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Special Paper

Radiotherapy After Chemotherapy for Metastatic Seminoma—a Diminishing Role

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In a retrospective study, data from 302 patients with metastatic testicular seminoma treated with chemotherapy between 1978 and 1990 in 10 European centres were analysed to evaluate the role, if any, of postchemotherapy treatment with irradiation. The primary endpoint of this study was the progression-free survival rate after chemotherapy with or without additional radiotherapy. This was related to the type of primary chemotherapy, sites and sizes of pre- and postchemotherapy masses, the extent of surgical resection after chemotherapy and the use of radiotherapy. 174 patients had residual disease at the end of chemotherapy. The most important prognostic factors for progression were the presence of any visceral metastases or raised LDH prechemotherapy, and the presence of residual disease at visceral sites after chemotherapy. Approximately half the patients with residual masses underwent postchemotherapy radiotherapy, with selection based predominantly on institutional practice. In patients receiving platinum-based chemotherapy, no significant difference was detected in progression-free survival whether or not radiotherapy was employed. Patients receiving BEP (bleomycin, etoposide and cisplatin) had a progression-free survival rate of 88% (95% CI, 80–96%) uninfluenced by postchemotherapy radiotherapy. In patients with residual masses confined to the abdomen after platinum-based chemotherapy, the absolute benefit to radiotherapy was estimated to be 2.3%. The potential benefit of postchemotherapy radiotherapy is minimal, and so it is concluded that the use of adjuvant radiotherapy to residual masses after platinum-based chemotherapy for metastatic seminoma is unnecessary. © **1997 Elsevier Science Ltd.**

Key words: metastatic seminoma, postchemotherapy radiotherapy, cisplatin

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INTRODUCTION

TREATMENT OF bulky Stage II or Stage III (Royal Marsden Hospital staging system) [1] seminoma with single modality primary radiation therapy is associated with high subsequent relapse rates. In patients with disease confined to infradiaphragmatic sites, relapse will occur within the irradiated field in around 15% of patients, and at distant sites in a further 25% [2]. While the long-term prognosis remains good after salvage chemotherapy [3], it is now widely accepted practice to use platinum-containing chemotherapy as the primary treatment modality [4–6].

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Residual masses are present at one month after chemotherapy in up to 80% of patients [7] and thereafter most gradually regress, often over a period of months or years. Several different strategies for managing these masses have been reported, and include multiple biopsy or surgical resection—which may dictate the use of further cytotoxic therapy—adjuvant irradiation or observation alone. Surgical resection of residual abnormalities may be hazardous because of the intense reactive fibrosis encountered, and not all masses will contain residual viable tumour. The Memorial Sloan-Kettering group [8] in a series reported in 1987, undertook laparotomy and complete resection of residual masses in 19 patients (13 greater than 3 cm in size) and found 4 to have residual seminoma and one teratoma. An additional one of 4 patients observed without surgery had a biopsy-proven relapse. On the basis of these findings, additional therapy was recommended for all those with residual masses greater than 3 cm in diameter. A recent publication from the same group [9] confirmed the finding of low risk of site failure (progression at the site of the residual mass) with residual masses under 3 cm, but demonstrated a 27% incidence of site failure in masses larger than this. A different experience was reported from Indiana [10], where of 21 patients (58% of all patients) with residual postchemotherapy masses (12 smaller and 9 larger than 3 cm), only 2 patients relapsed, and none of the 3 who underwent resection had evidence of viable tumour. With inconsistent data regarding the predictive value of residual mass size, this group has analysed the role of gallium scanning in detecting active seminoma either pre- or postchemotherapy, but the high false-negative rates with this procedure means that it has little value [11].

The disparities in the reported surgical series are mirrored by the division in opinion regarding the addition of radiation therapy for those with residual masses. The decision may be complicated by the slow nature of regression [12]. Relapse, when it occurs, tends to be at the site of bulk disease [4, 7, 13], particularly when disease width at presentation is greater than 10 cm [12, 14], but in most patients other prognostic features for relapse are unclear. Analysis is further complicated as not all series report the site of relapse. The addition of radiotherapy, like surgery, would only prove worthwhile if firstly, a residual local mass after chemotherapy is a strong predictor of relapse; secondly, that failure locally rather than with distant metastasis is the rule; and thirdly, that radiation effectively prevents local failure.

