2. Pietersz GA, Smyth MJ, McKenzie IFC. Immunochemotherapy of a murine thymoma with idarubicin-monoclonal antibody conjugates. *Cancer Res* 1988, **48**, 926–931.
3. Larson SM. Radioimmunology imaging and therapy. *Cancer* 1991, **67**, 1253–1260.
4. Uhr JW, Fulton RJ, Till MA, Vitetta ES. Monoclonal antibodies as carriers of toxins. *Prog Clin Biol Res* 1989, **299**, 403–412.
5. Zalcberg JR, McKenzie IFC. Tumour antigens—an overview. *J Clin Oncol* 1985, **3**, 876–882.
6. Epenetos AA, Snook D, Durbin H, Johnson PM, Taylor-Papadimitriou J. Limitations of radio-labelled monoclonal antibodies for localization of human neoplasms. *Cancer Res* 1986, **46**, 3183–3191.
7. Kanellos I, McKenzie JFC, Pietersz GA. Intratumour therapy of solid tumours with the use of ricin-antibody conjugates. *Immunol Cell Biol* 1989, **67**, 89–99.
8. Pietersz GA, Kanellos J, McKenzie IFC. Novel synthesis and *in vitro* characterization of disulfide linked ricin-monoclonal antibody conjugates devoid of galactose binding activity. *Cancer Res* 1988, **48**, 4469–4476.
9. Fodstad O, Kvalheim G, Godal A, Lotsberg J, Aamdal S, Host H, Pihl A. Phase I study of the plant protein ricin. *Cancer Res* 1984, **44**, 862–865.
10. Teh JG, Thompson CH, McKenzie IFC. Production of monoclonal antibodies to serum antigens in colorectal carcinoma. *J Immunol Meth* 1988, **110**, 101–109.
11. Tjandra JJ. PhD Thesis. University of Melbourne, 1989.
12. Shiina S, Tagawa K, Unuma T, *et al.* Percutaneous ethanol therapy for hepatocellular carcinoma. A histopathological study. *Cancer* 1991, **68**, 1524–1530.
13. Cortesina G, DE Stefani A, Giovarelli M, *et al.* Treatment of recurrent squamous cell carcinoma of the head and neck with low doses of Interleukin-2 injected perilymphatically. *Cancer* 1988, **62**, 2482–2485.
14. Sulis E, Floris C, Sulis ML, Zurrido S, Piro S, Pistus A, Contu L. Interferon administered intralesionally in skin and oral cavity lesions in heterosexual drug addicted patients with AIDS-related Kaposi's sarcoma. *Eur J Cancer Clin Oncol* 1989, **25**, 759–761.

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Predictors of Residual Mass Histology Following Chemotherapy for Metastatic Non-seminomatous Testicular Cancer: a Quantitative Overview of 996 Resections

E.W. Steyerberg, H.J. Keizer, G. Stoter and J.D.F. Habbema

Following chemotherapy for metastatic non-seminomatous testicular cancer, surgical resection may demonstrate that residual masses contain purely benign tissue (necrosis), or potentially malignant tissues (histologically viable cancer cells or mature teratoma). The morbidity, mortality and costs of resection demand that resection is based on empirical data rather than on subjective judgements. We reviewed 996 resections from 19 studies to quantify predictors of the histology at resection. Predictors were analysed for each study and combined in a pooled odds ratio (OR). Predictors of necrosis were: (1) a teratoma-negative primary tumour (OR = 5.1); (2) normal tumour markers before chemotherapy [α-fetoprotein (AFP): OR = 2.8; human chorionic gonadotrophin (HCG): OR = 1.9; both AFP and HCG: OR = 5.7]; (3) a smaller postchemotherapy abdominal mass (e.g. ≤20 mm: OR = 3.7); (4) a large shrinkage (≥90%: OR = 3.1); (5) lung resections versus abdominal resections (OR = 1.7). Cancer was found in only 4% of residual retroperitoneal masses ≤20 mm. Further research may combine the primary tumour histology, marker level and mass size to improve clinical guidelines, which define subgroups of patients for whom the benefits of resection do not outweigh the risks.

Keywords: histology, meta-analysis, resection, residual mass, testicular cancer
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INTRODUCTION

SURGICAL RESECTION is widely accepted as the treatment of choice in the presence of residual masses following chemotherapy for metastatic testicular non-seminomatous germ cell tumours (NSGCT) [1, 2]. Resection provides the histological diagnosis of the residual mass, which may be purely benign with necrotic and/or fibrotic remnants only (necrosis), may contain mature teratoma elements (mature teratoma) or viable cancer cells/active malignancy (cancer). Resection of masses containing necrosis only is assumed to have no therapeutic benefit and is usually not followed by additional treatment. Resection of mature teratoma or cancer is considered to be beneficial as it prevents growth of (potentially) malignant cells [3]. Finally, the presence of viable cancer cells in the residual mass directs the decision to administer additional chemotherapy [4]. The prognosis after resection is generally favourable, with 5-year relapse-free survival over 85%

after resection of necrosis or mature teratoma [3, 5–8], and between 50% [3, 5–7] and 80% [8–10] after resection of cancer followed by additional chemotherapy. Another aspect of resection is that incompletely resected patients have a poor prognosis [5, 8, 9].

As the benefit of resection depends on the histology present in the residual mass, attention has been paid to factors associated with the histology at resection [3, 11–16]. These analyses have focused on groups of patients with a high probability of necrosis, in whom resection might be omitted. In the present study, we analysed both the probability of necrosis and the probability of cancer, as both are important in the decision to perform a surgical resection. For example, it is clear that a patient with probabilities of 90% necrosis, 1% mature teratoma and 9% cancer should more definitely undergo resection than a patient with probabilities of 90% necrosis, 9% mature teratoma and only 1% cancer, as leaving cancer unresected may be considered more serious than leaving mature teratoma unresected.

