

## Controversies in the management of clinical stage I testicular seminoma

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**Introduction** Following orchiectomy patients with clinical stage I (CSI) testicular seminoma may be managed by active surveillance (AS) or adjuvant treatment (radiotherapy or chemotherapy). In view of the published data on long-term toxicity, mainly second malignant neoplasms (SMNs), adjuvant radiotherapy (ART) is currently no longer recommended as adjuvant therapy for these patients. The purpose of our recent study was to compare the impact of two selected treatment approaches – AS *versus* adjuvant chemotherapy (ACT) on survival in patients with CSI testicular seminoma.

**Material and methods** The cross-sectional study analyzed a total of 106 patients collected at a single centre between 4/2008–8/2015, with CSI testicular seminoma, stratified into two groups according to risk-adapted therapeutic approaches.

**Results** In group A (low-risk), consisting of 84 patients, who underwent AS, relapse occurred in 10 (11.9%) patients after a mean follow-up of 13.8 months. In group B (high-risk), consisting of 22 patients, who were treated with ACT, relapse occurred in two (9.1%) patients after a mean follow-up of 13.8 months. Overall survival of patients in both groups was 100% with a mean follow-up of 25.3 months. The statistically significant difference in progression-free survival (PFS) between these two groups was not found.

**Conclusions** ACT seems to be adequate treatment for patients with high-risk of relapse, as well as AS for those with low-risk of relapse. Despite its excellent prognosis, optimal management of CSI testicular seminoma remains controversial, with variations in expert opinion and international guidelines.

**Key Words:** testicular cancer <> seminoma <> surveillance <> chemotherapy <> relapse rate

## INTRODUCTION

Although testicular cancer (TC) is a rare disease, accounting for 1–2% of all malignancies in males, in many western countries the incidence has been increasing since the middle of the 20<sup>th</sup> century [1]. The worldwide geographical variation in age-standardized rate (World) (ASR-W) of incidence is considerable. The highest estimates of ASR-W

incidence of TC for the year 2012 are in Norway (12.2/100,000), Switzerland (12.1/100,000) and Denmark (11.9/100,000), and mainly in other regions of northern and western Europe. The Slovak Republic, with its high ASR-W estimated incidence placed 8<sup>th</sup> worldwide (9.3/100,000). The lowest ASR-W incidence (<0.5/100,000) was estimated to be in various African and Asian countries [1]. Approximately 80% of the patients with testicular seminomas

present with clinical stage I (CSI) [2]. National data from the Slovak Republic indicates that 76.9% of recorded seminomas were CSI [3].

Active surveillance (AS) is an option for CSI TC patients, but Oldenburg et al. [4] are not convinced that the majority of CSI TC patients should be encouraged to undergo AS as primary management, as was recently proposed by Nichols et al. [5]. Each patient should be informed of the potential advantages of adjuvant chemotherapy (ACT) before obtaining informed consent for either AS or ACT as personalized management.

Approximately 16% of patients with seminoma relapse during AS [6]. The enthusiasm for adjuvant radiotherapy (ART) has been tempered by the risk of radiation-induced second malignant neoplasms (SMNs) and consequently most European guidelines have removed this treatment option [2, 7]. Tumor size >4 cm and rete testis invasion have been identified as factors predicting relapse, but subsequent reports have questioned its validity [6, 8]. A recently published trial by the Spanish Germ Cell Cancer Group [9] evaluated a risk-adapted management approach and showed that absence of both risk factors predicted a very low risk of relapse.

A single cycle of ACT with carboplatin (AUC7) has been established as effective ACT when compared to ART in the largest TC phase III trial ever reported. Relapse rates were similar, but carboplatin resulted in fewer adverse effects, less sick leave, and a significant reduction in contralateral TC [10, 11]. Relapse rates after ACT in unselected populations are 5–6%, translating into a 60–70% relapse-reduction [6], which is acceptable to many patients given the low risk of complications. Therefore, ACT with carboplatin, using a dosage of one cycle AUC7, is a safe alternative to AS in CSI testicular seminoma [9].

