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Prognosis of metastatic giant cell tumor of bone in the pre-denosumab era. A systematic review and a meta-analysis

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Abstract

Background: Data on long-term prognosis of metastatic GCT (mGCT) is scant. The frequency of spontaneous regressions (SRs) is unknown. We aimed to estimate the prognosis of mGCT.
Methods: We searched electronic scientific literature databases and generic Internet from January 1980 to August 2017. After identifying eligible studies we performed descriptive analyses and meta-analyses to estimate overall survival (OS), disease specific survival (DSS) and frequency of SRs in the years before the widespread use of denosumab. We performed pre-specified subgroup analyses of studies published before and after 2000 and of those with more and less than 10 years of follow-up.
Results: After retrieving and combining data from 26 relevant retrospective case-series totaling 242 patients with a median follow-up of 6.9 years, the estimated pooled OS was 86.9% (95% CI 78.0–94.2). Pooled DSS was 88.0% (95% CI 79.7–94.7). SRs were observed in 4.5% of patients. In the subgroup of studies published after 2000 mGCT was the only cause of death of affected subjects. In case-series with a follow-up longer than 10 years pooled DSS was 69.7% (95% CI 25.5–99.8).
Conclusions: To our knowledge this is the first study to derive estimated pooled OS and DSS of mGCT based on a large dataset. SRs were not exceptional phenomena. In a long run the disease could impact in a significant way on the life expectancy of affected subjects.

Key words: Lung-Surg, Lung-Med, orthopedics/sarcoma

Introduction

Giant cell tumor of bone (GCT) is a benign neoplasia prone to an aggressive local behavior and, to a lesser extent, to metastasize (1,2). It represents 4–8% of all primary bone tumors in USA and Europe (3). Higher figures have been reported in Asian populations, up to 14% in China and up to 30% in Southern India (4). Estimating of the incidence of GCT is challenging, because few population-based cancer registries record benign bone tumors (5). Its incidence was 1.3 per million people per year in a population-based registry in Sweden (3). It originates in a mature bone tissue, and thus, more than a half of the cases is diagnosed between the third and fifth decade of life (4).

GCT is composed by three main cellular subtypes: fusiform stromal cells (SC), osteoclast-like giant multinucleated cells (GMC) and macrophage-like round mononuclear cells (RMC). The SC is the main component of neoplasia, responsible for its proliferative

capacity. Their biological properties are those of the osteoblastic linage cell. They express the ligand of receptor activator nuclear factor kappa-B (RANK-L) in their surface (6). The GMC exhibit osteoclast-like phenotypic features and have the bone resorption as their main function (1,2,7–9). The GMC are formed as a result of RMC fusion. The recruitment of RMC, their fusion, and the activity of GMC is dependent on numerous chemotactic factors derived from SC (1,2,7–13).

The biological behavior and clinical course of the disease are both difficult to predict: 18–50% relapse locally after surgical resection, and 2–3% metastasize systemically, mainly to lung (11,12,14). Pulmonary metastases (MTS) are histologically benign, and malignant transformation occurs in less than 1% of cases (15). Most of them are metachronic and only 6–23% are synchronic (16,17). Time to systemic relapse varies greatly from a few months to more than 10 years, averaging 1.5–5 years in large case-series (4,17–20). The data on long-term prognosis of metastatic GCT (mGCT) are mainly limited to small retrospective studies. The largest of them, recently published by Yang et al., found a 94.4% 5-year survival rate based on data from 42 patients (21).

Recommendations for the management of mGCT are mostly based on Phase 2 studies reporting on a mix of localized and metastatic GCT, small retrospective series and expert opinion, due to the lack of published randomized, comparative research, as a consequence of the rarity of the condition. Complete resection, when feasible, is the treatment of choice (17,18,22,23). For unresectable MTS, medical treatment or surveillance are the available options. The National Comprehensive Cancer Network (NCCN) most recent guidelines consider denosumab and interferon- alfa as options for the pharmacological treatment (24). Cytotoxic chemotherapy also has been used, frequently in combination with other modalities, mainly surgery (18,20,22,25–28), but its efficacy for benign mGCT has been scarcely reported, and its role is loosely determined.

While bisphosphonates (BP) actions both upon SC and GMC (29,30), denosumab, a fully human monoclonal (igG2) antibody against RANK-L, interferes with SC stimulation of GMC, producing a marked depletion of GMC, partial maturation toward the osteoblastic phenotype and osteoid formation (31–33).

Treatment with BP has shown to be effective in the adjuvant setting (34) with fewer data in mGCT, but significant tumor size reduction seems not to be a rule (35). Several published Phase 2 clinical trials using denosumab enrolled patients with mostly unresectable or unsuitable for resection GCT, with a variable proportion (near 20%) of patients with lung MTS (33,36–38). Although all showed very high response and disease control rates, none of them provided data on patients with lung MTS separately. The follow-up was short in all but one (37). In this study that reported on 54 patients treated with denosumab for a median of 54 months with no progression, 14 had MTS (37). However, 6% of treated patients had osteonecrosis of the jaw and 4% atypical femoral fractures as adverse effects, limiting the duration of the treatment (37). After denosumab discontinuation, 4 out of 10 patients experienced progression of disease (37). Similar rates of reduced compliance and tumor re-growth after the denosumab withdrawal was seen in a study from Norway (39). On the other hand, an indolent course with a 100% survival was reported even without treatment (28,40,41). Moreover, cases of spontaneous regressions (SRs) of lung MTS have repeatedly been published in the literature (16–18,20,22,42,43), but its frequency has been never determined. To our knowledge, no estimations of the prognosis of mGCT based on a large, representative sample with a long follow-up period have been published to date. These uncertainties could difficult the appraisal of the efficacy of treatments in non-comparative studies. In the absence of published randomized trials, pooled estimates with a better precision derived from meta-analyses could be useful in clinical practice. We aimed to estimate the overall survival (OS), disease specific survival (DSS) and SRs rate of mGCT, and depict whether there are some particular clinical and radiological features associated with this phenomenon.

Methods

We performed a systematic review and a meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (44), and the AMSTAR 2 guidance document (45).

All authors approved the study protocol prior to start. We searched Medline, EMBASE, LILACS and the Cochrane Library, from 1 January 1980 to 30 August 2017. Also, a generic Internet search was done. Reference lists of included documents were also hand-searched, as well as their related articles in PubMed and Scholar Google. Medline search terms included 'Giant Cell Tumor of Bone'[Mesh], 'Neoplasm Metastasis'[Mesh], 'Fatal outcome' [Mesh], 'Survival'[Mesh], 'Denosumab' [Mesh], 'Spontaneous regression'. Their combination into search strategies utilized with their yield is shown in Table A1.

We included journal articles and meeting's abstracts reporting on clinical studies of any design, describing at least four patients (less were considered a case reports) with benign mGCT, published between 1980 and 2017, in English, Spanish, Portuguese and Russian languages. Reliance on either histopathological examination or imaging studies for the diagnosis of MTS was allowed.