Recommendations for resection of abdominal residual masses vary to a considerable extent. For example, the size of the residual mass influences the decision to perform resection, but recommendations vary from laparotomy in any patient with initial abdominal lymph nodes >3 cm, even if no pathological mass could be detected on the postchemotherapy computed tomography (CT) scan [3], to resection of residual abdominal masses only if they exceed 20 mm [6]. Other factors which have been considered for patient selection include the presence of teratoma elements in the primary tumour [11, 14, 17], the reduction in size of the mass (shrinkage) [11], and the prechemotherapy level of tumour markers like α-fetoprotein (AFP) and human chorionic gonadotrophin (HCG) [14].

The associations of these factors with the histology at resection have been observed in relatively small studies. In the present paper, we therefore have combined the data from several published studies to obtain larger numbers and hence more precise estimates of the predictors. Moreover, the published studies differ with respect to the selection of patients and the chemotherapy regimens used. The predictive value of factors may depend on these study characteristcs (heterogeneity of effect). This potential heterogeneity is explicitly analysed in the present study. For example, we investigate whether the effects of predictors are different in lung and abdominal resections, or different in more recently published studies, where newer chemotherapy regimens were applied.

PATIENTS AND METHODS

Associations with the histology at resection (effects) were quantified using techniques of meta-analysis [18]. The following factors (or predictors) were considered: primary tumour histology, tumour markers before chemotherapy, abdominal mass size, shrinkage during chemotherapy, and type of resection. The primary tumour histology was defined as teratoma-postive or teratoma-negative [3, 11], indicating whether mature teratoma elements were present. The highest tumour marker level of AFP and HCG before chemotherapy was classified as elevated or normal, although normal values differed between studies, e.g. AFP <5 ng/ml [5] or <20 ng/ml [14, 26]. The effects of primary histology and tumour marker level were analysed in studies including laparotomies or thoracotomies only, or both. In those studies which included laparotomies only, associations with the histology at resection were quantified for pre- and postchemotherapy mass size as measured on CT scan, and for the reduction in size of the mass during chemotherapy (shrinkage). A large shrinkage has been defined as a reduction of more than 90% in area [3]. The corresponding reduction in one dimension is 68.4%, which was used if only measurements in transversal direction were available. The factor type of resection indicated if abdominal or lung masses were resected. The histology of the resected material was classified according to the worst histological element, either as cancer, mature teratoma or necrosis. Thus, mature teratoma refers to masses which contained mature teratoma and possibly also necrosis/fibrosis, but no viable cancer cells, and cancer refers to masses which contained viable cancer cells and possibly mature teratoma and/or necrosis.

Studies were selected using MEDLINE medical database and via references in articles. The studies had to contain frequency data on the association of a factor with the histology found at resection, either in tables or mentioned in the text. From some authors additional information on their patient series was obtained (Dr G. Pizzocaro, Milan, Italy [24] and Dr P.F.A. Mulders, Nijmegen, The Netherlands [26]). Furthermore, data were included from a series of 86 patients resected in three Dutch centres between July 1980 and June 1991. Details on the treatment of these 86 patients were described elsewhere [8]. The data used from each study are listed in the Appendix.

Statistical analysis

The probability of necrosis and the probability of cancer were related with factors known before resection. The odds ratio (OR) was used as the measure of association in 2 × 2 tables. The OR is the ratio of the odds of necrosis or cancer in one category divided by the odds in the other category. The OR may be interpreted as a relative risk, when the probabilities are small, e.g. <10%. When the probabilities are larger, the OR is larger than the relative risk. An OR of more than one for a category of patients means that the odds (or risk) is increased compared to the other category. Contrary, an OR smaller than one indicates a lower risk. ORs were calculated within each patient series (study OR) and subsequently pooled (pooled OR) using the Mantel–Haenszel method (StatXact version 2, CYTEL Software Corporation, Cambridge, Massachusetts, U.S.A.). The 95% confidence intervals (95% CI) of the pooled ORs were calculated with the exact variance estimate of Robins *et al.* [19]. In studies with a zero cell frequency the variance and study OR were estimated by the procedure of Peto [20]. Factors have statistically significant effects ($P < 0.05$) if the 95% CI of the pooled OR does not include one.

As the studies differed with respect to a number of relevant characteristics, it was investigated whether the effect of the predictors depend on any of these characteristics (heterogeneity of effect [18]). The following study characteristics were considered (see Table 1); the selection of patients (type of resection, markers at resection, size of resected masses), the time of treatment, which is related to the type of chemotherapy regimen used, and study size. The characteristic study size is used to detect publication bias, i.e. the phenomenon that statistically

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Table 1. Study characteristics considered for heterogeneity of effect of the associations with the histology at resection.

Characteristic	Coding
Type of resection	1. Abdominal resection only 2. Lung resection only 3. Both abdominal and lung resections or unclear
Markers at resection	0. Markers normal before resection 1. Some patients with elevated markers 2. Unclear
Size of the resected masses	0. Small masses only (CT normal/<20 mm) 1. Larger masses only (CT abnormal/ ≥20 mm) 2. Both small and larger masses
Time of treatment	Year of publication
Study size	Number of patients

CT, computed tomography. The codes of each characteristic are listed with the studies in Figure 1, Table 2 and Appendix.

significant results have a higher chance of being published than insignificant results, leading to on average higher effect estimates in smaller studies. The heterogeneity of effect was tested for statistical significance by fitting a weighted linear regression equation of ln(study OR) on the study characteristics [21], where each study OR was weighted by the reciprocal of its variance. If significant heterogeneity existed ($P < 0.10$ [18]), the pooled OR was calculated for each category of the study characteristic.

