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Surveillance Following Orchidectomy for Stage I Seminoma of the Testis

Hans von der Maase, Lena Specht, Grete Krag Jacobsen, Anders Jakobsen, Ebbe Lindegaard Madsen, Mogens Pedersen, Mikael Rørth and Henrik Schultz

From 1985 to 1988, 261 unselected patients entered a nationwide Danish study of surveillance only for testicular seminoma stage I. The median follow-up time after orchidectomy was 48 months, range 6–67 months. 49 patients relapsed (19%). Sites of relapse were paraaortic lymph nodes in 41 patients, pelvic lymph nodes in 5, inguinal lymph nodes in 2 and lung metastases in 1 patient. The median time to relapse was 14 months, range 2–37 months. The 4-year relapse-free survival was 80%. 37 of the relapsing patients (76%) had radiotherapy as relapse treatment. Of these patients, 4 (11%) had a second relapse and received chemotherapy. 1 died of disseminated seminoma. Of the relapsing patients, 12 (24%) had chemotherapy as relapse treatment because of bulky (11 patients) or disseminated disease (1 patient). None of these patients have had a second relapse. However, 2 patients died of infection due to chemotherapy-induced neutropenia. Thus, there have been three seminoma-related deaths (1.1%). The testicular tumour size had an independent prognostic significance. The 4-year relapse-free survivals were 94, 82 and 64% for tumours < 3, 3 to < 6 and ≥ 6 cm, respectively. Patients with tumours ≥ 6 cm will now be given prophylactic radiation treatment, whereas we will continue to use surveillance only after orchidectomy for patients with tumours < 6 cm.
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INTRODUCTION

CONVENTIONAL TREATMENT for patients with seminoma stage I of the testis has until recently been orchidectomy followed by irradiation to the paraaortic and ipsilateral iliac lymph nodes. This treatment strategy has been difficult to challenge because of the exceptionally good outcome. Thus, in a previous publication from the Danish Testicular Carcinoma Study Group (DATECA), we found that only 13 out of 424 patients experienced a relapse (3%) and there were only four cancer-related deaths (1%) [1]. Similar data were given by Zagars in a recent review based on 2376 patients showing a relapse rate of 4.5% and a seminoma-related death rate of 2.3% [2]. Nevertheless, it seemed likely that prophylactic irradiation following orchidectomy was unnecessary for a substantial proportion of these patients. Therefore, there was an obvious need to investigate the possibility of using a surveillance only strategy following orchidectomy—a study that became acceptable because a safe salvage therapy was available. Thus, we initiated a nationwide Danish study in 1985. Here we report the data from this study which comprises the largest study population hitherto reported for surveillance only following orchidectomy in patients with seminoma stage I.

PATIENTS AND METHODS

During the period from January 1985 to January 1988 all new patients with a diagnosis of testicular seminoma in Denmark had

Correspondence to H. von der Maase.
H. von der Maase and A. Jakobsen are at the Department of Oncology, Aarhus University Hospital, DK 8000 Aarhus C; L. Specht is at the Department of Oncology, Herlev Hospital, University of Copenhagen; G.K. Jacobsen is at the Institute of Pathological Anatomy, Gentofte Hospital, University of Copenhagen; E.L. Madsen is at the Department of Oncology, Odense University Hospital; M. Pedersen is at the Department of Oncology, Aalborg University Hospital; M. Rørth is at the Department of Oncology, Rigshospitalet, University of Copenhagen; and H. Schultz is at the Department of Oncology, Vejle Hospital, Denmark.
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an orchidectomy performed and were subsequently registered and followed by the Danish Testicular Carcinoma Study Group. The time period between orchidectomy and registration at the oncological department was within 3 weeks. All patients were staged with physical examination, chest X-ray, lymphangiography and/or abdominal computer tomography (CT) scan, and full blood chemistries as described previously [3]. 267 patients had stage I disease. 6 of these were unable, for various reasons, to follow a close surveillance programme and were, therefore, treated initially with prophylactic irradiation to paraaortic and ipsilateral iliac lymph nodes in accordance with our previous strategy [1]. The remaining 261 patients were followed closely after orchidectomy with no further treatment unless a relapse occurred. They form the study cohort of the present study.

The surveillance programme consisted of physical examination, blood samples and chest X-ray every 2 months for the first year, every 4 months for the second year, and then every 6 months for up to 5 years after orchidectomy. Follow-up radiographs after lymphangiography and/or CT scans were performed every 4 months for the first 2 years, and then every 6 months for the next 3 years. Informed consent to participate in the surveillance programme was obtained from all patients.

