, intermediate and poor prognosis patients treated between 1987 and 1996.[3] Germa-Llurch and colleagues reported a 3 year overall survival of 97%, 89% and 72% for patients treated between 1994 and 2001.[12] However, all relevant studies should be considered for a valid update of the survival estimates of the IGCC classification. We therefore conducted a meta-analysis to update the survival estimates of the prognosis groups in the IGCC classification, using the most recent studies reporting on the survival of non-seminomatous germ cell cancer patients.

2. Patients and methods

2.1. Literature search

We conducted a systematic literature search of the PubMed database and the Cochrane Central library for the period January 1997 to December 2004. The terms used for the search were the text words "igcc" (OR "igccc", "igcccg", "IGCC", "IGCCC", "IGCCCG"), "germ cell" (OR "germ-cell"), "cancer" or "tumor" (OR "tumour ", "tumors", tumours") and the MeSH terms "neoplasms, germ cell and embryonal" and "testicular neoplasms". The search was limited to "human", and the English language. Furthermore, we used the ISI Web of Science to screen all papers referring to the original report by the IGCCCG and we screened all papers of the EORTC Genito-Urinary Tract Group on testicular cancer published since 1997. This resulted in 350 papers.

Fig. 1 shows the selection of papers for the meta-analysis. Of the 350 papers, 284 papers reporting on children, other cancers, testicular cancer other than NSGCT (seminoma, relapse, residual mass, early disease), and the histology, biology, diagnosis, or treatment of testicular cancer, as well as review articles and double papers were excluded. The remaining 66 papers were retrieved for further evaluation. Forty-five papers were excluded because no survival estimates were given, patients were not classified according to the IGCC classification, overlapping datasets were described, no distinction between seminoma and non-seminoma was made, less than 20 patients were included, or papers were published in a journal without an impact factor. When studies reported on the same patient population, the most recent study or the one with the longest follow-up time was chosen. The 21 remaining papers mostly reported on previously published trials, in which patients were retrospectively allocated to the IGCC prognosis groups. Papers describing patients treated before 1989 ($n = 11$) were excluded due to possible overlap with the IGCCCG database resulting in 10 studies eligible for inclusion in the meta-analysis. One of these studies made no distinction in survival between seminomatous and non-seminomatous patients.[5] Since this was the largest study on good prognosis patients, we requested the original data so that the study could be included in the meta-analysis.

2.2. Data extraction and analysis

The following characteristics of the included 10 reports were extracted: treatment period, number of patients, median age, median follow-up and overall or disease-free survival. Furthermore, we noted the design of the study (Phase I, II or III trial, or hospital registry), IGCC prognosis group (good, intermediate, poor), number of patients per IGCC prognosis group and survival per IGCC prognosis group. Survival per prognosis group was obtained from tables or Kaplan–Meier plots.

Since studies differed in years of follow-up for which survival was given, survival estimates could not be obtained directly.[13] We therefore pooled the survival curves of the 10