Concerning the facts mentioned above, we decided to design a single-centre cross-sectional study to confirm the efficacy of risk-adapted therapeutic approaches (AS and ACT) for patients with CSI testicular seminoma.

## MATERIAL AND METHODS

The cross-sectional study analyzed the medical records and results of defined laboratory tests of 106 patients following orchiectomy, who were registered at a single medical center between 4/2008 and 8/2015, and who had histologically confirmed pure seminoma, CSI disease.

Routine staging procedures consisted of clinical history, physical examination, whole blood cell counts, serum chemistries including determination of tumor markers: lactate dehydrogenase (LDH),

$\alpha$ -fetoprotein (AFP) and  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG).

In order to assess the size of the retroperitoneal lymph nodes on computed tomography (CT), the cut-off value was considered to be a diameter of 10 mm in the shorter-axis of the (metastatic) lymph node. Increased values of  $\beta$ -hCG were acceptable preoperatively. However, the persistence of increased postoperative  $\beta$ -hCG levels or any pre- or postoperative elevation of AFP was considered as an exclusion criterium.

CSI was defined as a tumor confined to the testis without evidence of metastasis (normal findings on the chest, abdomen and pelvis) on radiological imaging at the time of diagnosis. Tumor markers were normal or normalized after radical orchiectomy.

These patients were stratified according to the selected risk factors for relapse with risk-adapted therapeutic approaches to: AS (group A) and ACT (group B). Informed consent was obtained from all patients from the defined study cohort (according to the inclusion criteria mentioned above).

All performed diagnostic and therapeutical approaches followed actual guideline recommendations for patients with TC [12, 13] were consecutively recorded and evaluated.

Group A consisted of 84 patients, with no rete testis invasion and with tumor size <4 cm at pT1 stage, who were managed with AS, consisting of regular life-long follow-up after orchiectomy. Tumor markers (LDH, AFP,  $\beta$ -hCG) were scheduled at months 3, 6, 9, 18, 24, 30, 36, and annually thereafter. Abdominopelvic CT scans were performed at months 6, 12, 18, 24, 30, 36, and 48, and annually thereafter. Chest x-ray examinations were not performed. Patients who relapsed during follow-up were treated with platinum-based combination chemotherapy – BEP regimen (bleomycin 30 U IV on days 1, 8, and 15 plus etoposide 100 mg/m<sup>2</sup> IV on days 1–5 plus cisplatin 20 mg/m<sup>2</sup> IV on days 1–5; every 21 days). According to the ESMO guidelines [2], patients with a complete response did not require further treatment and were followed-up. Patients with residual tumour on the CT scan underwent a [18F] fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) examination a minimum of 6 weeks after chemotherapy termination.

Group B consisted of 22 patients, sharing the same risk factors mentioned above or pT >2, who received one course of single-agent ACT – carboplatin (7AUC).

## Statistical analysis

The age-specific characteristics of all patients were analyzed using descriptive statistics. Data analysis was carried out in an R project setting. Normality

of the distribution of the age-specific data at the time of diagnosis in each study group was tested using the Kolmogorov-Smirnov test. Continuous variables were compared by independent sample t-tests. Statistical significance of differences was tested according to the variables in the Kruskal-Wallis, Fisher exact and Wilcoxon tests. All statistical tests were two-sided and statistical significance was set at  $p < 0.05$ .

## RESULTS

A total of 106 patients with CSI seminoma were distributed into two groups and treated with risk-adapted management approaches. Of these, 80 patients (75.5%) were followed-up at a minimum of one year after orchiectomy.

Group A consisted of 84 patients with mean age at time of diagnosis 36.6 years (median 35.9 years, range 21.0 to 63.6 years) of which, 10 (11.9%) patients experienced relapse. Mean time to relapse was 13.8 months (median 11.8 months, range, 3.6–30.7 months); however, in 5 (50%) patients the relapse occurred within 12 months. All relapses were located in the retroperitoneal lymph nodes and were subsequently successfully treated with 3xBEP chemotherapy.