In order to reduce bias we decided to limit our analysis to the pre-denosumab era, excluding studies in which denosumab was used. This drug, in the indirect comparisons, seems to be a more potent inhibitor of RANK/RANKL pathway than BP (30). Thus, while on-treatment, it could potentially improve the course of mGCT in a significant way, leading to selection bias in pooled analysis due to the inclusion of a mixture of subjects with unequal interventions. On the other hand, unlike zolendronic acid, in preclinical models denosumab fails to reduce SC viability (46,47) in line with the observation of SC persistence in spite of denosumab exposure and tumor re-growth after treatment cessation (37,39,48,49). In a very long run, with large periods of denosumab off, it might lead to the loosing of the initial advantage and even the appearance of a bias in the opposite direction. Apart from the aforementioned reasons for its exclusion, we found no study describing the prognosis of denosumab treated patients separately from the results observed in patients treated with other options in the same study, in order to perform subgroup analyses.

Other exclusion criteria were malignant GCT and the lack of data on disease status at the end of follow-up. When there was a suspicion that two case-series were sharing the same patients, we kept the one with a better methodological quality, and/or a larger size and/or a longer follow-up, as judged by the whole team of investigators in consensus.

Two rounds of article screenings were done, one with titles and abstracts, and the other with the full-texts of potentially eligible articles, each one of them done by pairs of authors according to pre-specified criteria. Data from included articles were extracted by two reviewers and, in the case of disagreements, group consensus was reached. Whenever deemed necessary, authors of articles were contacted by

e-mail for additional information. We extracted data on clinical characteristic of patients, follow-up length, treatment modalities and disease status at the end of follow-up. The follow-up period was defined as time elapsed from MTS diagnosis to the end of follow-up. Deaths due to treatment complications were considered as death from disease.

For the risk of bias assessment of the retrospective studies the ROBINS-I checklist was used (50). The assessment of publication bias was performed with Stats Direct, version 2.7.2.

We pooled data from included studies to estimate overall survival (OS), disease specific survival (DSS), non-related death rate (NRD), absence of disease at the end of follow-up (NED) and SR rate. DSS denotes cause-specific survival, considering for its calculation only deaths from the disease and discarding all other causes of death. Student's *t*-test for unknown variance was done at alpha level of 0.05. We conducted fixed and random effects proportion meta-analyses, using STATA 14.0 (StataCorp LP, College Station, TX, USA), since no individual prospective information on censoring was available due to the fact that all studies were retrospective case-series in nature. For the fixed effects model, we used the inverse of the generic variance method (51,52). We used the Freeman–Tukey variant of the arc-sine square-root of transformed proportions method to stabilize the variance of proportions. We applied DerSimonian–Laird weights for the random-effects model where heterogeneity between studies was found. We calculated the I^2 statistic as a measure of the proportion of the overall variation attributable to between-study heterogeneity. We performed two separate pre-specified subgroup analyses comparing studies published before and after 2000 and studies with follow-up greater and lesser than 10 years. The cut-off points were chosen under the presumption that they may reflect actual changes in disease management. A meta-regression analysis was done to explore the association between length of follow-up and DSS. To establish if there was an association between CR and DSS a univariate robust lineal regression model was used. Additionally we performed post-hoc analyses using individual patients data (IPD), when available, to explore associations between time from primary to systemic metastases, complete resection, and presence of local recurrence with the probability to stay alive at the end of follow-up expressed as a binary outcome.

Table 1. Metastatic GCT – data on survival and spontaneous regression rate

Author	Year	*N*	Years of follow-up	DOD (%)	NRD (%)	NED (% of total)	Alive with or without disease (%)	Spontaneous regression[a]	Ref.
Rock et al	84	8	5.4	2/8 (25.0)	0	2 (25.0)	6/8 (75.0)	0	59
Bertoni et al.	85	7	5.7	1/7 (14.3)	0/7 (0)	4/7 (57.1)	6/7 (85.7)	0	56
Bertoni et al.	88	6	4.6	0/6	0/0	6/6 (100)	6/6 (100)	2	57
Tubbs et al.	92	13	10.7	3/13 (23.1)	2/13 (15.4)	ND	8/13(61.5)	1	17
Kay et al.	93	6	7.5	1/6 (16.7)	0/6 (0)	3/6 (50.0)	5/6 (83.3)	1	22
Lausten et al.	96	5	13.1	5/5 (100)[f]	0/5 (0)	0/5 (0)	0/5 (0)	0	60
Cheng et al.	97	4	12.6[c]	0/4 (0)	0/4(0)	2/4 (50.0)	4/4 (100)	0	61
Osaka et al.	97	6	8.7	2/6 (33)	0/6 (0)	1/6 (16.7)	4/6 (66.7)	1	26
Siebenrock et al.	98	23	7.9	5/23 (21.7)	3/23 (13.0)	13/23 (56.5)	15/23(65.2)	1	18
Takanami et al.	98	4	4.9	0/4 (0)	0/4 (0)	4/4 (100)	4/4 (100)	0	23
Faisham et al.	04	6	2.0[b]	1/6 (7, 16)	0/6 (0)	2/6 (33.3)	5/6(83.3)	0	62
Dominkus et al.	06	14	6,3	0/14 (0)	0/14 (0)	10/14 (71.4)	14/14(100)	0	58
Donthineni et al.	08[d]	7	6.0	2/7 (28.6)[f]	0/7 (0)	2/7 (28.6)	5/7 (71.4)	2	27
Balke et al.	08	7	4.6	1/7 (14.3)	0/7 (0)	1/7 (14.3)	6/7 (85.7)	0	25
Klenke et al.	10	7	ND	1/7 (14.3)	0/7 (0)	3/7 (42.9)	6/7 (85.7)	0	41
Viswanathan et al.	10	24	1.9	0/21 (0)	0/24 (0)	ND	24/24(100)	0	28
Errani et al.	10	14	ND	0/14 (0)	0/14 (0)	3/14 (21.4)	14/14(100)	0	40
Takeuchi et al.	11	8	2.3	0/8 (0)	0/8 (0)	3/8 (37.5)	8/8 (100)	0	63
Kremen et al.	12	5	ND	0/5 (0)	0/5 (0)	1/5 (20.0)	5/5 (100)	1[e]	68
Niu et al.	12	21	6.3	3/21(14.3)	0/21 (0)	0/21(0)	18/21 (85.7)	0	4
Boriani et al.	12	6	7.8	2/6 (33.3)	0/6 (0)	4/6 (66.7)	4/6 (66.7)	0	64
Jiang et al.	13	11	ND	1/11 (9.0)	ND	ND	10/11	0	65
Xing et al.	13	6	5.0	2/6 (33.3)	0/13	ND	4/6 (66.7)	0	66
Liu et al.	13	5	5.1	0/5 (0)	0/5 (0)	1/5 (20.0)	5/5 (100)	1[e]	42
Chen et al.	16	7	9.2	2/7 (28.6)	0/7 (0)	5/7 (71.4)	5/7(71.4)	1	20
Kito et al.	17	12	13.3	1/12 (8.3)	0/12 (0)	4/12 (33.3)	11/12 (91.7)	0	19
Mean (95% CI)		9.3 (6.9–11.7)	6.9 (3.5–10.2)		2.2			4.5	
Median (IQR)		7.0 (6.0–11.7)	6.2 (4.9–8.5)	14.3 (0–24.5)	0	40.2 (20.4–57.0)	85.7 (71.4–100)		
Range		4–24	1.9–13.3	0–100	0–15.4	0–100	0–100		
Data available			205	242	231	188	242	242	
Total		242		35	5	76	202	11	

DOD, death of disease or its treatment; NRD, non-related deaths; NED, no evidence of disease; CI, confidence interval; IQR, interquartile range.