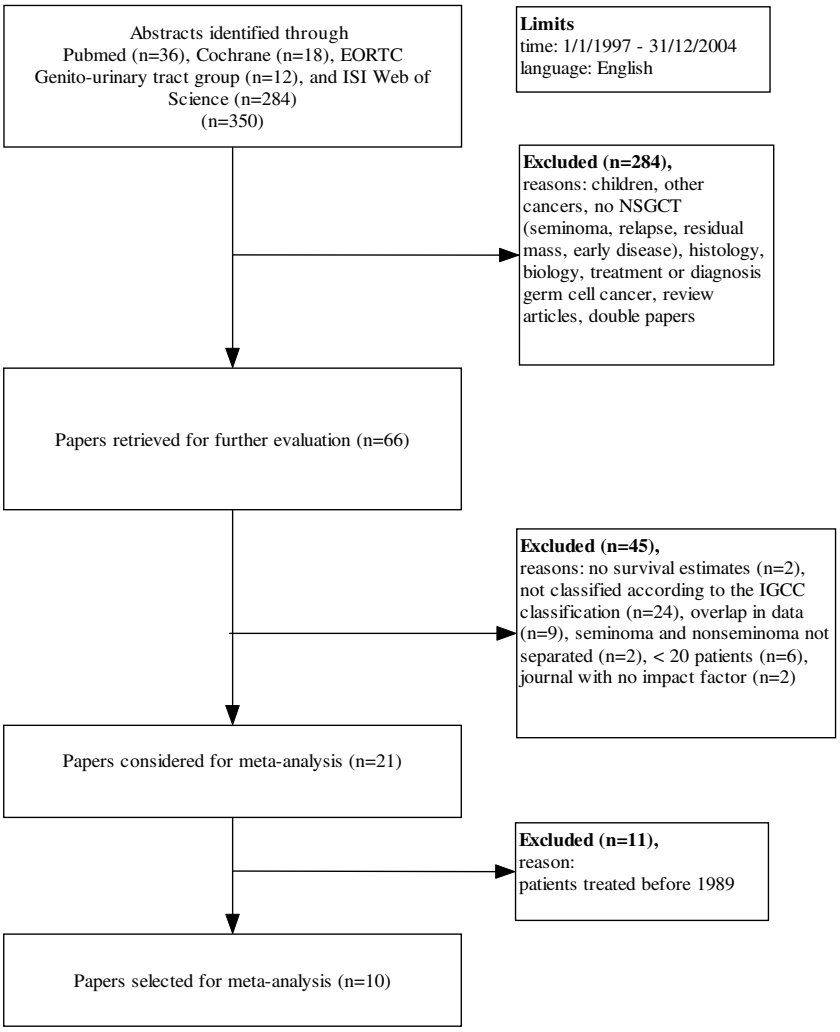

Fig. 1 – Flow chart showing the selection process of publications for meta-analysis. *Note:* NSGCT, non-seminomatous germ cell tumours.

selected studies. For each curve the survival probability at each year of follow-up was calculated by measuring the height of the curve at each year of follow-up. Since information on censoring was not given in all studies, survival estimates could not be pooled using the exact number of patients at risk and the exact number of deaths per year of follow-up. We therefore used a life table approach in which for each study the number of patients at risk and the number of deaths per year were based on the total number of patients in the study and the survival probability per year of follow-up.[13] Pooled survival estimates for each year were obtained by pooling the estimated number of patients at risk and the estimated number of deaths per year of follow-up from each study. In two studies no survival curves were available.[5,6] In these cases the reported 2-year overall survival was used to estimate the number of patients at risk and the number of events at one and two years of follow-up.

3. Results

The 10 included studies reported data on 1775 patients with non-seminomatous germ cell cancer, treated between 1989 and 2001 (Table 2). The median age varied from 26 to 32 years, and median follow-up time from 22 to 63 months. Eight studies reported overall survival as primary outcome, and two studies reported disease-specific survival.[14,15]

Table 3 shows study design, treatment regimen, number of patients per IGCC prognosis group and survival per IGCC prognosis group per study. Of the 1775 patients available for analysis, 1087 (61%) were classified as good prognosis, 232 (13%) as intermediate prognosis and 456 (26%) as poor prognosis patients. Three studies were based on hospital registries in which patients were treated with either standard-dose treatment cisplatin–etoposide–bleomycin (BEP), dose intensive regimens[12,16] or high-dose chemotherapy with stem cell support.[15] Muramaki and colleagues describe the treatment results of 8 good prognosis, 24 intermediate prognosis and 14 poor prognosis patients treated with either standard-dose chemotherapy ($n = 29$), or high-dose chemotherapy ($n = 17$).[15] No details were given on treatment received within the IGCC prognosis groups. Five-year disease-specific survival was 88% for good prognosis, 77% for intermediate prognosis, and 71% for poor prognosis patients. Of the 178 patients described by