In 1989 the Germ Cell Tumour Consensus Conference in Hull [15] endorsed a policy of observation after chemotherapy, but other groups [2, 16, 17] have recommended radiotherapy to prevent progression, even in the absence of a documented effect on overall survival. The uncertainty regarding the optimal policy was exemplified by clinical practice in the MRC Trial TE12 [18] assessing chemotherapy in advanced seminoma, in which there was no consistent pattern amongst participating centres in the use of postchemotherapy irradiation. We have, therefore, analysed the risk of relapse associated with different management strategies for all seminoma patients registered on the MRC U.K. and Norwegian database of patients who underwent chemotherapy for advanced metastatic seminoma, to determine optimal management.

PATIENTS AND METHODS

The study group was identified retrospectively, and consisted of all those patients with metastatic seminoma treated with chemotherapy between 1978 and 1990 in 9 centres in the United Kingdom and one in Oslo. All patients had histologically confirmed seminoma with normal serum alpha

Table 1. Patient characteristics (n = 302)

Parameter	Number of patients (%)	
Age (years)	38	
Median (range)	(15–75)	
Type of chemotherapy		
No platinum	16 (5%)	
Carboplatin single agent	58 (19%)	
Cisplatin single agent	15 (5%)	
BEP	68 (23%)	
PVB	70 (23%)	
Other platinum combination	75 (25%)	
Site of disease	Initial (%)	After chemotherapy
Abdomen only	161 (53%)	123 (41%)
Thorax only	50 (17%)	21 (7%)
Both	58 (19%)	19 (6%)
Liver/bone/brain +/– abdomen/thorax	25 (8%)	11 (4%)
Not all sites known	8 (3%)	
None	N/A	128 (42%)
Size of abdominal nodes		
None	67 (22%)	155 (51%)
<2 cm	4 (1%)	14 (5%)
2–5 cm	49 (16%)	59 (20%)
>5 cm	150 (50%)	21 (7%)
Present but unknown	32 (11%)	53 (17%)

BEP, bleomycin, etoposide and cisplatin; PVB, cisplatin, vinblastine and bleomycin.

fetoprotein (AFP) levels. The patient characteristics are shown in Table 1. The median age was 38 years, with a range 15–75 years. The majority of patients had abdominal lymphadenopathy, with or without thoracic node involvement, although some had thoracic lymphadenopathy only. All patients were given chemotherapy as primary treatment,

Table 2. Patients with residual masses postchemotherapy

(a) Influence of prechemotherapy factors on subsequent disease progression

Prechemotherapy factor	No. of patients	3 year PFS	Log rank χ^2 *P*-value
Abdominal mass			
None	27	74%	0.85
≤5.0 cm	23	91%	
5.1–10.0 cm	63	88%	
>10.0 cm	39	76%	
Size unknown	22		
Mediastinal mass			
None	146	84%	0.84
≤5.0 cm	10	78%	
>5.0 cm	13	85%	
Size unknown	5		
Neck mass			
None	147	86%	0.13
≤5.0 cm	20	70%	
>5.0 cm	4	75%	
Size unknown	3		
Lung metastases			
None	140	85%	0.008
<5	15	73%	
>5	10	56%	
Number unknown	9		
Non-pulmonary visceral metastasis			
None	155	86%	0.01
Present	19	62%	
LDH			
$<2 \times N$	56	89%	0.01
$\geq 2 \times N$	42	68%	
LDH unknown	76		
HCG			
Normal	87	83%	0.50
Raised	87	84%	
Prior radiotherapy			
No	154	85%	0.40
Yes	20	75%	

(b) Influence of postchemotherapy factors

Postchemotherapy factor	No. of patients	3 year PFS	Log rank χ^2 *P*-value
Residual mass site			
Abdomen only	123	88%	0.004
Thorax only	21	76%	
Abdomen and thorax	19	77%	
Other sites	11	55%	
Resection of residual abdominal mass			
None	116	84%	0.31
Biopsy	7	100%	
Complete resection	22	90%	
Extent of resection unknown	2		
Not applicable	27		
Size of residual abdominal mass			
None	27	74%	0.78
<2 cm	14	93%	
2.1–5.0 cm	58	89%	
>5.0 cm	22	86%	
Size unknown	26		

the majority receiving four cycles of platinum-based chemotherapy, prior to re-evaluation. The decision to offer adjuvant radiation therapy was taken on an individual basis.