[a]Complete and partial regressions.

[b]The follow-up of two out of six patients was reported.

[c]From this case-series of five patients the data of four treated surgically available in the abstract was included, due to the impossibility to access the full-text.

[d]Only spine GCT.

[e]Partial regression.

[f]One patient died from sarcomatous transformation of lung metastasis.

Further we described nine cases of SR retrieved through an additional non-systematic database and Internet generic search to determine if there exist some clinical o radiological peculiarities associated with a SR of MTS.

Results

The search in electronic databases and a generic Internet retrieved a total of 2095 citations. After removing duplicates and performing the screening by title and abstract, 116 documents remained. After the second round of screening by full-text 36 articles were considered (4,17–23,25–28,33,35–38,40–42,53–68). Of them, 10 studies were excluded after careful full-text examination: two due to the lack of information on disease status at the end of the follow-up (54,55), one because it was not clear if it had been reported on malignant or benign GCT (53), two studies because the sharing of the same participants with other included studies could not be ruled out (35,67), and five due to the denosumab use, an exclusion criteria (21,33,36–38) (Appendix, Table A2). The remaining 26 studies were included in qualitative and quantitative syntheses (4,18–20,22,23,25–28,40–42,56–66,68) (Table 1). The studies selection process is summarized in the study flow chart (Fig. 1).

Details of the methodological quality assessment of included studies are shown in the Appendix (Table A3). All were retrospective case-series, published between 1984 and 2017. Nine studies were from Asia Pacific Region (4,19,20,23,26,42,63,65,66), two from South Asia (28,62), four from Europe (25,40,58,60), seven from USA (17,22,41,56,59,61,68) and four were intercontinental collaborations (27,57,59,64). Sixteen studies had MTS as their exclusive or main topic (17–20,22,23,26,27,42,56–62), two studies reported on recurrent GCT, including distant MTS (41,63). The remaining case-series, although referred to localized GCT, provided information on patients with systemic relapse. The median number of patients in a case-series was of 7, interquartile range (IQR) 6–11.7. Although the majority of studies carried biases inherent to their epidemiological design, all provided data on survival status of patients at the end of follow-up. The information on treatment was lacking in seven out of 26 studies. The type of data on non-surgical treatments precluded any analyses of their impact on survival (Table 2). No evidence of publication bias was detected (see Appendix, Fig. A4).

The total number of subjects analyzed was 242. The mean age was of 29.1, median male to female ratio 1.33. Almost all described MTS were to lung. Across all studies 14 extrapulmonary MTS were identified: to muscle, bone, scalp, lymph nodes, heart, tongue, chest, small intestine and brain (4,28,35,59,60,64). Median of patients with pathologically verified MTS was 70% (IQR: 35–100%). Data on the elapsed time from primary tumor to systemic MTS (TTM) was available in 202 subjects. Mean TTM was 2.4 years. In 64% of patients with systemic MTS a local relapse also occurred. Treatment modalities used were: surgical removal (complete or incomplete, including 're-resections'), chemotherapy (CT), BP, biological therapy, radiotherapy, observation and

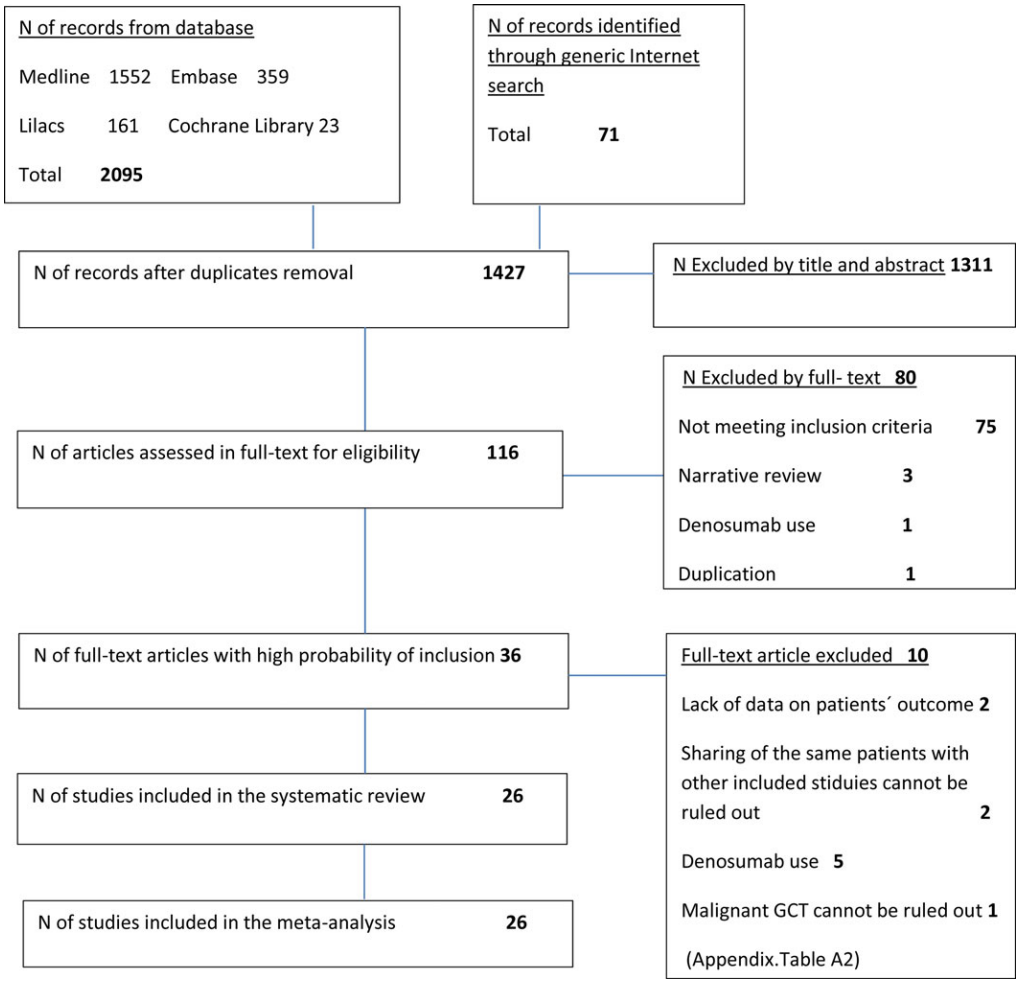

Figure 1. Flow diagram of study selection.