RESULTS

The analysis included 901 resections from 18 articles [3, 5, 9, 11–17, 22–29] published between 1983 and 1992 and 95 resections (75 abdominal, 20 lung) from our own Dutch series [8]. Table 2 shows that the overall distribution of the histologies at 996 resections was necrosis in 480 (48%), mature teratoma in 361 (36%) and cancer in 555 (16%).

Probability of necrosis

The relation between the finding of necrosis only in the resected material and the primary tumour histology was described in many publications. Figure 1 depicts the OR for each study with the corresponding 95% CI and the pooled OR with its 95% CI. The effect of teratoma elements in the primary tumour is consistent in all analyses; no heterogeneity of effect was found in relation to any of the study characteristics. The pooled OR was 5.1 (Figure 1, Table 3), which means that patients without teratoma elements in their primary tumour (teratoma-negative) have more often necrosis in their residual masses (see Appendix: 289/451 = 64%), compared to patients with teratoma elements in their primary tumour (see Appendix: 126/438 = 29%).

Similarly, the associations of other factors with the finding of necrosis only at resection were summarised. As no heterogeneity of effect was found, one pooled OR is presented for each factor in Table 3. Patients with normal tumour markers AFP or HCG, or both AFP and HCG before chemotherapy had necrosis more often at resection. Smaller abdominal masses before chemotherapy had a higher probability of necrosis (not significant, $P > 0.10$). Smaller postchemotherapy masses (normal CT scan or ≤10, ≤15, ≤20, ≤50 mm) contained necrosis more often than larger masses (abnormal CT scan or >10, >15, >20, >50 mm, respectively). A large shrinkage indicated a higher probability of finding necrosis only. The type of resection was associated with the probability of necrosis: necrosis was found more often at lung resections ($P = 0.04$).

Probability of cancer

Further analysis related the probability of cancer to the factors described in the literature (final column in Table 3). The association of the primary tumour histology with cancer was significantly different in abdominal and lung resection ($P = 0.002$). In abdominal resections, teratoma-negative patients had a significantly lower probability of cancer (OR 0.48, 95% CI 0.28–0.83, $P = 0.008$). In lung resections this association seemed, however, to be reversed (OR = 3.7, 95% CI 0.99–14, $P = 0.051$), as illustrated by the following numbers (see Appendix): in 9 (24%) of 37 teratoma-negative patients cancer was found, compared to 4 (9%) of 45 teratoma-positive patients. Note that no mature teratoma was found in the 37 teratoma-negative patients. Thus, the probability of necrosis was higher in teratoma-negative patients undergoing thoracotomy, but the probability of cancer also seemed higher. In studies including both abdominal and lung resections, the effect of the primary tumour histology was between the effects found in studies including abdominal or lung resections only.

Table 2. Distribution of the histology at resection for the studies analysed

Code	Author	Ref	Year	*n*	Nec	Ter	Can
100	Bracken *et al.*	27	1983	22	14 64%	3 14%	5 23%
100	Gelderman *et al.*	22	1986	24	17 71%	7 29%	0 0%
100	Fossa *et al.*	13	1989	37	24 65%	12 32%	1 3%
100	Fossa *et al.*	14	1992	76	51 67%	22 29%	3 4%
101	Bracken *et al.*	27	1983	22	8 36%	7 32%	7 32%
102	Stomper *et al.*	15	1985	30	12 40%	10 33%	8 27%
102	Donohue *et al.*	11	1987	80	35 44%	33 41%	12 15%
102	Sagalowsky *et al.*	16	1990	15	6 40%	5 33%	4 27%
102	Mulders *et al.*	26	1990	34	20 59%	11 32%	3 9%
102	Toner *et al.*	3	1990	122	57 47%	48 39%	17 14%
102	Steyerberg *et al.*	8	1993	75	31 41%	30 40%	14 19%
112	Carter *et al.*	23	1987	26	7 27%	10 38%	9 35%
122	Suurmeijer *et al.*	28	1984	33	20 61%	12 36%	1 3%
202	Bracken *et al.*	27	1983	15	5 33%	4 27%	6 40%
202	Mulders *et al.*	26	1990	8	5 63%	2 25%	1 13%
202	Toner *et al.*	3	1990	39	25 64%	10 26%	4 10%
202	Steyerberg *et al.*	8	1993	20	12 60%	6 30%	2 10%
302	Gelderman *et al.*	17	1988	35	15 43%	16 46%	4 11%
302	Harding *et al.*	9	1989	39	17 44%	14 36%	8 21%
312	Garnick *et al.*	29	1983	29	9 31%	13 45%	7 24%
312	Tait *et al.*	5	1984	73	25 34%	32 44%	16 22%
312	Pizzocaro *et al.*	24	1985	34	14 41%	10 29%	10 29%
312	Fossa *et al.*	12	1989	92	47 51%	34 37%	11 12%
322	Dexeus *et al.*	25	1989	16	4 25%	10 63%	2 13%
Total				996	480 48%	361 36%	155 16%

The first column (code) indicates the major study characteristics, as shown in Table 1. The studies are ordered according to these study characteristics and year of publication. Ref denotes the reference number; *n*, the total number of resections in the patient series; Nec, necrosis; Ter, mature teratoma; Can, cancer.