Group B consisted of 22 patients with mean age at time of diagnosis 39.1 years (median 37.4 years, range 25.7 to 67.7 years). Two (9.1%) patients relapsed at 13.1 and 14.5 months respectively. Both relapsed patients had diagnosed locoregional nodal relapse and were successfully treated with 3xBEP chemotherapy. Complete response was confirmed using post-chemotherapy PET/CT scanning.

There was no statistically significant difference in the age-distribution of patients (at the time of their diag-

nosis) when comparing groups A and B. Considering these facts, we tested the differences in progression-free survival (PFS); however, we did not find any statistically significant difference in PFS when comparing these two study groups (Table 1). On the other hand, the two cases (out of 22) of relapse registered in Group B might be related to the small numbers of subjects in this cross-sectional study. The overall survival rate of all CSI testicular seminoma patients in both groups reached 100% (up to August 31, 2015) with mean follow-up of 25.3 months (median, 25 months, range, 2.5–89.0 months) following orchiectomy.

## DISCUSSION

For several decades, ART to the paraaortic/retroperitoneal  $\pm$  ipsilateral pelvic lymph nodes (dog-leg port) was considered to be standard therapy for patients with CSI seminoma, leading to recurrence rates of less than 5–10%. Patients, who relapse after ART, are almost always cured with BEP chemotherapy. Thus, disease-specific survival for patients managed initially with ART is near 100% [14].

Management of CSI testicular seminoma has changed in recent years due to the results of long-term follow-up studies, which confirmed its association with increased risk of cardiovascular toxicity and SMNs. Randomized trials have shown that it has been possible to reduce the radiation field and the applied total dose, thus reducing the risk of radiation-induced SMNs [15].

Nevertheless, for patients with CSI testicular seminoma, the option of ART has been removed from European guidelines on TC due to long-term toxicity, represented by the risk of radiation-induced SMNs [7, 13].

Although ART had been the standard approach for the last 50–60 years, it has now been accepted that AS provides the optimal outcome. ACT using carboplatin has been investigated as an alternative strategy to ART or AS in these patients [16].

The optimal treatment strategy for CSI testicular seminoma is highly controversial and generates debate at every consensus meeting on TC [7, 12]. There are no randomized trials to show the superiority of AS or adjuvant treatment.

Several large prospective nonrandomized studies of AS have been conducted over the past 20 years, of which, the largest are from the Danish Testicular Carcinoma Study Group (DATECA), the Princess Margaret Hospital (PMH), the Royal Marsden Hospital (RMH) and the Royal London Hospital. On multivariate analysis, tumor size and rete testis invasion were identified as factors that predicted

**Table 1.** Patients' characteristics

Descriptive characteristics	AS	ACT	Total	p value
Absolute number	84	22	106	
Age at the time of diagnosis				
mean	36.6	39.1	37.1	NS
Median	35.9	37.4	36.0	
age – min (years)	21	25.7	21	
age – max (years)	63.6	67.7	67.7	
Progression rate (%)	10 (11.9%)	2 (9.1%)	12 (11.3%)	NS
mean time to progression	13.8	13.8	13.8	NS
Median	11.8	13.8	13.0	
time – min (months)	3.6	13.1	3.6	
time – max (months)	30.7	14.5	30.7	
PFS(%)	74 (88.1%)	20 (90.9%)	94 (88.7%)	NS
Mean PFS (months)	30.0	20.6	25.3	

