Journal of Radiotherapy & Medical Oncology

ORIGINAL REPORT

Long Term Results and Risk Factors in Stage I Seminoma Treated at the Institute of Oncology "Prof. Dr. Ion Chiricuta"

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Purpose: Retrospective study to assess treatment results and risk factors for relapse in stage I seminoma patients treated at the Institute of Oncology „Prof Dr Ion Chiricuta". **Material and methods**: This study evaluated 112 patients aged between 18 and 78 years (medium age-37.4 years) stage I testicular seminoma between January 1982-January 2007, treated at Ion Chiricuta Cancer Center, Cluj-Napoca. The medium follow-up period was 135.8 months (range minimum 3 months-maximum 233 months). Demographic, clinical and paraclinical parameters of patients were observed. Chemotherapy regimen administered in adjuvant setting was 1 cycle Carboplatin AUC 7 or 2 cycles Carboplatin AUC 6 for 31 (27.68%) patients for stage I seminoma, 44 (39.29%) patients were treated with adjuvant radiotherapy and 37 (33.04) were managed by surveillance. **Results**: Overall survival at 10 years was 92%(CI: 85%-96%). Eighty seven seminoma patients (77.68%) have not presented relapse; metastatic relapse was observed in5 patients (4.46%), pelvic or lomboaortic lymph nodes was present in17 patients (15.18%), metastatic and adenopatic relapse in 2 patients (1.79%) and seric relapse int 1 patient(0.89%). Risk factors evaluated for relapse were age ($p=0.1$), performance status($p<0.1$), stage of disease at presentation($p<0.1$) and positivity of tumor markers($p=0.1$). Chemotherapy toxicity was moderate, main toxicity for Carboplatin was thrombocytopenia (6.67%), anemia(3,7%), leucopenia (3.33%), and nausea and vomiting (3.33%). **Conclusion**: In our retrospective study, stage I seminoma tumor prognosis has been excellent. The rate of curability for adjuvant treatment was high, the overall survival at 10 years with adjuvant chemotherapy was 96% and with adjuvant radiotherapy 93%.

Key words: stage I seminoma, risk factors, long term survival.

Introduction

Testicular germ cell tumor (TGCT) is the most common cancer in men between the ages of 15 and 35 years, representing 1%-1.5% of male neoplasms and 5% of urologic tumors in general (1). The two major histological subgroups are seminoma (40%-50%) and nonseminoma. Histological diagnosis of a TGCT is made by radical orhiectomy or by testis- conserving surgery. The tumor markers α fetoprotein (AFP) , human chorionic gonadotropin (HCG) and lactate dehydrogenase (LDH) are assessed before and after orhiectomy. The staging and risk grouping should be performed according to the AJC/UICC and the International Germ Cell Cancer Collaborative Group (IGCCCG) reflecting the extent of the disease based on clinical and imagistic examinations and levels of serum tumor markers after orhiectomy (2). For stage I seminoma the standard treatment options after orhiectomy are surveillance, radiotherapy or chemotherapy with 1-2 cycles of Carboplatin, priority being a minimal treatment related toxicity. The risk adapted approach (considering the presence of the controversial 'risk factors' rete testis infiltration and tumour size ≥4 cm) is used to undergo either one course of Carboplatin (AUC 7) or radiotherapy (20 Gy/10fractions to para-aortic target volume) as adjuvant treatment. Compared to radiotherapy, one course of Carboplatin results in similar relapse rates, but less adverse effects (3). Two courses of Carboplatin have also been reported to reduce the relapse rate (4). In either case stage I seminoma has a very high curable rate (around 99%). The relapse rate is around 15-20% at 5 years and is usually first detected in the retroperitonealor iliac lymph nodes.

Patients and methods

Between January 1982 and January 2007, one hundred and twelve stage I pure seminoma patients were analyzed retrospectively in our center diagnosed after orchiectomy. For inclusion in the final analysis, patients had to fulfill the following inclusion criteria: male sex, minimum age of 14 years, confirmed GCT either by histology and/or serum tumor markers, and sufficient follow-up 135.8months (range 3 to 233.5 months), information to allow the calculation of long-term survival.