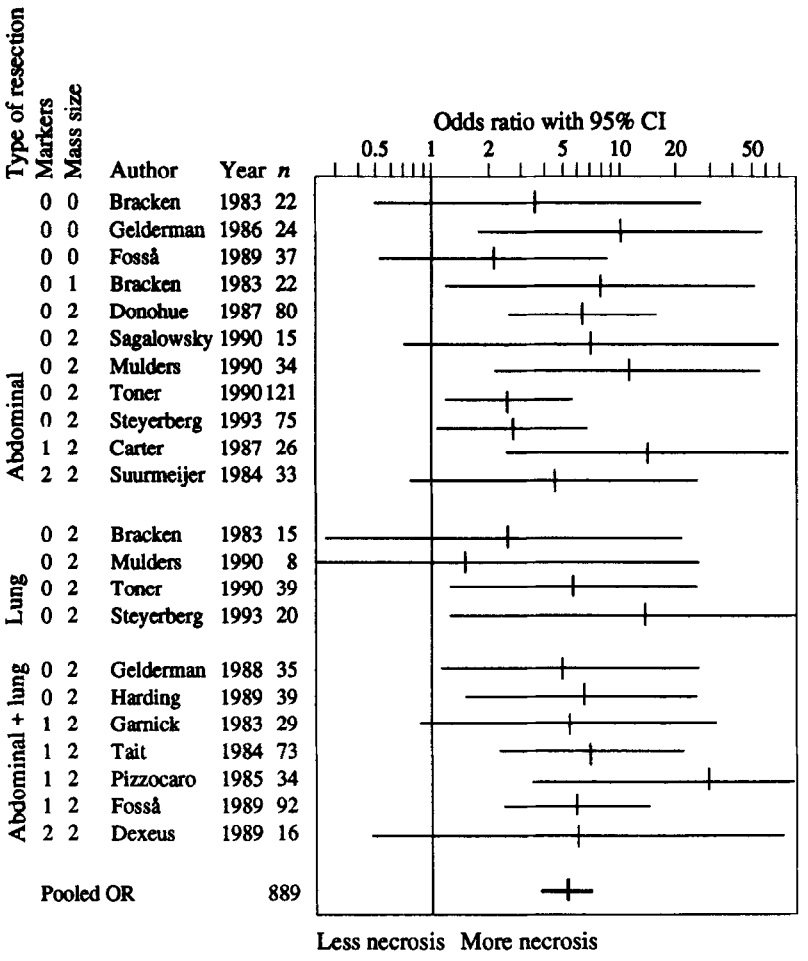

Figure 1. The effect of the absence of mature teratoma elements in the primary tumour on the probability of necrosis at resection. Studies are ordered according to the study characteristics as shown in Table 1.

No significant heterogeneity of effect was found for the other factors (normal AFP and/or normal HCG before chemotherapy, smaller pre- or postchemotherapy masses, a large shrinkage, lung resection compared to abdominal resection). Smaller pre- or postchemotherapy retroperitoneal masses were statistically significantly associated with a lower probability of cancer.

DISCUSSION

This study is the first quantitative overview of predictors for the histology at resection of residual masses in patients with NSGCT. Results from 19 published studies were summarised with statistical techniques. In 996 resections, necrosis was found in 48%, mature teratoma in 36% and cancer in 16%. In a recently published large study [30] the frequency of cancer was comparable (21%). The frequency of necrosis was, however, somewhat lower (22%) and the frequency of mature teratoma was somewhat higher (57%), probably reflecting the selection policy for resection (masses > 20 mm [30]).

Predictors for necrosis did not significantly depend on study characteristics such as the selection of patients or the time of treatment. Predictors for cancer, however, appeared to have different effects in lung and abdominal resections. Heterogeneity based on study size was not found, indicating that no major publication bias was present in the articles analysed.

The predictor of necrosis which appeared from this analysis as the most important is the absence of mature teratoma elements in the primary tumour. The fact that this primary histology is related to the finding of necrosis at resection was already evident from many individual studies, but the magnitude of the association could now be estimated more precisely (pooled OR 5.1, 95% CI 3.8–6.9). Secondly, in this meta-analysis normal levels of tumour markers AFP and/or HCG before chemotherapy were clearly associated with a higher probability of necrosis at resection. Note that this association was statistically significant in two out of seven individual studies only, [5, 24] and [14, 29]. Thirdly, the analysis indicated that smaller residual retroperitoneal masses contained necrosis more often at resection. Associations of similar magnitude were found for several cut-off points (10, 15, 20 or 50 mm). Finally, other predictors for necrosis were a large shrinkage (≥90%) and the location of the mass: resection of pulmonary nodules versus retroperitoneal masses.

Predictors for cancer were not considered explicitly in any previous publication, as it has been argued that both patients with mature teratoma or cancer in a residual mass require resection [3]. However, the consequences of leaving viable cancer cells unresected are not equivalent to the consequences of leaving mature teratoma unresected. Resection of residual cancer is usually followed by two additional chemotherapy courses, which is effective in the majority [8, 10] of these patients. A much lower efficacy may be expected in these patients if they relapse, due to development of drug resistance and a more extensive tumour bulk. Although the risks of leaving mature teratoma unresected include a more difficult resection after a rapid growth of the mass and malignant change [3], most

Table 3. Pooled odds ratios (OR) with the corresponding 95% confidence intervals for the factors described in the literature combined with own data