Standard relapse treatment was radiotherapy. The radiation treatment was given in accordance with our previously published strategy for seminoma stage II [1], with the exception that prophylactic supradiaphragmatic irradiation was abandoned. The infradiaphragmatic radiation field encompassed paraaortic, ipsilateral common iliac, ipsilateral external iliac and contralateral common iliac lymph nodes. Patients with an abdominal mass with a diameter larger than 5 cm, patients with supradiaphragmatic lymph node involvement, and patients with extranodal disease received chemotherapy. This treatment consisted of four courses of cisplatin, vinblastine and bleomycin (PVB) according to the method of Einhorn and Donohue [4] or four courses of cisplatin, etoposide and bleomycin (PEB) according to the method of Peckham *et al.* [5].

All orchidectomy specimens were reviewed for the present study by one pathologist without prior knowledge of the clinical outcome. With the aim of defining prognostic factors for an increased risk of relapse, the following clinical and histopathological features were examined: age at diagnosis (number of years), tumour size measured as the largest tumour diameter, histological subtype (i.e. classic, anaplastic defined as five or more mitoses per high power field in 10 fields, or spermatocytic), presence of syncytiotrophoblastic giant cells, necrosis, granulomatous reaction, lymphocytic infiltration, vascular invasion, invasion of the rete testis and funicle, and of carcinoma *in situ* in the surrounding tissue. A detailed description of the histopathological findings is published separately [6].

Survival curves from the time of orchidectomy were calculated according to the method of Kaplan and Meier [7], and comparisons in univariate analyses were performed by the log rank test (for trend if appropriate) [8]. In order to determine the independent contribution of each factor to prognosis, multivariate analyses were undertaken using the method developed by Cox [9]. In the multivariate analyses, the factors analysed were scored according to their natural order. The 4 patients with spermatocytic seminoma did not relapse. As pure spermatocytic seminoma is known not to metastasise, these patients were excluded from the multivariate analyses.

RESULTS

The median follow-up time after orchidectomy for the 261 patients was 48 months, range 6–67 months. 49 patients (19%) had a relapse. Relapse localisations are given in Table 1. The median time to relapse was 14 months, range 2–37 months. Figure 1 shows the relapse-free survival for all patients. The 4-year relapse-free survival was 80%.

Table 1. Sites of relapse in 49 patients treated with orchidectomy alone for seminoma stage I

Site	No. of patients
Paraaortic lymph nodes	41
Pelvic lymph nodes	5
Inguinal lymph nodes	2
Lungs	1

Patients' characteristics in terms of selected clinical and histopathological features are summarised in Table 2. Among the factors analysed for influence on relapse-free survival, tumour size, histological subtype, necrosis and invasion of the rete testis had a statistically significant impact in univariate analysis (Table 3). However, in multivariate analysis the tumour size turned out to be the only factor with independent prognostic significance for relapse-free survival. Histological subtype, necrosis and invasion of the rete testis were all correlated with the tumour size and without independent prognostic significance. None of the other factors analysed acquired significance in multivariate analysis [6]. Relapse-free survival according to tumour size is shown in Fig. 2. The cumulative risk of relapse after 4 years was 6% in patients with tumours less than 3 cm in largest diameter, 18% in patients with tumours from 3 to < 6 cm in largest diameter, and 36% in patients with tumours 6 cm or larger. Figure 3 shows relapse-free survival according to histological subtype. The cumulative risk of relapse after 4 years was 16% in patients with classic seminoma, and 35% in patients with anaplastic seminoma. However, as mentioned above, histological subtype was correlated with tumour size and did not possess independent prognostic significance. It was not possible to correlate any of the parameters with the type of recurrence, i.e. localisation or size.

37 of the relapsing patients (76%) had radiotherapy as relapse treatment. 4 of these patients (11%) had a second relapse. Characteristics such as size of primary tumour and size or location of lymph node metastasis were not different for these 4 patients compared with those of the 33 patients who did not experience a second relapse. The interval between the first and second relapse was 11, 17, 8 and 10 months, respectively. Relapse localisations were mediastinal lymph nodes and lymph

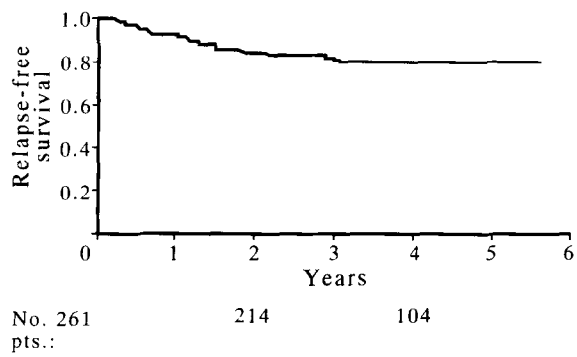

Fig. 1. Relapse-free survival of 261 patients with seminoma stage I treated with orchidectomy alone.