Table 2. Treatment of metastatic GCT in the included case-series

Author	Year	*N*	OBS	CR	PR	ST[a]		MT	NA	Ref
Rock et al.	84	8	0	6	1	1	CT	5 (CR + CT) (4) (CT + RT) (1)	0	59
Bertoni et al.	85	7	0	0	0	0		7 (CR + CT) (1) (PR + CT) (4) (PR + CT + BCG) (2)	0	56
Bertoni et al.	88	6	2	3	0	1	RT		0	57
Tubbs et al.	92	13	0	4	8	1	NA		0	17
Kay et al.	93	6	1	3	2	0		(CR + CT) (1)	0	22
Lausten et al.	96	5	–	–	–	–		–	5	60
Cheng et al.[b]	97	4	–	–	–	–		–	4	61
Osaka et al.	97	6	0	3	0	3	CT	3 (CR + CT) (1) (RT + CT) (2)	0	26
Siebenrock et al.	98	23	2	14	2	2	CT	3 (CR + CT) (2) (RT + CT) (1)	3	18
Takanami et al	98	4	0	4	0	0		0	0	23
Faisham et al.	04	6	2	2	0	2	CT	0	0	62
Dominkus et al.	06	14	0	11	1	2	CT	0	0	58
Donthineni et al.	08	7	0	1	1	5	CT	2 (CR + CT) (1) (CT + RT)(1)	0	27
Balke et al.	08	7	0	5	0	2	Interferon alpha +BP (1) CT (1)	5 Interferon alpha or BP or CT + CR (4) (CR + RT) (1)	0	25
Klenke et al.	10	7	–	–	–	–		–	7[c]	41
Viswanathan et al.	10	24	10	8	0	4	CT	2 (CR + CT)	2	28
Errani et al.	10	14	–	–	–	–		–	14	40
Takeuchi et al.	11	8	5	3	0	0		0	0	63
Kremen et al.	12	5	0	3	0	2	NA	0	0	68
Niu et al.	12	21	0	0	0	5	CT (1) BP (4)	0	16	4
Boriani et al.	12	6	–	–	–	–		–	6	64
Jiang et al.	13	11	–	–	–	–		–	11	65
Xing et al.	13	6	–	–	–	–			6	
Liu et al.	13	5	0	1	1	3	CT BT'	0	0	42
Chen et al.	16	7	4	1	0	2	CT	1 (CR + CT)	0	20
Kito et al.	17	12	2	5	4	1	CT	0	0	19
Total N (%)		242	28 (16%)	77 (44%)	20 (11%)	36 (21%)		29 (17%)	67 (38%)	
Median			0	41.7	0	14.3		0		
Data available		175								

A/T, available for analysis/Total; OBS, observation; CR, complete resection with or without other modalities; PR, partial resection; ST, systemic therapy (any) without surgery; MT, multimodality treatment; NA, not available; CT, chemotherapy; RT, radiation therapy; BT, biological therapy; BP, bisphosphonates

[a]Systemic Therapy (ST): Any pharmacological treatment.

[b]From this series of five patients the data on four patients treated surgically were included due to the impossibility to access the full-text.

[c]Patients were subject to surgical treatment, chemotherapy and radiotherapy, but cannot provide more information.

[d]Not specified.

their combinations (Table 2). The mean follow-up was 6.9 (range 1.9–13.3) years (Table 1).

For all 26 studies considered together, the estimated pooled OS was 86.9% (95% CI: 78.0–94.2), with an I^2 test for heterogeneity of 58.7 (Fig. 2A). Pooled DSS was 88.0% (95% CI: 79.7–94.7%), $I^2 = 53.7\%$ in a random effects model (Fig. 2B). Under a fixed effects model very similar results were obtained (see Supplemental digital content S1). When the 22 case-series with available follow-up time were taken into account, the pooled OS and DSS were similar, 84.6% (95% CI: 74.0–93.3) and 85.8% (95% CI: 75.9–93.9) respectively (Fig. 2C, D).

Overall, 40 (16.5%) out of 242 subjects died, 35 (14.5%) from the disease or treatment complications and five (2.1%) from non-related causes (Table 1). Four out of 242 (1.7%) patients died from CT toxicity, three in the older studies and one in post-2000 subgroup. Malignant transformation was reported in six out of 242 (2.5%) patients. The information on the presence or absence of