Factor	Necrosis OR (95% CI)	Cancer OR (95% CI)
Primary tumour histology		Abdominal: 0.48 (0.28–0.83)
Teratoma-negative vs teratoma-positive	5.1 (3.8–6.9)	Lung+abd.: 0.71 (0.39–1.3)
		Lung: 3.7 (0.99–14)
Tumour markers before chemotherapy		
AFP normal vs elevated	2.8 (1.7–4.6)	0.54 (0.26–1.1)
HCG normal vs elevated	1.9 (1.2–3.0)	1.33 (0.72–2.4)
Both AFP and BHCG normal vs one or both elevated	5.7 (2.5–13)	0.59 (0.19–1.9)
Retroperitoneal mass size		
Prechemotherapy size*		
≤20 vs >20 mm	1.3 (0.54–3.1)	0.32 (0.04–2.4)
≤50 vs >50 mm	1.6 (0.81–3.3)	0.25 (0.08–0.77)
Postchemotherapy size*		
≤10 vs >10 mm	3.6 (2.1–5.9)	0.40 (0.18–0.88)
≤15 vs >15 mm	8.4 (3.2–22)	0.33 (0.09–1.3)
≤20 vs >20 mm	3.7 (2.0–6.8)	0.12 (0.03–0.43)
≤50 vs >50 mm	4.3 (2.0–9.1)	0.35 (0.16–0.77)
Shrinkage		
≥90% vs <90%	3.1 (2.0–4.8)	0.63 (0.33–1.2)
Type of resection		
Lung vs abdominal	1.7 (1.0–2.7)	0.83 (0.42–1.6)

*Note that the ORs calculated at the different cut-off points are not totally independent, as the same observations of some studies were used in multiple calculations. An OR > 1 indicates that the probability was higher in the first category of a factor, e.g. the probability of necrosis was higher if the primary histology was teratoma-negative (OR=5.1).

patients with mature teratoma may presumably be resected successfully at a later date. Thus, a higher risk of leaving mature teratoma unresected might be accepted compared to the risk of cancer. The probability of cancer, therefore, requires explicit analysis. The probability of mature teratoma can be calculated once the probabilities of necrosis and cancer are known.

Remarkably, the association of the primary tumour histology with the probability of cancer appeared different in lung and abdominal resections. At lung resection, the absence of mature teratoma elements in the primary tumour was found to be related to a higher probability of necrosis, but also to a higher probability of cancer. This association might be explained by coincidence, because of the large number of tests for heterogeneity that were performed. Further empirical research may confirm our findings or explain why, for example, no mature teratoma elements are found in lung masses of patients with initially teratoma-negative tumours.

At abdominal resection, cancer was found significantly less often when the primary tumour was teratoma-negative. Also, smaller pre- or postchemotherapy abdominal masses were associated with a lower probability of cancer, especially residual masses ≤20 mm. Note that in these small residual masses the odds of necrosis were 3.7 times as high, while the odds of cancer were 8.3 times as low (OR = 0.12, Table 3) compared to residual masses >20 mm. Thus, residual retroperitoneal masses ≤20 mm contain necrosis more often, but in addition these masses contain cancer relatively less often. This is illustrated by the absolute frequencies of the histology at resection in our series [8]: necrosis 57%, mature teratoma 43%, and cancer in 0% of 23 retroperitoneal masses ≤20 mm after chemotherapy. When we combine these data with some recent publications presenting data on the histology of small residual masses (≤15 mm [3], <20 mm [14], ≤20 mm [26]) we observe the following distribution for the total of 155 small masses: necrosis 71%, mature teratoma 25% and cancer 3.9% (6/155). The policy to resect residual abdominal masses only if they exceed 20 mm [6, 30] thus implies that masses will be left unresected which have a risk of circa 25% of containing mature teratoma, but a risk of only 4% of containing cancer.

This analysis identified no single factor that indicated subgroups with a probability of necrosis only as high as 80 or 90%, nor were factors identified which excluded the finding of residual cancer. Presently, the size of the residual mass is the foremost important factor to select patients for resection [3, 6]. This analysis confirms that several other factors might be taken into account when considering resection, especially the absence of teratoma elements in the primary tumour. The association of the primary tumour histology with the finding of cancer at resection may, however, be markedly different in lung resections. This illustrates that selection guidelines for laparotomy may not apply to thoracotomy.

The combination of factors will possibly allow the definition of subsets of patients in whom resection might be omitted. Fossa [14] found necrosis only in 15 patients with residual masses smaller than 2 cm, with malignant teratoma undifferentiated (MTU) (embryonal carcinoma) in their primary tumour and with both AFP and HCG normal before chemotherapy. In our study group of 75 patients, only 2 fulfilled these criteria, 1 had necrosis and 1 had mature teratoma at laparotomy. Donohue [11] found necrosis only in 15 patients who showed a shrinkage over 90% in volume and without teratoma elements in their primary tumour. 5 of our patients met these criteria: 4 had

necrosis and 1 had cancer at laparotomy. Thus, attempts to define groups of patients who will not have mature teratoma or cancer based on a few factors are not very reliable so far and include a small fraction only of the total number of patients with CT scan-detected residual masses.

It may be expected that refinement and extension of the number of factors can make more accurate predictions of the histology at resection than the above mentioned studies [11, 14]. Therefore, we initiated a collaborative effort with other research groups to perform a multivariate analysis, using the primary tumour histology, the levels of tumour markers before chemotherapy (AFP, HCG, lactate dehydrogenase [3]), mass size after chemotherapy and shrinkage of the mass to estimate the probability of necrosis, mature teratoma and cancer at resection. These multivariate estimates may guide the decision to resect a residual mass. Optimal treatment is then determined on a more individual basis by weighing the benefits of resecting mature teratoma or cancer against the morbidity, mortality, financial costs and the patient's personal preferences.