The main endpoint used was progression-free survival, recorded from the start of chemotherapy to the date of first disease progression (local or distant), and the progression-free survival rates were compared in patients with and without residual masses. In those patients with residual masses, the following factors were assessed for their impact on progression-free survival:

- prechemotherapy sites and sizes (maximum transverse diameter) of disease;
- prechemotherapy markers;
- primary chemotherapy;
- sites and sizes of residual masses;
- extent of resection of residual masses (complete versus incomplete resection);
- use of postchemotherapy radiotherapy (dose was not recorded).

Kaplan–Meier progression-free survival rates were compared in univariate analyses using the log rank test. The effect of postchemotherapy radiotherapy was assessed in a multivariate analysis using Cox's proportional hazards regression model, adjusting for other potential confounding factors.

RESULTS

The study included 302 patients with histologically confirmed seminoma with normal AFP pre- and postorchidectomy. Median follow-up time is 6.5 years, with over 90% of patients having been followed-up for more than 3 years. A total of 54 patients have had disease progression, and 48 have died. Overall, 128 patients (42%) entered complete remission with chemotherapy alone. Of 174 patients with residual disease on completion of chemotherapy (defined as a lymph node mass > 1.5 cm, or visible lung metastases on chest X-ray), 123 had residual disease in the abdomen alone, 21 in the thorax (lung or mediastinum) alone and 19 in both sites. The 11 remaining patients had residual masses in the liver or other visceral sites.

Prognostic factors for progression

In the 174 patients with residual masses, pre- and postchemotherapy factors were examined for the potential association with postchemotherapy progression. Table 2a gives the 3 year progression-free survival rates (PFS) for a number of prechemotherapy factors. The presence of visceral metastases (pulmonary or non-pulmonary e.g. liver, bone, brain) was an adverse factor, as was prechemotherapy elevation of LDH (lactate dehydrogenase). There was no significant trend towards an increased risk of progression with increasing abdominal, supraclavicular or mediastinal mass size. Of the postchemotherapy factors (Table 2b), site of residual mass was highly significant, with progression-free survival rates lower in patients with thoracic or other visceral masses compared with abdominal residuum only. In patients with residual abdominal mass, resection was not associated with a significant increase in PFS, nor was smaller mass size. Few patients had resection of mediastinal or lung metastases, but all those who did remained progression-free at 3 years. Similarly, few patients had raised markers after chemotherapy, but those who did had a poor prognosis; with only 1 of 9 patients with raised HCG (human chorionic gonadotrophin) being progression-free at 3 years.

The impact of radiotherapy was then assessed in relation to a number of potential confounding factors.

Sites of residual masses after chemotherapy

The effect of irradiation of residual masses was examined according to mass site (Table 3). No significant differences in progression-free survival were found in any of the groups between irradiated and observed patients. Although there is a suggestion that progression-free survival was slightly higher with irradiation, the difference did not reach statistical significance. In the most homogenous group, those with residual masses only in the abdomen, the estimated difference in progression-free rate at 3 years was 4% in favour of radiotherapy (log rank P-value = 0.38). However, of 8 relapses in the non-irradiated group, 6 had progressive disease in the abdomen while of 7 relapses in the irradiated group, 5 had progressive disease in the abdomen. This suggests either that the radiation was ineffective, or that it covered an inadequate volume. There was no significant difference in the progression-free interval for relapsing patients between those irradiated or observed, with a median of 213 days to relapse for those observed (range 105–1779 days) compared with 318 days (range 106–758 days) for those irradiated.