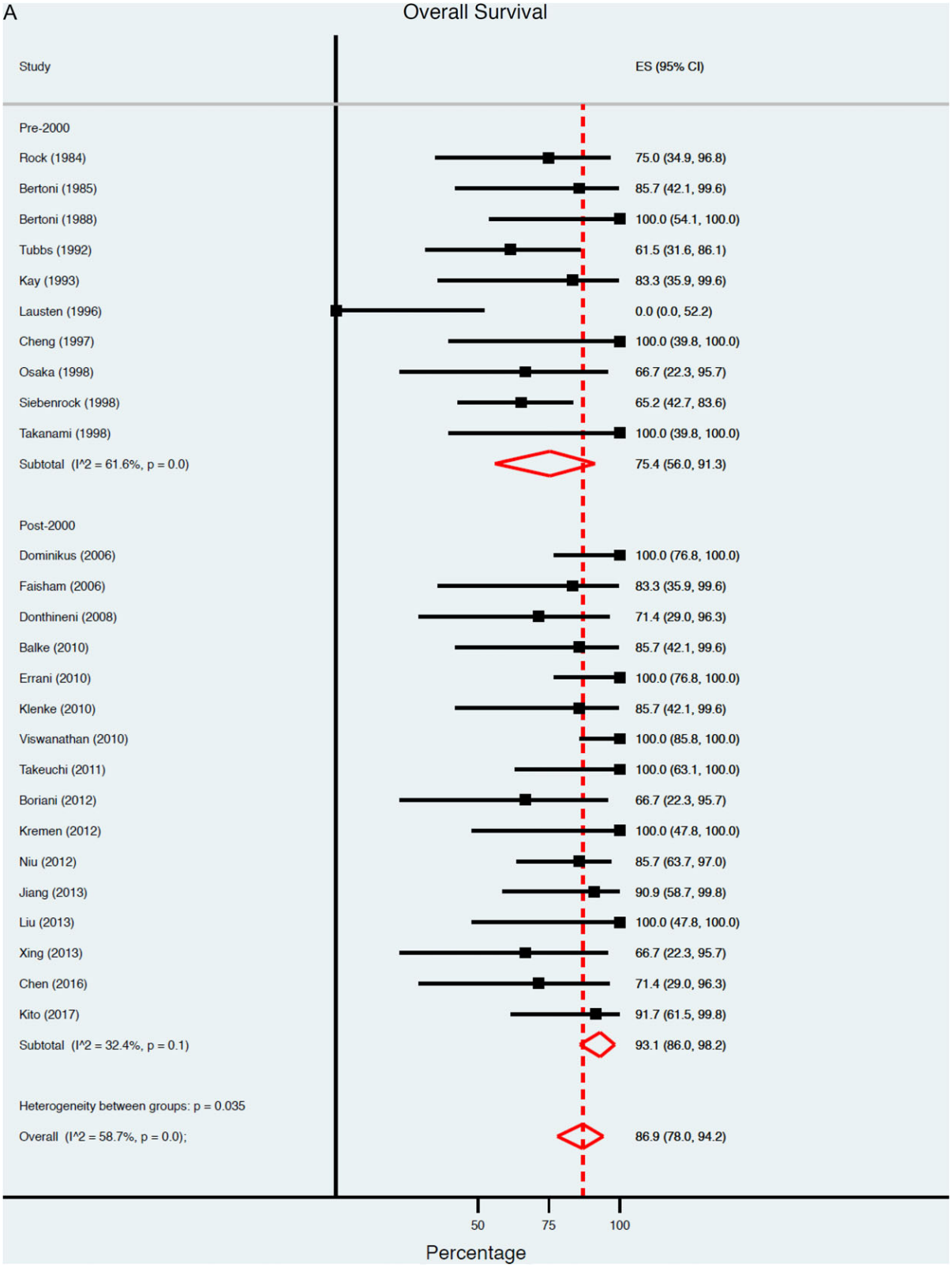

Figure 2. Metastatic GCT. Estimated pooled overall and disease specific survival. (A) Overall survival in studies published before and after 2000. (B) Disease specific survival in studies published before and after 2000. (C) Overall survival in studies with the length of follow-up of more and less than 10 years. (D) Disease specific survival in studies with a follow-up length more and less than 10 years. Black squares and black lines indicate percentage of survivors in each study with their respective 95% CIs. The size of red diamonds is proportional to 95% CIs of each subgroup. Red dashed line indicates the estimated pooled survival in the whole study population. Abbreviations: DSS, disease specific survival.

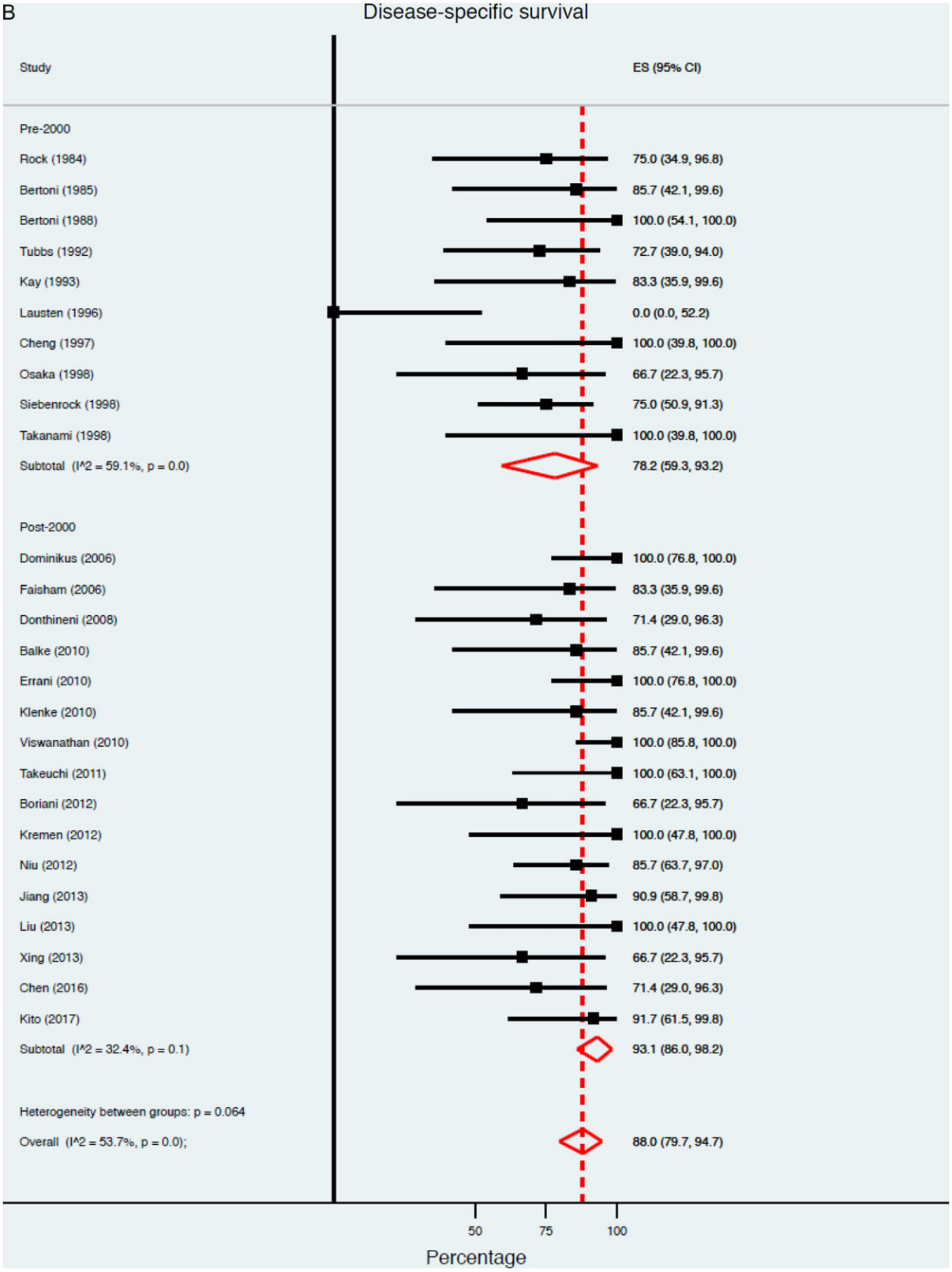

Figure 2. *Continued*

disease at the end of follow-up was available in 188 out of 242 (77.7%) patients from 22 studies. The median of patients with NED was of 40.2%.

SRs were observed in 11 subjects (4.5% of cases); about two-thirds of them were complete regressions and one-third–partial ones (data not shown, available on demand).