Table 2 – Characteristics of 12 studies included in meta-analysis

No. (Refs.)	Author	Year of publication	Study period	Number of patients	Median age (yr)	Median follow up (months)	Primary outcome
1[15]	Muramaki et al.	2004	1990–2001	46	31	63	5-yr DSS
2[18]	Anthoney et al.	2004	1995–1999	43	27	59	3-yr OS
3[16]	Bhala et al.	2004	1989–2001	178	29	22	5-yr OS
4[14]	Schmoll et al.	2003	1993–1999	182	29	47	5-yr DSS
5[19]	Christian et al.	2003	1989–2000	54	27	48	3-yr OS
6[20]	Fizazi et al.	2002	1993–1998	57	28	31	3-yr OS
7[12]	Germa-Lluch et al.	2002	1994–2001	523	26	33	3-yr OS
8[5]	De Wit et al.[a]	2001	1995–1998	630	32	25	2-yr OS
9[22]	Decatris et al.	2000	1994–1999	20	28	27	4-yr OS
10[6]	Bokemeyer et al.[b]	1998	1990–1995	42	–	31	2-yr OS
Total				1775			

OS, overall survival; DSS, disease specific survival.
a Only nonseminoma included.
b Intermediate prognosis patients only, poor prognosis patients included in study 4.

Table 3 – Design, treatment, IGCC prognosis group, number of patients and survival per IGCC prognosis group of 12 included studies

No. (Refs.)	Design	Treatment	IGCC	Number of patients	OS (95% CI)
1[15]	Hospital registry	BEP or HD − CT	Good	8	88%
			Intermediate	24	77%
			Poor	14	71%
2[18]	Phase II	BOP + BEP	Intermediate	24	79% (57–91%)
			Poor	19	84% (59–95%)
3[16]	Hospital registry	BEP or POMB + ACE	Good	120	95% (91–100%)
			Intermediate	25	82% (65–98%)
			Poor	33	57% (36–79%)
4[14]	Phase I/II	HD − VIP + PBSC	Poor	182	73%
5[19]	Phase II	CBOP + BEP	Poor	54	88% (71–95%)
6[20]	Phase II	BOP + CISCA + BOMP + ACE	Intermediate	19	83% (67–100%)
			Poor	38	67% (53–84%)
7[12]	Hospital registry	BEP or BOMP + EPI	Good	329	97% (95–99%)
			Intermediate	98	89% (81–96%)
			Poor	96	72% (62–82%)
8[5]	Phase III	BEP vs. BEP + EP	Good	630	97%
9[22]	Phase II	BEP + HD − CEC + PBSC	Poor	20	66%
10[6]	Phase II	HD − VIP + PBSC	Intermediate	42	89%
Total			Good	1087	94%
			Intermediate	232	83%
			Poor	456	71%

Treatment details: BOP + BEP = bleomycin, vincristine, cisplatin + bleomycin, etoposide, cisplatin; BEP = bleomycin, etoposide, cisplatin; POMB + ACE = cisplatin, vincristine, methotrexate, bleomycin + actinomycin D, cyclophosphamide, etoposide; HD − VIP + PBSC = high dose cisplatin, etoposide, ifosfamide + peripheral blood stem cell support; CBOP + BEP = carboplatin, bleomycin, vincristine, cisplatin + bleomycin, etoposide, cisplatin; BOP + CISCA + BOMP + ACE = bleomycin, vincristine, cisplatin + cisplatin, cyclophosphamide, doxorubicin + cisplatin, vincristine, methorexate + bleomycin, etoposide, dactinomycin, cyclophosphamide; BOMP + EPI = bleomycin, vincristine, methotrexate, cisplatin + etoposide, ifosfamide, cisplatin; BEP + EP = bleomycin, etoposide, cisplatin + etoposide, cisplatin; HD − CEC = high dose carboplatin, etoposide, cyclophosphamide.

Bhala and colleagues, 125 received standard-dose chemotherapy of whom 108 were good prognosis, 9 intermediate prognosis and 8 poor prognosis patients. Forty-eight patients received dose intense alternating chemotherapy, POMB-ACE, of which 10 were good prognosis, 15 intermediate prognosis and 23 poor prognosis patients.[16] Five-year survival was 95% for good prognosis patients, 82% for intermediate prognosis, and 57% for poor prognosis patients. Germa-Llurch and colleagues reported on 523 patients, of whom 485 patients were treated with standard-dose chemotherapy, and 38 of 96 poor prognosis patients with modified standard treatment BOMP-EPI.[12,17] Three-year overall survival was 97% for good prognosis, 89% for intermediate prognosis, and 72% for poor prognosis patients.