1. Einhorn LH. Treatment of testicular cancer: a new and improved model. *J Clin Oncol* 1990, **8**, 1777–1781.
2. Peckham M. Testicular cancer. *Rev Oncol* 1988, **1**, 439–453.
3. Toner GC, Panicek DM, Heelan RT, *et al.* Adjunctive surgery after chemotherapy for nonseminomatous germ cell tumors: recommendations for patient selection. *J Clin Oncol* 1990, **8**, 1683–1694.
4. Donohue JP, Rowland RG. The role of surgery in advanced testicular cancer. *Cancer* 1984, **54**, 2716–2721.
5. Tait D, Peckham MJ, Hendry WF, Goldstraw P. Post-chemotherapy surgery in advanced non-seminomatous germ-cell tumours: the significance of histology with particular reference to differentiated (mature) teratoma. *Br J Cancer* 1984, **50**, 601–609.
6. Mead GM, Stenning SP, Parkinson MC, *et al.* The second medical research council study of prognositic factors in nonseminomatous germ cell tumors. *J Clin Oncol* 1992, **10**, 85–94.
7. Jansen RLH, Sylvester R, Sleyfer DT, *et al.* Long-term follow-up of non-seminomatous testicular cancer patients with mature teratoma or carcinoma at postchemotherapy surgery. *Eur J Cancer* 1991, **27**, 695–698.
8. Steyerberg EW, Keizer HJ, Zwartendijk J, *et al.* Prognosis after resection of residual masses following chemotherapy for metastatic nonseminomatous testicular cancer: a multivariate anlaysis. *Br J Cancer* 1993, **68**, 195–200.
9. Harding MJ, Brown IL, Macpherson SG, *et al.* Excision of residual masses after platinum based chemotherapy for non-seminomatous germ cell tumours. *Eur J Cancer Clin Oncol* 1989, **25**, 1689–1694.
10. Fox EP, Weathers TD, Williams SD, *et al.* Outcome analysis for patients with persistent nonteratomous germ cell tumor in postchemotherapy retroperitoneal lymph node dissections. *J Clin Oncol* 1993, **11**, 1294–1299.
11. Donohue JP, Rowland RG, Kopecky K, *et al.* Correlation of computerized tomographic changes and histological findings in 80 patients having radical retroperitoneal lymph node dissection after chemotherapy for testis cancer. *J Urol* 1987, **137**, 1176–1179.
12. Fosså SD, Aass N, Ous S, *et al.* Histology of tumor residuals following chemotherapy in patients with advanced nonseminomatous testicular cancer. *J Urol* 1989, **142**, 1239–1242.
13. Fosså SD, Ous S, Lien HH, *et al.* Post-chemotherapy lymph node histology in radiologically normal patients with metastatic nonseminomatous testicular cancer. *J Urol* 1989, **141**, 557–559.
14. Fosså SD, Qvist H, Stenwig AE, *et al.* Is postchemotherapy retroperitoneal surgery necessary in patients with nonseminomatous testicular cancer and minimal residual tumor masses? *J Clin Oncol* 1992, **10**, 569–573.
15. Stomper PC, Jochelsen MS, Garnick MB, *et al.* Residual abdominal masses after chemotherapy for nonseminomatous testicular cancer: correlation of CT and histology. *AJR* 1985, **145**, 743–746.
16. Sagalowsky AI, Ewalt DH, Molberg K, *et al.* Predictors of residual mass histology after chemotherapy for advanced testis cancer. *Urology* 1990, **35**, 537–542.
17. Gelderman WAH, Schraffordt Koops H, Sleijfer DTh, *et al.* Results of adjuvant surgery in patients with stage III and IV nonseminomatous testicular tumors after cisplatin–vinblastine–bleomycin chemotherapy. *J Surg Oncol* 1988, **38**, 227–232.
18. Dickersin K, Berlin JA. Meta-analysis: state-of-the-science. *Epidemiol Rev* 1992, **14**, 154–176.
19. Robins JM, Greenland S, Breslow NE. A general estimator for the variance of the Mantel–Haenszel odds ratio. *Am J Epidemiol* 1986, **124**, 719–723.
20. Yusuf S, Peto R, Lewis J, *et al.* Beta blockade during and after myocardial infraction: an overview of the randomized trials. *Prog Cardovasc Dis* 1985, **27**, 335–371.
21. Brand R, Kragt H. Importance of trends in the interpretation of an overall odds ratio in the meta-analysis of clinical trials. *Stat Med* 1992, **11**, 2077–2082.
22. Gelderman WAH, Schraffordt Koops H, Sleijfer DTh, *et al.* Treatment of retroperitoneal residual tumor after PVB chemotherapy of nonseminomatous testicular tumors. *Cancer* 1986, **58**, 1418–1421.
23. Carter GE, Lieskovsky G, Skinner DG, *et al.* Reassessment of the role of adjunctive surgical therapy in the treatment of advanced germ cell tumors. *J Urol* 1987, **138**, 1397–1401.
24. Pizzocaro G, Salvioni R, Pasi M, *et al.* Early resection of residual tumor during cisplatin, vinblastine, bleomycin combination chemotherapy in stage III and bulky stage II nonseminomatous testicular cancer. *Cancer* 1985, **56**, 249–255.
25. Dexeus FH, Shirkhoda A, Logothetis CJ, *et al.* Clinical and radiological correlation of retroperitoneal metastasis from nonseminomatous testicular cancer treated with chemotherapy. *Eur J Cancer Clin Oncol* 1989, **25**, 35–43.
26. Mulders PFA, Oosterhof GON, Boetes C, *et al.* The importance of prognostic factors in the individual treatment of patients with disseminated germ cell tumours. *Br J Urol* 1990, **66**, 425–429.
27. Bracken RB, Johnson DE, Frazier OH, *et al.* The role of surgery following chemotherapy in stage III germ cell neoplasms. *J Urol* 1983, **129**, 39–43.
28. Suurmeijer AJH, Oosterhuis JW, Sleijfer DTh, *et al.* non-seminomatous germ cell tumors of the testis: morphology of retroperitoneal lymph node metastases after chemotherapy. *Eur J Cancer Clin Oncol* 1984, **20**, 727–734.
29. Garnick MB, Canellos GP, Richie JP. Treatment and surgical staging of testicular and primary extragonadal germ cell cancer. *JAMA* 1983, **250**, 1733–1741.
30. Hendry WF, A'Hern RP, Hetherington JW, Peckham MJ, Dearnaley DP, Horwich A. Para-aortic lymphadenectomy after chemotherapy for metastatic non-seminomatous germ cell tumours: prognostic value and therapeutic benefit. *Br J Urol* 1993, **71**, 208–213.