relapse, with an incremental rise in the 5-year relapse rate in the presence of zero, one or both of these factors (12.2%, 15.9% and 31.5%, respectively) [17]. Yuasa et al. [18] observed relapses in 14.2% of patients without risk factors after AS. In our group of CSI testicular seminoma patients managed by AS, the relapse rate was determined to be 11.9%. All relapses were located in the retroperitoneal lymph nodes. Risk factors associated with relapse are weak and controversial. In a study by Warde et al. [19], size of the primary tumor >4 cm, and rete testis invasion were found to be independent prognostic risk factors for relapse. Rete testis invasion was found to be a predictive factor for relapse in another Japanese study [20], but was not determined in the nationwide Danish study [21]. Nevertheless, these factors have not yet been validated in a prospective study [9, 15]. Vascular invasion was also identified as important prognostic factor for relapse. The role of ACT in the form of single-agent carboplatin (one or two courses) has also been investigated, with relapse rates similar to those of ART and an acceptable acute toxicity profile. ACT has been advocated by many clinicians over the other modalities. However, long-term data on late relapses and survival are lacking [13]. In our group of CSI testicular seminoma patients managed by ACT, we identified relapse in 9.1%. All the relapsed patients were treated with 3xBEP chemotherapy. PET/CT was the method confirming therapeutical response.

The role of PET/CT is somewhat controversial but data suggest that a negative PET scan may reliably exclude disease in masses >3 cm. Some centers recommend resection of all masses >3 cm, while others recommend observation [14]. The advantage of FDG-PET/CT is certainly the fact that a whole-body scan is performed, allowing all tissues and organs to be evaluated in a single-step examination. Moreover, PET/CT can identify metabolically active tissues and therefore the presence of viable tumor cells, which need further treatment [22]. The majority of authors, however, noticed that PET/CT cannot be considered as a standard diagnostic tool in the staging of TC [2, 22, 23].

The success of AS policy in CSI testicular seminoma, the availability of curative chemotherapy for early metastatic disease together with the improvement of diagnostic imaging have led to the introduction of AS in CSI testicular seminoma.

The median time to relapse post-orchidectomy for CSI testicular seminoma ranges from 12 to 18 months, but up to 29% of relapses can develop later than this [13]. In the largest published series describing the clinical outcome and relapse data of patients with CSI testicular seminoma treated with a sin-

gle cycle of ACT with carboplatin, 21/517 patients (4.1%) relapsed, the median time to relapse was 22.7 months, with no relapses detected before 12.5 months [24]. The most common site of relapse are the paraaortic lymph nodes (in up to 82%), in contrast to the findings from our current study, in which all patients experienced relapse in the retroperitoneal lymph nodes (100%). We also identified similar ranges of median time to relapse (13.8 months) without statistically significant difference in PFS between patients managed by AS or ACT. Most relapses can be successfully treated by platinum-based (BEP regimen) chemotherapy. All patients from our ACT study group (after previous BEP treatment) were alive (at time of study completion) with no evidence of disease. According to recent EAU Guidelines, due to high and often late rates of relapse, close and active follow-up is mandatory for at least 5 years [13]. Chau et al. [24] declare that time to ACT did not appear to influence outcome, although 75% of their patients received chemotherapy within 60 days post-orchidectomy. Given the late toxicity of ART (particularly SMN) and higher relapse rates of AS, it is not surprising that ACT has emerged as a further option in the management of CSI testicular seminoma in recent years [25]. According to recent EAU Guidelines, ART is not recommended as adjuvant treatment in this malignancy [13].

Having excluded ART, ACT and AS remain the principal options for management, and the choice between them is a subject of debate amongst experts in the field. Both options are used with substantial variations in international practice. The AS versus ACT debate is partly the result of differences in perception of the sequelae – both physical and psychosocial – of these treatment options, but is also due to the lack of clear data regarding the long-term and very long-term risks of therapy. More in-depth information concerning these risks over the patient's lifespan is desperately needed [26].

Despite its excellent prognosis, optimal management of CSI testicular seminoma remains controversial, with variations in expert opinion and international guidelines [26]. AS in these patients is a safe approach, and the majority of them can avoid further treatment after orchidectomy. The benefit of using risk-adapted approaches in CSI testicular seminoma patients is evident; however, it requires a long-term follow-up and experience with the management of this type of malignancy.

International consensus on risk factors of relapse in CSI testicular seminomas patients is expected.

#### CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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