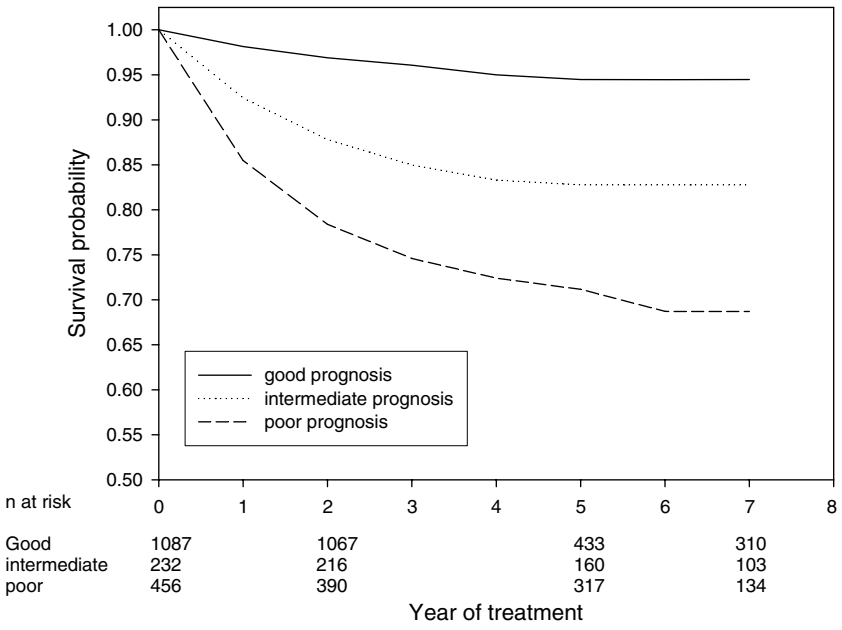

Fig. 2 – Pooled survival data for patients with non-seminomatous germ cell tumours treated after 1989, with either good, intermediate or poor prognosis according to the IGCC classification.

Six Phase I or II trials evaluated new treatment regimens against standard treatment.

Three Phase I/II trials evaluated the effect of dose intensive alternating chemotherapy (BOP + BEP), intensive induction chemotherapy (CBOP + BEP) or dose dense alternating chemotherapy (BOP + CISCA + BOMP + ACE).[18–20] These studies give survival estimates for 154 intermediate and poor prognosis patients ranging from 67% to 88%.

Three studies evaluated the effect of high-dose chemotherapy with peripheral blood stem cell support.[6,14,21] Survival for 202 poor prognosis patients was 66% and 73%, respectively.[14,21] The 42 intermediate prognosis patients receiving high-dose chemotherapy had a 2-year overall survival of 89%.[6] Only one study was a RCT.[5] It showed the equivalence of 3 versus 4 cycles of bleomycin, etoposide and cisplatin for good prognosis patients, resulting in a 2-year overall survival of 97%.

In Fig. 2 survival estimates up to 7 years follow-up are given for patients with good, intermediate and poor prognosis separately. At 5 years follow-up, pooled survival estimates were 94, 83 and 71% respectively for patients with good, intermediate and poor prognosis.

4. Discussion

This meta-analysis demonstrated that survival of recently treated poor prognosis patients with non-seminomatous germ cell tumours was better than the survival reported by the IGCC classification. There was only a small increase in survival for patients with a good or intermediate prognosis.

Based on a systematic review, we included 10 studies reporting on 1775 patients of which 1087 had a good prognosis, 232 intermediate and 456 poor.

Five-year survival of poor prognosis patients has increased strongly (71% vs. 48%). This may partly be due to promising results obtained in Phase I/II trials with new treatments, although these results still need to be confirmed in RCTs. However, survival for poor prognosis patients may have increased over time irrespective of these more recent treatment regimens.