Size of residual mass and selection for postchemotherapy irradiation

Of those patients entering complete remission on chemotherapy alone (128), 7 (all stage II at the start of chemotherapy) received adjuvant radiotherapy to the abdomen, all of whom maintained long-term disease-free survival and a further 3 (all with stage III disease with presentation) had

Table 3. The effect of adjuvant radiotherapy on progression-free survival

Residual masses Postchemotherapy	Progression-free survival at 3 years (95% CI)	Radiotherapy given		3 year progression-free survival (95% CI)
Absent	81% (74%, 88%)	Yes	10	89% (69%, 99%)
		No	118	80% (72%, 88%)
Present – abdomen only	88% (82%, 94%)	Yes	70	90% (83%, 97%)
		No	53	86% (76%, 96%)
Present – thorax only	76% (58%, 94%)	Yes	7	71% (38%, 99%)
		No	14	79% (57%, 99%)
Present – abdomen, all*	85% (79%, 92%)	Yes	79	87% (80%, 94%)
		No	68	83% (74%, 91%)

*Represents those with abdominal disease only, and those with abnormalities both in the thorax and abdomen.

adjuvant radiotherapy to the mediastinum, one of whom subsequently relapsed in the abdominal nodes. The progression-free survival of the remaining 118 who achieved CR and did not have adjuvant radiotherapy was 80% (95% CI, 73–87%) at 3 years. There appeared to be no selection bias, based on residual mass size, for radiation therapy. The median size (maximum transverse diameter) of the residual abdominal mass for those receiving radiotherapy was 2.9 cm (range 0.5–20 cm), and for those observed 3 cm (range 1–11 cm). The treatment era likewise made no impact on the decision to use radiotherapy. The main influence appeared to be simply the management policies of the individual treating centres; the proportion of patients with residual abdominal masses which were irradiated varied across centres from none to 84%.

In the group of patients with residual abdominal masses (147 in total), there was a suggestion that risk of progression might increase with residual mass size: 7% with masses less than 2 cm, 12% with masses 2–5 cm, and 14% greater than 5 cm progressed, but the numbers progressing overall were too small to be able to comment on the validity of this observation (log rank test for trend, $P = 0.49$).

Effect of surgery

In the earlier study years surgical resection of residual masses was attempted more commonly than in later years; the proportion of patients in whom abdominal mass resection was attempted halved from 26% before 1986 to 13% after. The histology of 34 resected masses was available; 4 masses contained viable seminoma, 2 contained teratoma differentiated (TD), 2 contained viable non-seminomatous germ cell tumour and the remaining 26 contained only necrosis or fibrosis. Of patients with residual abdominal mass only, 18 patients had a resection of abdominal nodes classified as complete, while 5 had a biopsy only. The histology of the 18 completely resected masses was necrosis/fibrosis only in 15 (one of whom subsequently relapsed), seminoma in 1, TD in 1 and malignant teratoma undifferentiated (MTU) in 1. Three year progression-free survival for the whole completely resected group was 94% (84%, 99%). Three patients received adjuvant radiotherapy, none of whom relapsed, while 1 of 15 not irradiated relapsed. The majority of patients were managed without surgical intervention and of the remaining 105 patients with residual abdominal disease, 3 year PFS was 87% (81%, 94%). 67 patients were irradiated, and had slightly better 3 year PFS compared to observation; 89% (80%, 96%) at 3 years versus 83% (70%, 98%), respectively. Again this is a statistically non-significant result (log rank $P = 0.23$). When looking at the endpoint of survival in these patients, the estimated 3 year survival rate was 88% in both irradiated and non-irradiated groups (log rank $P = 0.58$).

Type of chemotherapy

Before the introduction of cisplatin into germ cell tumour protocols, patients were treated with a variety of schedules, which were combined for the purposes of this analysis into non-platinum-containing schedules. 16 patients fell into this category; 5 of 8 patients given chemotherapy alone relapsed compared with only one of 8 given radiation therapy in addition. Only 4 of the 16 patients achieved complete remission with chemotherapy alone.