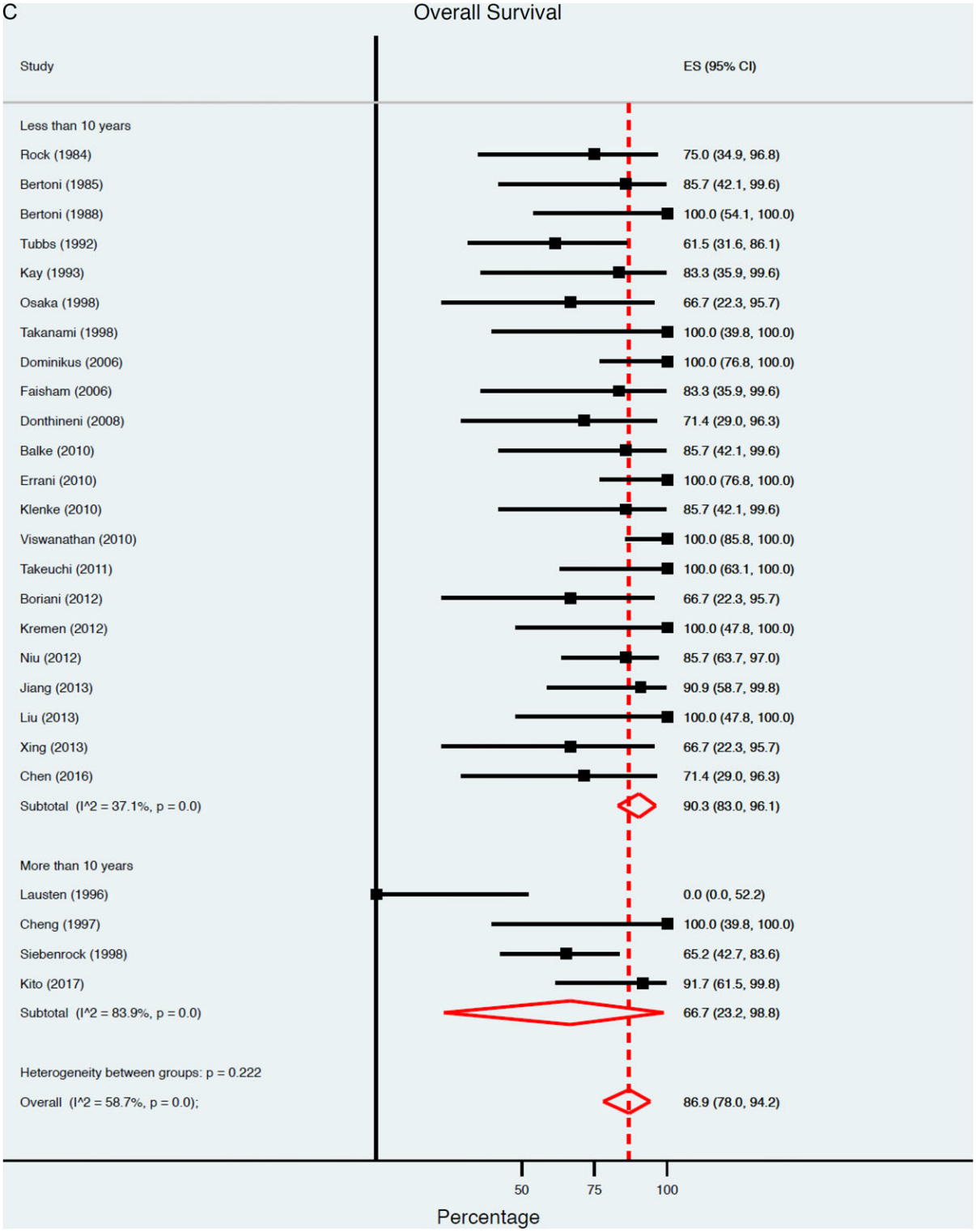

Figure 2. *Continued*

A comparison between studies published before and after 2000 is shown in Table 3 and Fig. 2A, B. Demographic characteristics were similar. There was a trend to a longer mean follow-up, 8.1 vs 5.8 years, $P = 0.054$, higher complete resection rate (CR) 53.9% vs 38.0%, $P = 0.20$ and higher proportion of patients with NED, 53.3% vs 32.4%, $P = 0.11$ in the subgroup of pre-2000 studies. A trend to a greater proportion of patients on surveillance in the post-2000 subset 21.8%, $P = 0.053$ was observed. NRD in the pre-2000 cohort was of 6.2%, while no NRD in the post-2000 subgroup was observed.

In the pre-2000 cohort pooled OS and pooled DSS were 75.4% (95% CI: 56.0–91.3) and 78.2% (95% CI: 59.3–93.2), respectively. In the post-2000 cohort pooled OS and pooled DSS were both of