Journal of Radiotherapy & Medical Oncology
December 2013 Vol. 19 No 2: 28-32
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To be classified as pure seminoma, patients had to have histologically pure seminoma at initial diagnosis without any other germ-cell compounds and without elevations of serum alpha fetoprotein (AFP). All other patients were classified as with non-seminomatous tumors and were not included in the trial.

Median patient age was 37.4 years (range, 19 and 78 years). All of the patients underwent an inguinal orchiectomy.

Routine staging procedures consisted of physical examination, chest X-rays, computed tomography, ultrasonography of contralateral testis, serum markers, including lactate dehydrogenase (LDH), alpha-fetoprotein (AFP), beta-human chorionic gonadotrophin (BHCG), whole blood counts and chemistry.

Thirty one male patients received one postoperative adjuvant courses of Carboplatin AUC 7 (area under curve 7) or two cycles of Carboplatin AUC6 (area under curve 6). All patients gave written informed consent for chemotherapy in the present indication. There was no delay of treatment because of toxicity. The serum creatinine values of all 112 patients were in the normal range (0.5 to 1.3 mg/dL) before chemotherapy. Prophylactic antiemetic therapy was administered. On day 1 of each course, an interval history, whole blood count, serum chemistry, and serum tumor markers LDH, AFP and bHCG were measured.

Regarding radiotherapy, the RT dose was assignment between 30 Gy in 15 fractions and 20 Gy in 10 fractions by physician choice.

Approximately one third of patients decided not to receive adjuvant treatment either due to acute toxicity of chemotherapy or late toxicity of radiotherapy and elected active surveillance.

Results

Of 112 patients clinical stage I seminoma, 31 (27.68%) patients received chemotherapy regimen administered as 1 cycle Carboplatin AUC 7 or 2 cycles Carboplatin AUC 6, 44 (39.29%) patients were treated with adjuvant radiotherapy and 37 (33.04) were managed by surveillance.

Main patient characteristics, distribution of risk factors and treatment groups are depictedin Table I.

At the time of this analysis, median follow-up time was 135.8 months (range 3 to 233.5 months), and 101 patients (10%) have been followed for more than 10 years.

As of September 2013, 101 patients are still alive and free of disease, and 11 had died.

The overall survival at 10 years is 92% (CI: 85%-96%) (Fig. 1).

The 10 years disease-free survival is 76% (CI: 67%-83%) (Fig. 2).

The rate of curability is high; the overall survival at 10 years with adjuvant chemotherapy is 96%, followed by adjuvant radiotherapy 93%. Overall survival for patients treated with orchiectomy followed by active surveillance is only 41% (Fig. 3).

Table I. Patient characteristics

Patients characteristics		n=112	%
Age	Min	19	
	Max	78	
	Median	36	
	Average	37.44	
Stage AJCC	IA	51	45.54%
	IB	51	45.54%
	IS	10	8.93%
Risk	Low	111	0.89%
	Medium	1	99.11%
Performance status	0	64	57.14%
	1	45	40.18%
	2	3	2.88%
Adjuvant treatment	CH	37	33.04%
	CH+CT	31	27.68%
	CH+RT	44	39.29%