First, because standard treatment improved when etoposide replaced vinblastine, after a RCT demonstrated that etoposide was more active and less toxic than vinblastine.[3,22] Second, because research centres gained experience with the treatment of advanced testicular cancer.[23] Furthermore improvements in second-line treatment may also have contributed to an increase in survival, especially for poor prognosis patients.[24] This is supported by two studies, excluded from the meta-analysis because of possible overlap with the IGCCG data. These two studies included patients who were treated with standard-dose chemotherapy and who were selected from hospital registries.[3,8] Hinton and colleagues[8] reported 5-year overall survival of 60% for poor prognosis patients treated with either standard-dose BEP or VIP, and Sonneveld and colleagues reported a 10-year disease-specific survival of 66% for poor prognosis patients treated with standard-dose BEP.[3,8] Furthermore, survival for poor prognosis patients treated after 1985 was 59% in a retrospective analysis of the IGCCCG data.[25]

We found only a small increase in 5-year survival for good and intermediate prognosis patients compared to survival estimates reported by the IGCC classification (94% vs. 92% and 83% vs. 80%, respectively). While for good prognosis patients it has been established that 3 cycles and 4 cycles of BEP are equivalent,[5] not much research has been done regarding intermediate prognosis patients, which explains the limited number of intermediate prognosis patients in this review compared to the original IGCC data (13% vs. 28%). Intermediate prognosis patients described in trials were initially selected for trials as having 'advanced' testicular cancer

according to the Indiana classification, and were retrospectively classified as intermediate prognosis according to the IGCC classification.[26] One RCT by the EORTC compared BEP and VIP in intermediate prognosis patients and found no difference.[27] However the use of different criteria than the IGCC classification to define intermediate prognosis patients limits the interpretation of the results of this RCT.[9,28] Alternatives to standard-dose BEP could further improve survival for intermediate prognosis patients. Currently, intermediate prognosis patients are also being considered for high-dose chemotherapy with stem cell support in a RCT including both intermediate prognosis and poor prognosis patients.[10] Furthermore the EORTC is currently conducting a large RCT comparing BEP with T-BEP (BEP + paclitaxel) for intermediate prognosis patients.[29]

Our study has some limitations. The survival estimates in our study might be overestimated due to publication bias. Trials showing good results for a certain treatment are more likely to be reported on. This effect could be even stronger in our study, since most data were published previously and later re-analysed according to the IGCC classification. This may have been done selectively, only considering those studies favouring an alternative treatment such as high-dose chemotherapy with stem cell support.

Survival estimates might also have been overestimated due to selection bias within the studies. Patients participating in clinical trials are usually selected because of their relatively 'good' health (e.g. adequate renal function, adequate bone marrow function, no other major organ dysfunction) compared to patients not treated in a clinical trial. Since follow-up differed between studies, we could not directly combine 5-year overall survival. Since not all studies provided information on number of patients at risk or 95% confidence intervals of survival estimates, the 95% confidence intervals of pooled estimates could not be provided. This illustrates the importance of reporting adequate information on survival, e.g., 95% confidence intervals and number of patients at risk.

In studies describing poor prognosis patients all or almost all patients were treated with alternative treatment regimens, even in studies based on hospital registries.[12,15,16] Since no RCTs have been published demonstrating the effect of these treatment regimens, it cannot fully be determined what causes the increase in survival for poor prognosis patients.

Patients in the selected studies were mostly treated in clinical trials and centres specialized in the treatment of testicular cancer. This may limit the generalisability of the survival estimates to patients treated in other hospitals. However, Collette and colleagues concluded that poor prognosis patients should be treated in specialized treatment centres since larger centres with more experience had a better survival than smaller centres with less experience.[23]

We will have to wait for the completion of ongoing RCTs for poor prognosis patients to know what survival of patients receiving standard treatment is nowadays, and if new treatment regimens are really more effective. Currently two RCTs are investigating the effect of high-dose chemotherapy, one in Europe which is still including poor prognosis patients and one in the US for which accrual of patients has closed.[10,11] Unfortunately, it may take years before the final results of these RCTs are published, although insight into the 2-year survival would already be helpful.

Meanwhile we will have to use the information available in the literature. Based on our meta-analysis we conclude that there was a large increase in survival for poor prognosis patients, while there was only a small increase in survival for good prognosis and intermediate prognosis patients. Although this could be explained by alternative treatment regimens investigated since the introduction of the IGCC classification, there is also evidence that survival increased over time irrespective of treatment received. We therefore recommend that results of Phase I/II trials for poor prognosis patients should no longer be compared with the survival estimates for poor prognosis patients reported by the IGCC classification as this may overestimate the effect of new treatment regimens.

Conflict of interest statement

None declared.

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