For platinum-containing combinations, the proportion of patients achieving complete remission was 43% (124/286) of whom 21 progressed; the 3 year PFS was 84%. The remaining 162 patients had residual masses, of whom 83 received radiotherapy and 79 were observed. In the radiotherapy group, 14 patients progressed compared with 13 in the observation group. Progression-free rates were lower overall in the single agent carboplatin-treated patients than those receiving combination platinum-based therapy (3 year PFS 79% versus 85%); despite this, the addition of radiotherapy did not appear to influence the risk of progression.

68 patients received BEP chemotherapy (bleomycin, etoposide and cisplatin). In this group the overall 3 year PFS was 88% (95% CI, 80–96%). The complete remission rate with chemotherapy alone was 49% (33/68), and the 3 year PFS of these patients was 90%. 35 patients had residual masses (29 in the abdomen, 3 in the thorax, 3 at other sites), of whom 12 had abdominal radiotherapy and 2 progressed, but neither in the site of the residual mass, giving a 3 year PFS of 83%. Of the 23 patients with non-irradiated residual masses, 3 patients had progressive disease (none at the site of their residual disease) and the 3 year progression-free rate was, at 87%, similar to that for patients entering CR on chemotherapy alone.

Table 4 gives the progression-free survival rates for patients with residual abdominal masses only, according to initial chemotherapy regimen and use of radiotherapy.

Table 4. Chemotherapy regimen used and progression-free survival patients with residual abdominal mass only

Chemotherapy regimen used	3 year progression-free survival (95% CI)	Radiotherapy given		3 year progression-free survival (95% CI)
Non-platinum	67% (37%, 97%)	Yes	6	83% (43%, 99%)
		No	3	33% (0%, 87%)
s.a. carboplatin	85% (59%, 99%)	Yes	10	80% (54%, 99%)
		No	10	90% (71%, 99%)
s.a. cisplatin	100% (40%, 100%)	Yes	1	100%
		No	3	100% (29%, 100%)
BEP	89% (77%, 99%)	Yes	10	90% (71%, 99%)
		No	17	88% (72%, 99%)
PVB/other cisplatin combination	92% (85%, 99%)	Yes	43	93% (85%, 99%)
		No	20	90% (76%, 99%)

BEP, bleomycin, etoposide and cisplatin; PVB, cisplatin, vinblastine and bleomycin.

Adjusted analyses

Taking only those patients who received platinum-based chemotherapy, and subsequently had residual disease confined to the abdomen (114 patients), a further analysis of prognostic factors for disease progression was carried out. In univariate (log rank) analyses, the most significant factor was LDH level, despite unavailable data for 55 patients. Three year PFS was 100% in the 38 patients with a prechemotherapy LDH of $< 2 \times N$, but only 70% in the 21 with LDH $\geqslant 2 \times N$ ($\chi^2 = 13.3$, $P = 0.0003$). Size of prechemotherapy abdominal mass was of borderline statistical significance, with 3 year PFS of 100%, 88% and 84% in patients with mass sizes of $\leqslant 5$ cm, 5.1–10.0 cm and $\geqslant 10$ cm, respectively (χ^2 (trend) 4.29, $P = 0.04$).

The number of events was too few to enable the effect of radiotherapy to be assessed after adjustment for all the potential confounding factors. Instead, the effect of radiotherapy on progression rates was analysed in a series of two-factor Cox regression models, including all the pre- and postchemotherapy factors described in Table 2. The hazard ratio associated with radiotherapy was 0.76 (95% CI, 0.25, 2.36) unadjusted. This corresponds to an absolute progression-free survival increase at 3 years of just 2.3%, although the 95% CI is wide (−12%, +7.4%). Adjustment for the only significant prognostic factors led to an increase in the hazard ratio to 1.13 after adjustment for prechemotherapy mass size, and to 2.88 after adjustment for prechemotherapy LDH, both indicating an adverse effect of radiotherapy. Adjustment for the "non-significant" factors in most cases resulted in slight increases in the hazard ratio. The only exception was the completeness of resection; adjustment for this factor led to a radiotherapy hazard ratio of 0.63, corresponding to an absolute PFS increase at 3 years of 3.6%.