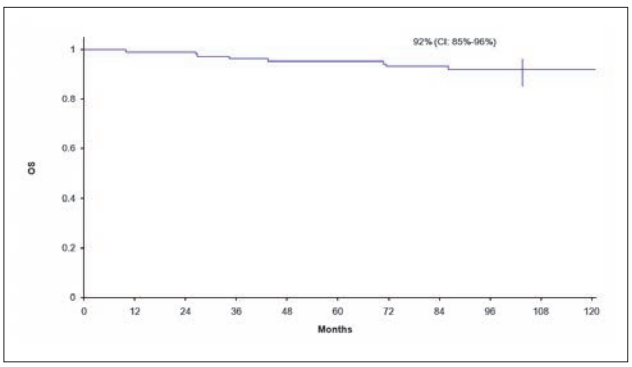

Fig. 1. Overall Survival

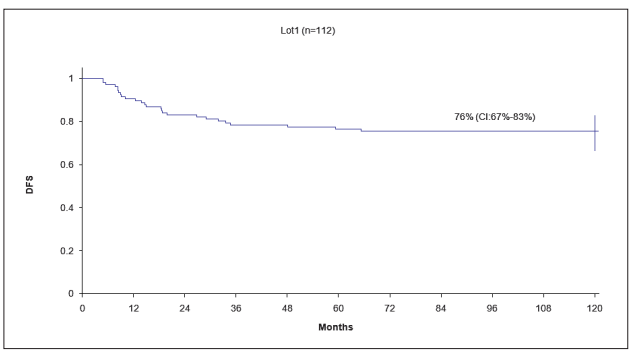

Fig. 2. DFS

Regarding relapse rate, eighty seven seminoma patients (77.68%) did not present relapse, metastatic relapse was observed at 5 patients (4.46%), pelvic or lumboaortic lymph nodes was present at 17 patients (15.18%), metastatic and adenopathy relapse in 2 patients (1.79%) and seric relapse in1 patient(0.89%).

Figure 4 shows a flowchart of the relapse rate vs site.

Relapse rate according to treatment was observed in 1 (3%) patient treated with adjuvant Carboplatin, 3 (7%) patients with adjuvant radiotherapy presented relapse and 21 (57%) patients managed with surveillance presented relapse (Fig. 5).

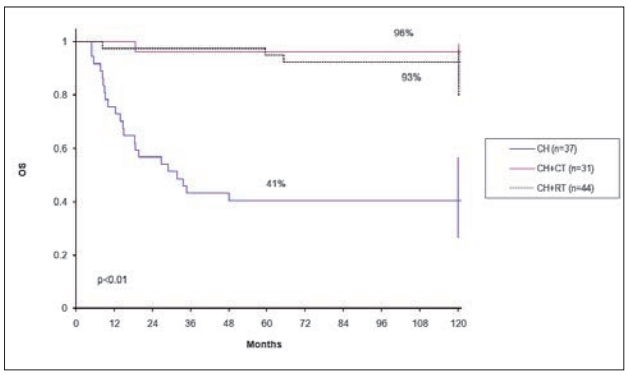

Fig. 3. OS vs treatment.

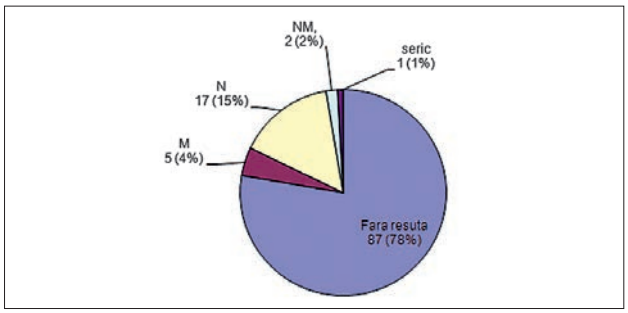

Fig. 4. Relapse rate vs site of relapse.

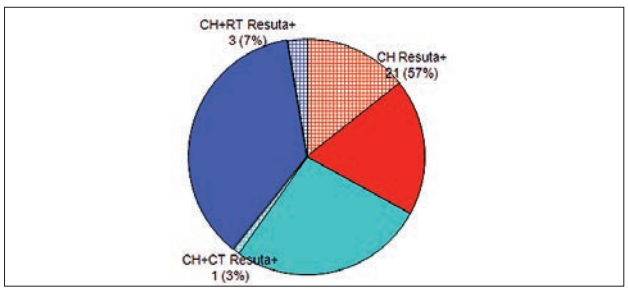

Fig. 5. Relapse rate vs treatment

Carboplatin AUC 7 (area under curve 7) or AUC6 (area under curve 6) given in adjuvant setting for stage I seminoma showed mild toxicity. The most `aggressive` side effect was thrombocytopenia, (6.67%), followed by anemia(3.7%), leucopenia (3.33%), and nausea and vomiting (3.33%).