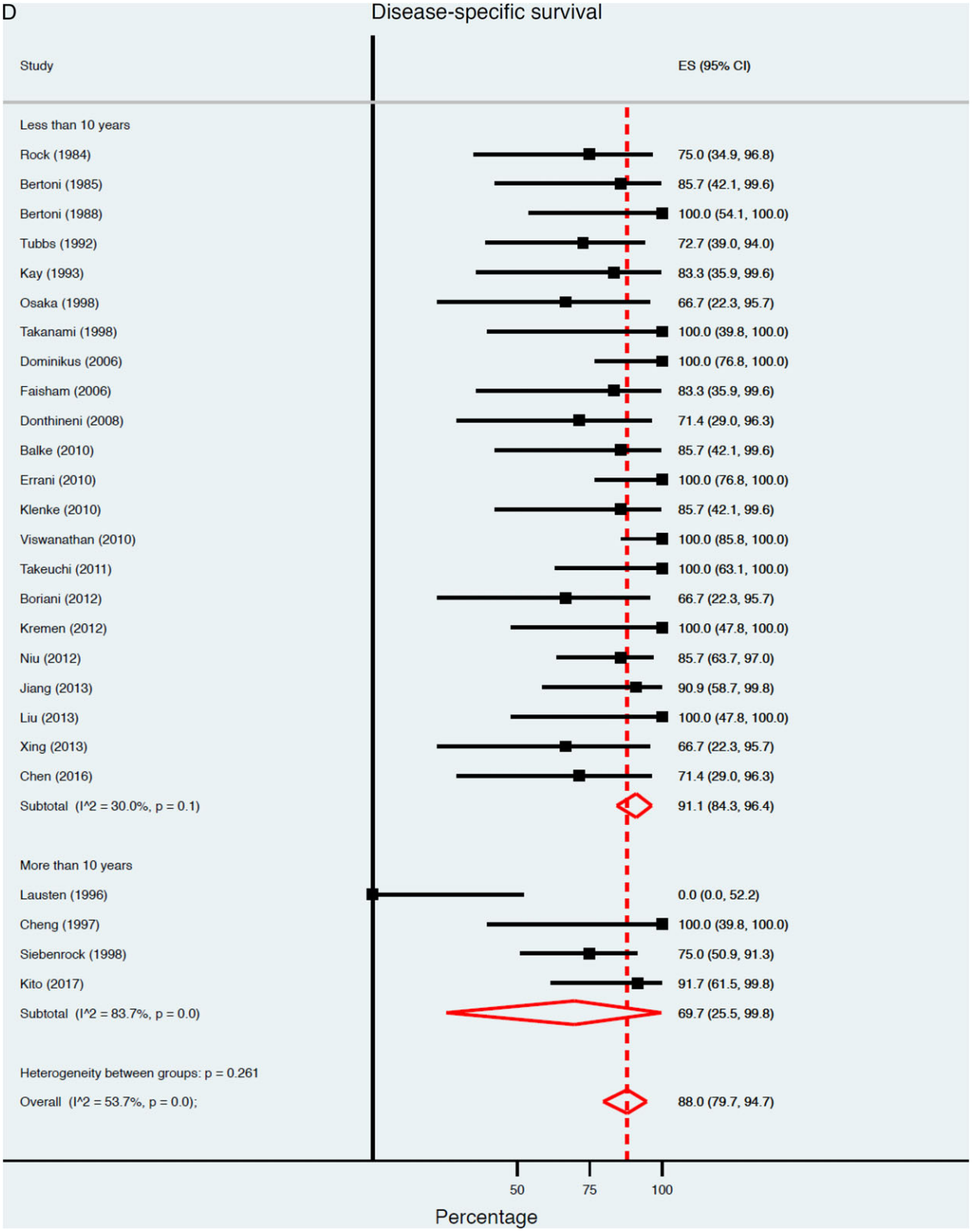

Figure 2. *Continued*

93.1% (95% CI: 86.0–98.2). In a meta-regression analysis, even after adjusting for follow-up length, the DSS was better in the post-2000 period (Fig. 3A).

In an exploratory analysis using a multivariable logistic regression model, based on individual data of 127 patients, after adjustment by age and gender, a greater interval from primary to diagnosis of MTS was associated with a greater probability to be alive at the end of the follow-up, OR 0.84 (95% CI: 0.74–0.96) $P = 0.02$, while no statistically significant association with neither the presence of local recurrence nor the achievement of complete resection was found based on individual data of 116 and 115 subjects, respectively (data not shown, available on demand).

Table 3. Comparison between the case-series of metastatic GCT published before and after 2000

	Before 2000	After 2000	*P* value, one-tailed Student's *t*-test
N of series	10	16	
N of patients	82	160	
Age. Mean (95% CI)	27.8 (24.1–31.6)	30.5 (28.0–33.0)	0.15
Male: Female. Median (IQR)	1.0 (0.9–2.0)	1.7 (1.3–2.9)	0.33
Follow-up in years. Mean (95% CI)	8.1 (5.9–10.3)	5.8 (3.7–7.9)	0.054
Observation %. Mean (95% CI)	7.3 (6.3–8.3)	21.8 (5.5–38.1)	0.053
Complete resection %. Mean (95% CI)	53.9 (32.0–75.6)	38.0 (21.0–54.1)	0.20
Death rate from disease and its treatment %. Mean (95% CI)	23.4 (2.4–44.4)	10.5 (4.2–16.7)	0.11
Death rate from non-related cause. *N* (%)	5/82 (6.1)	0/160 (0.0)	
NED as % of the total. Mean (95% CI)	53.3 (28.1–78.5)	32.4 (17.9–46.9)	0.09
Spontaneous regression. *N* (%)	6/82 (7.3%)	5/160 (3.12%)	

IQR, Interquartile range; CI, confidence interval, NED, no evidence of disease.

In the subset of studies with a follow-up shorter than 10 years pooled OS and DSS were 90.3% (95% CI: 83.0–96.1) and 91.1% (95% CI: 84.3–96.4) respectively. In those followed-up for more than 10 years pooled OS and DSS were 66.7% (95% CI: 23.2–98.8) and 69.7% (95% CI: 25.5–99.8) (Fig. 2C, D). In a meta-regression analysis of DSS adjusting by follow-up time the regression coefficient was –0.027, $P = 0.22$ (Fig. 3B).

Finally, we describe nine cases of SRs (Table A4) (16–18,20,22,42,43). Four of them were retrieved through an additional generic Internet search (16,43). Time from the lung MTS diagnosis to their regression varied from 1 to 16 years. Most of the regressions were complete. Few articles reported on the duration of SRs. However, after a spontaneous disappearance no cases of 're-metastasis' were detected. We failed to identify any particular clinical feature associated with the SR phenomenon, possibly with exception of the freedom of primary tumor relapse. We found two case-reports each one reporting on a patient with multiple radiologically calcified pulmonary nodules (43,69). After the surgical removal, all of the nodules exhibited either hyalinosis or ossification without viable tumor (43,69). Interestingly, a massive calcification of the primary and MTS in patients treated with denosumab reported by Palmerini et al. kept some similarity with these cases (37). If true, the radiologic sign of 'spontaneous' ossification, although infrequent, may, hypothetically, be regarded as an argument against the surgical resection of lung MTS.

Discussion

The natural history of GCT with pulmonary MTS is extremely variable (23). Published case-series show a very wide spectrum of possible routes of its evolution which spans from an overt progression with respiratory failure to a complete long-standing spontaneous regression, probably equivalent to healing, including in most cases intermediate situations, like partial spontaneous regressions, long periods of stability o very slow growth (17,18,20,60,68). Even though lung MTS are persistent, patients may stay alive for very many years (70). Our study addressed this uncertainty.

We found that the pooled OS was of 86.9% and the pooled DSS was of 88.0% at 7 years of follow-up. Equal DSS and OS of 93.1% in those studies published after 2000 was observed. This means that mGCT was the only cause of death in that patients and thus, it cannot be regarded as inoffensive for persons typically aged between 20 and 40.

Although in a meta-regression a trend to inverse relationship between DSS and follow-up was not statistically significant, in cases-series with more than 10 years of follow-up DSS was 69.7%, rather low for a condition considered benign. This decrease of survival rates was associated with a pronounced widening of the confidence interval (Fig. 2C, D). This may be interpreted as that although with a longer follow-up the uncertainty about the mGCT prognosis would increase, in a very long run the impact on the life expectancy may be greater than established by us.

Although confidence intervals slightly overlap, there has been a considerable increase in OS and DSS in the post-2000 series in comparison with older ones. It can be hardly attributed to a more aggressive surgical treatment, as CR and NED rates were not statistically different, and even a trend to an inverse relation was observed. Likewise, the proportion of patients on surveillance in post-2000 showed a three-fold increase ($P = 0.053$). Due to the exploratory nature of the analyses based on retrospective data this results should be taken with caution. This increase of DSS and OS can only partially be explained by the shorter follow-up and the reduction of CT related deaths in the post-2000 subgroup (Table 3). The findings reported by Lausten et al., showing 0% survival at 13 years of follow-up, and possibly some unknown factors, may additionally contribute for this apparent DSS improvement. A stage migration, given to the continuous amelioration of imaging studies quality, cannot be ruled out, especially since in older case-series MTS diagnosis was made by plane chest radiographs in some cases (18). A parallel reduction of NRD observed, attributable to an overall life expectancy improvement over time, in addition to a shorter follow-up, may account for the OS difference (Table 3).