DISCUSSION

While the majority of patients with seminoma present with stage I or small volume stage II disease which is effectively managed with orchidectomy and radiation therapy, the minority with more extensive disease are treated with systemic chemotherapy. In the patients left with residual masses after chemotherapy, the use of adjuvant radiation therapy would improve disease-free survival rates if chemotherapy failed to sterilise a significant proportion of cells in sites of bulk disease. The conflicting reports [8, 10] from surgical series from two oncology centres leave the question of the proportion of residual masses containing viable cells unanswered. Both these centres used combination chemotherapy schedules (usually cisplatin, vinblastine and bleomycin) and yet reported very different experiences. One reason may be the difficulty of assessing tumour cell viability in surgical specimens in the presence of extensive necrosis and fibrosis. Variable patterns of disease relapse after chemotherapy have been reported in the literature. With single-agent carboplatin [13], relapse appears to be confined to nodal sites previously known to be involved. In the current series, relapse occurred more commonly at previously involved sites, although distant relapses were also documented. Failure at sites of bulk disease would, therefore, seem to be the predominant pattern with any type of chemotherapy.

Analysis of this retrospectively identified database has in fact demonstrated very little benefit in terms of progression-free survival for the addition of radiation therapy to residual masses. There appeared to be a striking benefit for the small number of patients treated without platinum-containing schedules, but for the majority who received platinum the improvement in progression-free survival was less than 5% and did not reach conventional levels of significance. As would therefore be expected, there was no significant effect on overall survival. The major underlying reason must be assumed to be effective sterilisation of malignant cells by platinum-based chemotherapy. Radiation would then obviously provide no additional advantage. Where there is extensive initial disease, it may be technically difficult to cover all sites with radiotherapy, allowing potential distant relapse and so again diminishing the efficacy of radiation. Finally, it might be that those cells which are resistant to chemotherapy and survive may also be radioresistant.

This study is not a randomised comparison of the use of radiotherapy and clearly patient selection may have affected the results, although the use of radiotherapy appeared to be related to institutional preference rather than individual patient characteristics. However, the excellent prognosis for patients receiving platinum-based chemotherapy—and hence the minimal potential for benefit to radiotherapy—is indisputable.

It is notable that the progression-free survival rates reported in a number of publications from the 1980s averaged around 80% [7, 8, 12, 19–22]. In this more recent patient cohort the equivalent rates are approaching 90%. Improvements in chemotherapy combinations may have therefore obviated the additional benefit that adjuvant radiation therapy previously provided. This progression-free survival rate is also similar to the 90% of patients designated by Puc and associates [9] as 'site non-failures', treated with cisplatin-based combination chemotherapy, and surgery for residual masses. It is particularly interesting to note the superiority of BEP, with etoposide, over PVB, with vinblastine. The overall complete remission rate for platinum-based schedules other than BEP in this series is 34% at one month, whereas that with BEP is 49%. An equivalent increase in total sterilisation of seminoma cells in residual masses would be expected, again reducing the potential benefit of adjuvant radiation. Seminoma cells are exquisitely sensitive to etoposide, and its inclusion with platinum has contributed to the improved disease-free survival rates.

The question of relative toxicities of the various modalities has not been directly addressed in this study. Cisplatin has significant acute and late toxicity [20] and other drugs used in combination may also have long-term effects; for example, etoposide has been associated with secondary leukaemia [23]. The use of radiotherapy is associated with acute nausea and increases the incidence of subsequent duodenal ulceration. Furthermore, a recent review suggested a 2–3-fold increase in the risk of second solid tumours following radiotherapy for germ cell tumours [24]. Up to 50% of patients report residual treatment-related symptoms, especially after chemotherapy, up to 7 years after treatment [25]. It might be argued that using less toxic combination chemotherapy supplemented by adjuvant radiation therapy might be on balance more acceptable than intensive chemotherapy alone, or with surgery, as recommended by the Memorial Sloan–Kettering group [9]. The current recommendation, however, from this series is not to employ adjuvant radiation in any patients. Suitable patients with

metastatic seminoma should be entered into the joint EORTC (Protocol 30941) and MRC (Protocol TE20) randomised trial of 3 versus 4 courses of 3-day or 5-day BEP/EP where data on pattern and timing of relapse and toxicity and quality of life data will be collected prospectively.

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