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APPENDIX

Distribution of the histology at resection according to the predictors analysed. The first column (code) indicates the major study characteristics, as shown in Table 1. The studies are ordered according to these study characteristics and year of publication. *n* denotes the number of resections. Nec, necrosis; Ter, mature teratoma; Can, cancer.

Primary tumour histology

Code	Author	Year	Teratoma-negative				Teratoma-positive			
			n	Nec(%)	Ter(%)	Can(%)	*n*	Nec(%)	Ter(%)	Can(%)
100	Bracken *et al.* [27]	1983	17	71	6	24	5	40	40	20
100	Gelderman *et al.* [22]	1986	10	100	0	0	14	50	50	0
100	Fosså *et al.* [13]	1989	23	74	22	4	14	50	50	0
101	Bracken *et al.* [27]	1983	16	50	25	25	6	0	50	50
102	Donohue *et al.* [11]	1987	48	60	27	13	32	19	63	19
102	Sagalowsky *et al.* [16]	1990	6	67	17	17	9	22	44	33
102	Mulders *et al.* [26]	1990	18	83	6	11	16	31	63	6
102	Toner *et al.* [3]	1990	75	55	33	12	46	33	50	17
102	Steyerberg *et al.* [8]	1993	35	54	40	6	40	30	40	30
112	Carter *et al.* [23]	1987	13	54	23	23	13	0	54	46
122	Suurmeijer *et al.* [28]	1984	11	82	18	0	22	50	45	5
202	Bracken *et al.* [27]	1983	7	43	0	57	8	25	50	25
202	Mulders *et al.* [26]	1990	3	67	0	33	5	60	40	0
202	Toner *et al.* [3]	1990	18	83	0	17	21	48	48	5
202	Steyerberg *et al.* [8]	1993	9	89	0	11	11	36	55	9
302	Gelderman *et al.* [17]	1988	10	70	10	20	25	32	60	8
302	Harding *et al.* [9]	1989	18	67	22	11	21	24	48	29
312	Garnick *et al.* [29]	1983	15	47	27	27	14	14	64	21
312	Tait *et al.* [5]	1984	34	56	24	21	39	15	62	23
312	Pizzocaro *et al.* [24]	1985	19	68	16	16	15	7	47	47
312	Fosså *et al.* [12]	1989	39	74	15	10	53	34	53	13
322	Dexeus *et al.* [25]	1989	7	43	43	14	9	11	78	11
Total			451	64	22	14	438	29	53	18

Prechemotherapy highest AFP level

Code	Author	Year	AFP normal				AFP elevated			
			n	Nec(%)	Ter(%)	Can(%)	*n*	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	35	77	17	6	41	59	39	2
102	Mulders *et al.* [26]	1990	13	77	23	0	19	47	37	16
102	Steyerberg *et al.* [8]	1993	16	63	25	13	59	36	44	20
202	Steyerberg *et al.* [8]	1993	7	71	14	14	13	54	38	8
312	Garnick *et al.* [29]	1983	16	31	38	31	10	30	40	30
312	Tait *et al.* [5]	1984	16	56	31	13	58	28	45	28
312	Pizzocaro *et al.* [24]	1985	10	70	20	10	24	29	33	23
Total			113	65	24	12	224	39	41	20

Prechemotherapy highest HCG level

Code	Author	Year	HCG normal				HCG elevated			
			n	Nec(%)	Ter(%)	Can(%)	*n*	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	35	83	17	0	41	54	39	7
102	Mulders *et al.* [26]	1990	11	55	36	9	22	59	32	9
102	Steyerberg *et al.* [8]	1993	23	57	30	13	52	35	44	21
202	Steyerberg *et al.* [8]	1993	6	67	17	17	14	57	36	7
312	Garnick *et al.* [29]	1983	11	55	18	27	18	17	56	28
312	Tait *et al.* [5]	1984	18	33	22	44	55	35	49	16
312	Pizzocaro *et al.* [24]	1985	9	33	22	44	25	44	32	24
Total			113	59	23	18	227	41	42	16

Prechemotherapy highest AFP and HCG level

Code	Author	Year	AFP and HCG normal				AFP or HCG elevated			
			n	Nec(%)	Ter(%)	Can(%)	*n*	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	24	92	8	0	52	56	38	6
102	Mulders *et al.* [26]	1990	6	67	33	0	27	56	33	11
102	Steyerberg *et al.* [8]	1993	8	75	13	13	67	37	43	19
202	Steyerberg *et al.* [8]	1993	2	100	0	0	18	56	33	11
312	Garnick *et al.* [29]	1983	7	57	0	43	22	23	59	18
312	Pizzocaro *et al.* [24]	1985	3	100	0	0	31	35	32	32
Total			50	82	10	8	217	44	40	16