Table 2. Selected clinical and histopathological features of 261 patients with seminoma stage I treated with orchidectomy alone

	No. of patients	No. of patients with relapse
Age (years)		
≤ 29	46	4 (9%)
30–39	108	19 (18%)
40–49	59	16 (27%)
50–59	31	8 (26%)
≥ 60	17	2 (12%)
Tumour size (cm)		
0–0.9	2	0 (0%)
1–1.9	32	1 (3%)
2–2.9	34	3 (9%)
3–3.9	45	7 (16%)
4–4.9	45	9 (20%)
5–5.9	34	6 (18%)
6–6.9	30	10 (33%)
7–7.9	19	5 (26%)
8–8.9	8	4 (50%)
≥ 9	10	4 (40%)
Unknown	2	
Histological subtype		
Classic	205	32 (16%)
Anaplastic	52	17 (33%)
Spermatocytic	4	0 (0%)
Necrosis		
None	119	16 (14%)
Slight	82	16 (20%)
Moderate	29	8 (28%)
Extensive	31	9 (29%)
Invasion of rete testis		
Absent	146	20 (14%)
Present	98	23 (23%)
Unknown	17	

nodes of the neck, mediastinal lymph nodes and pleura, mediastinal and supraclavicular lymph nodes, and supraclavicular lymph nodes, respectively. These patients received chemotherapy. 3 patients had a complete response and were alive with no evidence of disease at 38, 29 and 18 months, respectively, after chemotherapy. 1 patient died of disseminated seminoma.

Of the relapsing patients, 12 (24%) had chemotherapy as relapse treatment because of bulky (11 patients) or disseminated disease (1 patient). None of these patients had a second relapse.

Table 3. Relapse-free survival in 261 patients with seminoma stage I treated with orchidectomy alone. Univariate effect of selected prognostic factors

Prognostic factor	*P* (log rank)
Age	0.12
Tumour size	< 0.0001
Histological subtype	0.01
Necrosis	0.01
Invasion of rete testis	0.04

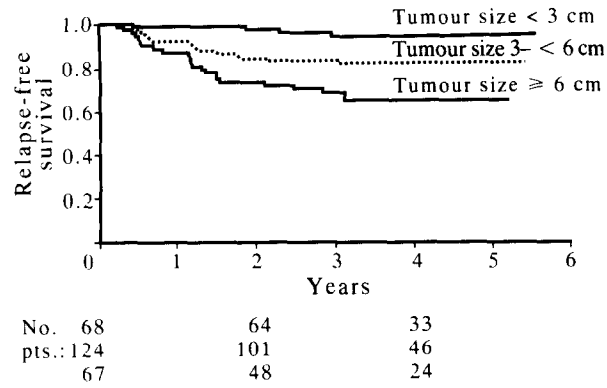

Fig. 2. Relapse-free survival according to tumour size in 259 patients with seminoma stage I treated with orchidectomy alone.

However, 2 patients died of infection due to chemotherapy-induced neutropenia.

Six deaths have occurred so far in this cohort of patients (2.3%). Three of these deaths (1.1%) were seminoma-related as mentioned above (one due to progressive disease, two due to complications of treatment). The three remaining deaths were from other causes. 1 patient died of gastric cancer 4.5 years after orchidectomy. This patient had never had a seminoma relapse and had, thus, not received radiotherapy. 1 patient died from heart failure and 1 committed suicide.

DISCUSSION

Our study shows that the incidence of subclinical disease in patients classified as seminoma stage I is about 20%. This data is in accordance with that reported by the Royal Marsden Hospital (U.K.) [10] whereas the relapse frequency was somewhat lower (6%) in the study from the Princess Margaret Hospital [11, 12]. There are no obvious explanations for this apparent difference as the staging investigations seem to be similar in these studies.