Risk factors evaluated for relapse were age at presentation (p=0.1), performance status (p<0.1), stage of disease at presentation(p<0,1) and presence of markers(p=0,1).

a) Age

For survival, age was not found as an independent factor (p=0.1), in patients aged between 19 years and 40 years and for those over the age of 40, respectively.

b) Performance status

Survival at 10 years according to performance status ECOG was as an independent factor (p<0.01), with 88% 10-year overall survival in patients with performance status 0 and with 59% in patients with performance status 1 or 2.

c) Stage

Stage at initial diagnosis was another valid prognostic factor for survival (p<0.01) with 90% for stage IA at 10 years, 71 % for stage IS and 62% for stage IB.

d) Serum markers levels

Survival according to serum markers at initial diagnosis has not revealed a significant difference (p=0.1) between negative markers patients (80% OS at 10 years) versus 66% in positive markers as we expected.

Discussion

Stage I seminoma has a cure rate greater than 95%. Almost no one dies as a result of stage I seminoma. Treatment-related toxicity represents a major concern. There are three treatment options for clinical stage I seminoma: radical orchidectomy followed either by surveillance, adjuvant radiotherapy or a single-dose of Carboplatin AUC 7 (2, 3).

Concern regarding the late effects of the treatment is the basis from changing from adjuvant therapy to surveillance: in a report including patients with seminoma treated with radiotherapy (all stages), the overall relative risk of second non-testiculary cancer was 2.0 (95%CI 1.8, 2.2) (5).

Adjuvant chemotherapy with Carboplatin has been investigated as an alternative to radiotherapy and surveillance. The MRC TE19 and EORTC trial compared one cycle of Carboplatin AUC 7 with adjuvant radiotherapy in 1447 patients, and the trial confirmed the non-inferiority of single dose Carboplatin versus radiotherapy and there was a significant difference in the rate of new germinal tumors (2 on Carboplatin versus 15 on radiotherapy) (p=0.03) (6).

The patients who received at least 99% of carboplatin AUC 7 had a 5-year PFS of 96.1% compared with those who received lower doses with a 5-year PFS 0f 92.6% (p=0.08) (6).

In a very recent study performed on 1,384 patients with stage I and stage IIA/B , treatment in stage I consisted of surveillance, adjuvant radiotherapy or adjuvant carboplatin, with radiotherapy replaced gradually by carboplatin, and finally abandoned as an adjuvant treatment in Scandinavia. With a median follow-up of 5 years, the latest relapsed occurred at 7 years, which emphasizes the need of 10-years follow-up, but with excellent survival and cause-specific survival of 99.6% (7).

The management of this condition should be a matter of informed choice, because the anticipated relapse rate in patients managed expectantly is in the range of 15% to 20% (8, 9).

We retrospectively analyzed 112stage I seminoma patients, and 31 (27.68%) patients were treated with chemotherapy administered as 1 cycle Carboplatin AUC 7 or 2 cycles Carboplatin AUC 6, 44 (39.29%) patients were treated with adjuvant radiotherapy and 37 (33.04) were managed by surveillance, respectively.

At the time of this analysis, the median follow-up was 135.8 months (range 3 to 233.5 months), and 101 patients (10%) have been observed for more than 10 years. As of

September 2013, 101 patients are still alive and free of disease, and 11 are died.

The overall survival at 10 years is 92% (CI: 85%-96%) and the 10 years disease-free survival is 76% (CI: 67%-83%).

In our series, the overall survival at 10 years with adjuvant chemotherapy is 96%, followed by adjuvant radiotherapy 93%. Overall survival for patients treated with orchidectomy followed by active surveillance was only 41%.