Determination of the impact of chemotherapy on survival based on retrospective data is usually troublesome and prone to criticism. With the type of data like ours, the analysis would be further biased by the diversity of chemotherapy regimens used, variable duration of therapy, lack of detailed information about chemotherapy in many studies, use of chemotherapy in combination with other modalities. In some patients with persistent lung MTS, several years elapsed from chemo to the end of follow-up, which poses an additional difficulty when an inference about a cause–effect relation is attempted. Considered potentially misleading, estimates were not performed.

The main methodological limitation of our work is the retrospective nature of observational studies, prone to some time-related biases, such as lead time bias and immortal time bias, and the lack of data on follow-up length in some studies. Other methodological flaws are the lack of data on treatment and freedom of disease in some case-series. Additionally, diagnostic misclassification could have taken place in some few cases, as histopathological diagnosis was verified

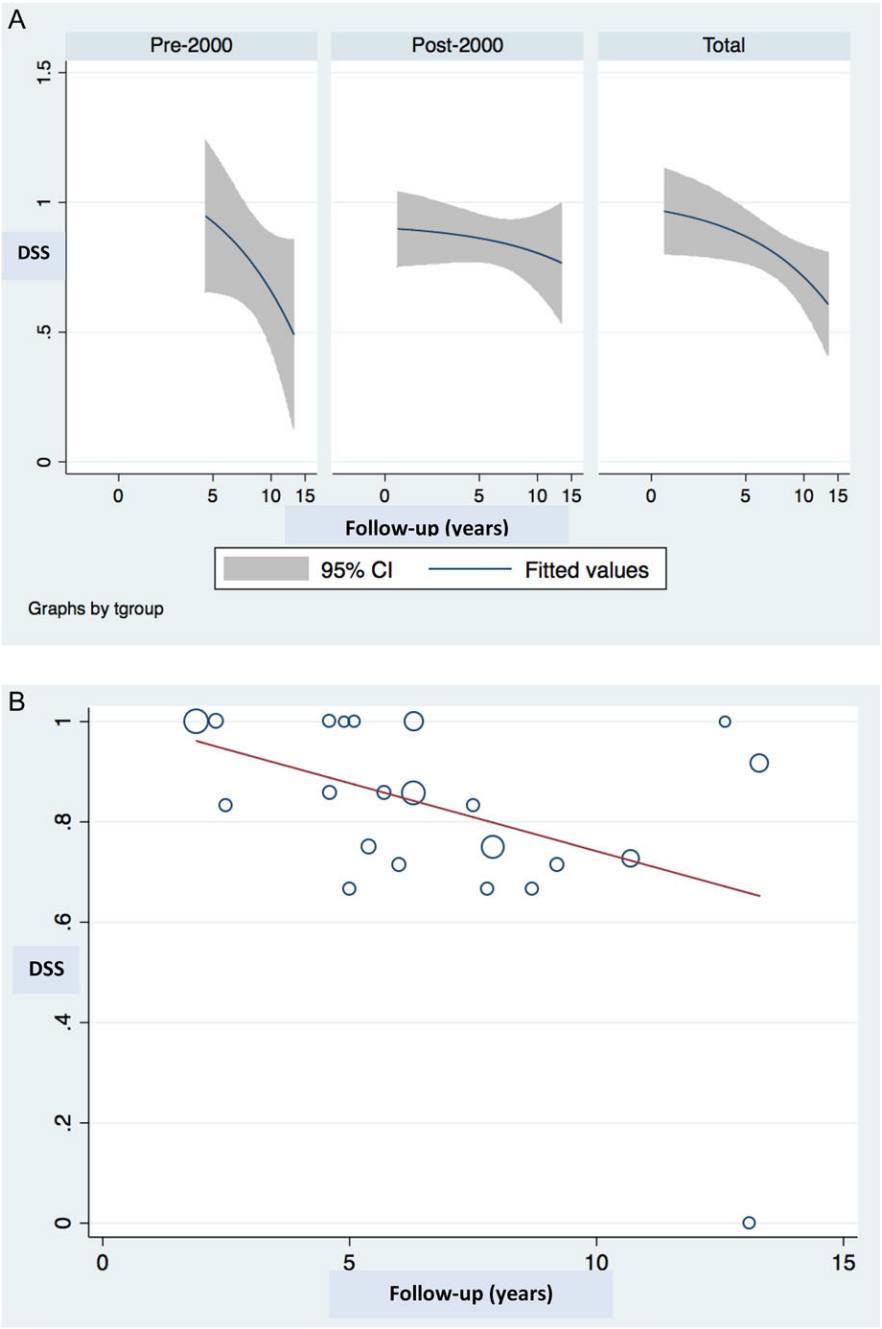

Figure 3. Metastatic GCT. Estimated pooled disease specific survival adjusted by the follow-up time. (A) Before and after 2000. (B) Circle size is proportional to the number of patients in each study. Abbreviations: DSS, disease specific survival.

in only 70% of patients and H3F3A and H3F3B gene mutation analyses were not performed.

As individual data was available in 122 out of 242 patients (not shown), we combined the extracted from published literature aggregated data on survival at a single fixed point in time. Although this approach was criticized when applied to time to event continuous outcome, it may be suitable when a binary outcome is used (71).

The main strength of this study is its comprehensiveness gathering a relatively large number of subjects for a rare condition. The design and number of participant of selected studies were rather uniform. To our knowledge, this is the first systematic review on mGCT published to date and a first meta-analysis attempting to estimate the prognosis of the disease based on a large dataset. Also, this is the first synthesis of data on SR.

The study addressed the unmet need for a more precise knowledge about the prognosis of mGCT circumscribing reference values of DSS and SR. Data provided by us can be useful as an historical control in the assessing of long-term results of mGCT treatment.

As a hypothesis to put forward, we propose to consider mGCT not like a benign, but rather like a premalignant lesion. In analogous way to other premalignant lesions it, sometimes, may be multifocal,

persist for large periods, progress to high-grade malignancy or retrograde spontaneously. In contrast to typical well-known epithelial premalignancy, which acquire the capacity to uncontrolled proliferation first and the metastasing capacity later in their evolution, in the case of mGCT there is an inversion of this order. A reported case of malignant recurrence at the primary site with simultaneous benign multiple lung MTS provide some empiric support for this hypothesis (72).

We hope that in the future the development of new biomarkers focused on identification of differential expression of genes, proteins, micro-RNAs and cytogenetic alterations will allow a better assertion of mGCT prognosis and individualization of the therapeutic decision (73–78).

In conclusion, we derived estimated pooled OS and DSS of mGCT based on a large dataset. SRs were not exceptional phenomena. Metastatic GCT was the only cause of death of patients with this condition in studies published after 2000. With follow-up greater than 10 years a trend to a lower DSS was observed. In a long run the disease could impact in a significant way on the life expectancy of affected subjects.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

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Conflict of interest statement

None declared.

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