The time to relapse in these seminoma patients was, as expected, longer than in patients with non-seminoma stage I followed by surveillance only. Thus, the median time to relapse in our non-seminoma patients was 4 months (range 2–62 months), and about 95% of the relapses occurred within 2 years [13]. In contrast, the median time to relapse in the present study was 14 months (range 2–37 months). We expect a few more recurrences after a longer follow-up period but about 95% of the relapses seem to occur within 3 years after the orchidectomy. This means that the follow-up programme including regular CT or ultrasound scans has to be maintained for about 3 years if a

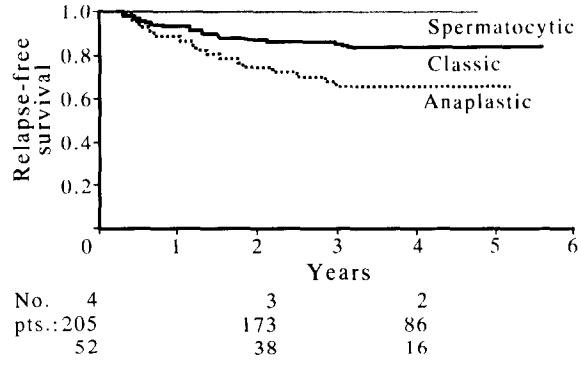

Fig. 3. Relapse-free survival according to histological subtype in 261 patients with seminoma stage I treated with orchidectomy alone.

surveillance only strategy for seminoma stage I patients is to be applied.

The survival data are equivalent to those based on prophylactic radiation treatment following orchidectomy [1, 2], which, of course, is mandatory if a surveillance only strategy is to be pursued. The problem in our study was, therefore, not the final survival data but the high proportion of relapsing patients in whom it was necessary to institute chemotherapy. Optimally, all recurrences should be diagnosed as small volume retroperitoneal lymph node metastases, in which case it is possible to cure nearly all of the patients by the use of a standard radiation treatment. In such an optimal situation, about 80% of the patients would avoid radiotherapy and the remaining 20% would be cured by radiation treatment similar to the one they would have received anyway as prophylactic treatment. However, a total of 16 patients received chemotherapy, i.e. 33% of relapsing patients or, which is probably more important, 6% of the whole study population. 12 patients received chemotherapy initially at relapse, whereas 4 patients received chemotherapy due to a second relapse after radiation treatment. Some of the first cases might have been avoided by better patient education. About half of these patients did not follow the regular surveillance programme, and relapse was consequently diagnosed at a stage where bulky disease rendered the use of chemotherapy necessary.

Another concern has been that the delay of radiation treatment for occult retroperitoneal lymph node metastases may result in further dissemination either to supradiaphragmatic lymph nodes or to extranodal areas. We observed a total of 5 cases with such further dissemination. However, the frequency of recurrences outside the infradiaphragmatic lymph node areas was similar in the present surveillance group and in our previous group of seminoma stage I patients receiving prophylactic radiation treatment [1], the frequency being 1.9% (5 out of 261 patients) and 1.7% (7 out of 424 patients), respectively. So whether a surveillance only strategy or prophylactic radiation treatment is applied, the risk of dissemination outside the infradiaphragmatic lymph node areas is probably about the same. The most important factor is to diagnose the infradiaphragmatic lymph node recurrences as small volume metastases by use of close surveillance and to make sure that the patients comply with the follow-up programme.

We found that the size of the testicular tumour had a significant impact on relapse-free survival. The group of patients with a tumour of 6 cm or larger had a relapse frequency of 34%. These patients represented about 25% of the study population (Table 2). The remaining 75% of the patients with smaller tumours had a relapse frequency of 14% (Table 2). Based on these data, we have decided that patients with a testicular tumour of 6 cm or larger should be offered prophylactic radiation treatment whereas we will continue the surveillance only strategy in patients with tumours less than 6 cm. If the size of the testicular tumour is not available, the treatment strategy may possibly be based on the histopathological parameters which were found to be associated with the tumour size, especially the histological subtype [6].

If one wishes to use prophylactic radiation treatment instead of surveillance only either to all patients with seminoma stage I or, as we have decided, to patients with large testicular tumours, the radiation treatment should be given on a standard infradiaphragmatic radiation field encompassing paraaortic, ipsilateral common iliac, ipsilateral external iliac and contralateral common iliac lymph nodes [1]. It is not sufficient to use only a radiation field encompassing paraaortic lymph nodes as 7 out of 49 recurrences (14%) were located within the pelvic area of a standard radiation field (Table 1).

In conclusion, we consider surveillance only after orchidectomy for seminoma stage I patients to be a safe strategy if a close follow-up programme including regular examinations of the abdominal lymph node areas (CT or UL scans) up to 3 years after orchidectomy is accomplished and accepted by the patients. This is of course mandatory. Patients who for various reasons cannot comply with such a follow-up programme, should receive prophylactic radiotherapy. We have decided to continue the surveillance only strategy with the exception that patients with a testicular tumour of 6 cm or more in the largest diameter will be offered prophylactic radiation treatment.

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