Adjuvant chemotherapy with carboplatin was associated with minimal short-term toxicity (10).

Patients treated with carboplatin AUC 7 or AUC6 showed mild toxicity. The most `aggressive` side effect was thrombocytopenia (6.67%), followed by anemia(3.7%), leucopenia (3.33%), and nausea and vomiting (3.33%).

In the study of Oliver, an unexpected advantage of carboplatin was reported, in term of reduction in the risk of contralateral cancer and this has been maintained with extended follow-up, as all additional contralateral tumors reported subsequently were in patients receiving radiotherapy (3).

Accurate pathology, staging, and risk assignment are essential to avoid over- or undertreatment. Most experts recommend that pathologic material be carefully reviewed by experts in genitourinary pathology (11-13).

For seminomas, clinical risk factors for recurrence are incompletely confirmed. The previously described factors (e.g. tumor size more than 4 cm and rete testis involvement conferring a high risk of recurrence has not been validated (8, 14). It is difficult to reliably define a group of patients with seminoma who have a risk of recurrence much higher than 15% to 20%, and patients with multiple putative high-risk features are uncommon (15).

Overall, adjuvant radiotherapy reduces recurrence by two thirds from 15% to 5%, but clinical prognostic factors have not been able to define a high-risk group that may be more suitable for preventive therapies. Disadvantages include extreme overtreatment and impacted survivorship (15).

A single dose of Carboplatin AUC 7 as an adjuvant treatment seems to result in a reduction of recurrence risk similar to adjuvant radiotherapy, from 15% with active surveillance to 5% with adjuvant treatment (3).

In patients with seminoma with multiple putative high-risk features, some experienced investigators recommend two cycles of Carboplatin (16).

In the third Spanish study, investigators restricted carboplatin only to subjects with both risk criteria, in order to minimize potential overtreatment, and relapse rates observed seemed reasonable in all groups (9.8% on surveillance and 1.4% after carboplatin). Authors concluded that probably the 20% rate of recurrences among patients with rete testis involvement may require further studies with larger numbers (17).

In our series, eighty seven patients (77.68%) had no relapse, metastatic relapse was observed in 5 patients (4.46%), pelvic or lomboaortic lymph nodes relapse was present in17 patients (15.18%), metastatic and adenopathiescombined relapse in two patients (1.79%) and seric relapse in one (0.89%).

Relapse rate according to treatment was observed in one patient (3%) treated with adjuvant Carboplatin, 3 patients (7%) with adjuvant radiotherapy and 21 (57%) patients managed with surveillance, respectively.

Risk factors evaluated for relapse were age at presentation ($p=0.1$), performance status($p<0.1$), stage ($p<0.1$) and positivity of tumor markers($p=0.1$).

For survival, age was not found as an independent factor ($p=0.1$), in patients aged between 19 years and 40 years and for those over the age of 40, respectively.

Survival at 10 years according to performance status ECOG was an independent factor ($p<0.01$), with 88% 10-year overall survival in patients with performance status 0 and with 59% in patients with performance status 1 or 2.

In our analysis, stage at initial diagnosis was another valid prognostic factor for survival ($p<0.01$) with 90% for stage IA at 10 years, 71 % for stage IS and 62% for stage IB.

Survival according to serum markers at initial diagnosis has not revealed a significantdifference ($p=0.1$) between negative markers patients (80% OS at 10 years) versus 66% in positive markers as we expected.

Conclusions

In our series, stage I seminoma prognostic is excellent. The rate of curability for adjuvant treatment is high, the overall survival at 10 years with adjuvant chemotherapy is 96% and with adjuvant radiotherapy 93%, so management decisions should therefore rest on the likely morbidity and convenience of different treatment choices.

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Author`s disclosures of potential conflicts of interest. The authors indicated no potential conflicts of interest.
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Final approval of manuscript: All authors

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