Prechemotherapy maximum tranversal abdominal lymph node size

Code	Author	Year	Category	*n*	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	<20 mm	13	54	38	8
			≥20 mm	63	70	27	3
102	Mulders *et al.* [26]	1990	20–49 mm	14	71	29	0
			≥50 mm	20	50	35	15
102	Steyerberg *et al.* [8]	1993	≤20 mm	10	40	60	0
			21–49 mm	24	50	42	8
			≥50 mm	15	37	34	29
312	Pizzocaro *et al.* [24]	1985	≤20 mm	1	100	0	0
			21–49 mm	6	33	33	33
			≥50 mm	27	41	30	30

Postchemotherapy maximum tranversal abdominal lymph node size

Code	Author	Year	Category	*n*	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	0–10 mm	49	71	22	6
			11–20 mm	27	59	41	0
102	Bracken *et al.* [27]	1983	Clinical complete response	22	64	14	23
			Residual mass	22	36	32	32
102	Stomper *et al.* [15]*	1985	11–20 mm	17	59	35	6
			21–50 mm	10	50	30	20
			>50 mm	18	33	39	28
102	Toner *et al.* [3]	1990	0–15 mm	39	79	13	8
			>15 mm	60	32	48	20
102	Mulders *et al.* [26]	1990	0–10 mm	9	89	11	0
			11–20 mm	8	88	13	0
			21–50 mm	11	45	36	18
			>50 mm	6	0	83	17
102	Steyerberg *et al.* [8]	1993	10–20 mm	23	57	43	0
			21–50 mm	38	39	37	24
			>50 mm	14	21	43	36
312	Garnick *et al.* [29]	1983	CT normal	7	43	43	14
			CT abnormal	15	27	33	40
312	Fossa *et al.* [12]	1989	CT normal	34	79	18	3
			CT abnormal	58	34	48	17
312	Pizzocaro *et al.* [24]	1985	0–10 mm	8	75	13	13
			11–20 mm	4	50	25	25
			21–50 mm	7	43	29	29
			>50 mm	15	20	40	40

*n indicates in this study the number of residual masses, not the number of resections.

Shrinkage of the mass (≥68.4%/70% in size /≥90% in area)

Code	Author	Year	Shrinkage ≥90% n	Nec(%)	Ter(%)	Can(%)	Shrinkage <90% n	Nec(%)	Ter(%)	Can(%)
100	Fosså *et al.* [14]	1992	34	71	23	6	42	64	33	2
102	Stomper *et al.* [15]*	1985	10	70	10	20	21	57	29	14
102	Donohue *et al.* [11]+	1987	24	71	25	4	56	32	48	20
102	Sagalowsky *et al.* [16]+	1990	7	40	40	20	10	40	30	30
102	Mulders *et al.* [26]	1990	12	83	17	0	22	45	41	14
102	Toner *et al.* [3]	1990	25	72	16	12	61	39	44	16
102	Steyerberg *et al.* [8]	1993	11	73	9	18	64	36	45	19
312	Pizzocaro *et al.* [24]	1985	13	69	15	15	21	24	38	38
Total			134	71	19	11	297	41	41	17

*n indicates in this study the number of residual masses, not the number of resections
+A reduction over 90% in volume was used as a criterium for 'large reduction in size'.

Type of resection

Code	Author	Year	Lung resection n	Nec(%)	Ter(%)	Can(%)	Abdominal resection n	Nec(%)	Ter(%)	Can(%)
302	Bracken *et al.* [27]	1983	15	33	27	40	22	36	31	32
302	Mulders *et al.* [26]	1990	8	63	25	13	34	59	32	9
302	Toner *et al.* [3]	1990	39	64	26	10	122	46	40	14
302	Steyerberg *et al.* [8]	1993	20	60	30	10	75	41	40	19
312	Fosså *et al.* [12]	1989	9	56	33	11	92	51	47	12
Total			91	57	27	15	345	47	38	15

Pergamon

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Long-term Results of Two VAB-like Regimens (Vinblastine + Actinomycin-D + Bleomycin + Cyclophosphamide + Cisplatin) in Malignant Germ Cell Tumours of the Ovary

S. Culine, C. Lhomme, J. Kattan, P. Duvillard, G. Michel and J.-P. Droz

21 patients with malignant germ cell tumours of the ovary were treated with two chemotherapy regimens including vinblastine, actinomycin-D, bleomycin, cyclophosphamide and cisplatin. Chemotherapy was delivered as primary postoperative therapy in 15 patients and for recurrent disease in 6 patients. 3 of 4 patients with pure dysgerminomas and 10 of 17 patients with non-dysgerminomatous tumours are alive without evidence of disease. The overall progression-free survival is 62% (95% confidence interval 45–77) with a median follow-up of 7 years. Two toxic deaths were observed. Less toxicity and better efficacy favour etoposide- and cisplatin-based regimens as standard chemotherapy for germ cell tumours of the ovary.

Keywords: germ cell tumours, ovary, chemotherapy
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INTRODUCTION

MALIGNANT OVARIAN germ cell tumours account for <5% of all ovarian neoplasms, and their incidence is approximately one tenth that of testicular cancer [1]. The pathological classification mainly distinguishes pure dysgerminoma, the female equivalent of seminoma, and tumours other than pure dysgerminoma, the so-called non-seminomatous germ cell tumours (NSGCT) [2].

Dysgerminoma is radiosensitive, and radiotherapy has been used in the postoperative treatment of patients with primary disease as well as in patients with recurrent disease. Several