

## Comment – Active Surveillance vs. Adjuvant Therapy in Clinical Stage I Non-seminomatous Germ Cell Testicular Cancer

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Over the last 35 years, the distribution of stage in initial diagnosis of non-seminomatous germ cell testicular tumors (NSGCTT) has changed with more patients being diagnosed at earlier stages. Approximately 30–50% of patients with NSGCTT present with clinical stage I (CSI) of disease [1,2]. Owing to high success rate in the salvage of disseminated cancer, it has become reasonable to propose management of CSI NSGCTT patients by orchiectomy alone followed by surveillance only [3].

Optimal management of CSI NSGCTT patients after orchiectomy has been controversial for several decades because of the difficulty of distinguishing actual CSI NSGCTT in patients from those with occult lymph node and distant metastases. Primary retroperitoneal lymph node dissection (RPLND) was for many years considered to be the golden standard in CSI NSGCTT [4]; it has remained a viable up-front option after orchiectomy.

RPLND provides both accurate staging and curable treatment for the microscopic stage II disease [5]. Among CSI NSGCTT patients undergoing RPLND, 70–77% were found to be a pathological stage I, so the majority of patients were over-treated. The introduction of surveillance strategy after orchiectomy has gained a lot of popularity because of reducing unnecessary treatment-related morbidity for patients in CSI [6–8]. Patients who relapse during follow-up are treated with systemic chemotherapy; those who do not relapse are spared unnecessary treatment. Preliminary results were enthusiastic [3,6], but critical voices have been raised against general use of this option as a routine management [8]. With longer observation, the relapse rate has been found to increase up to 25% or more after orchiectomy [7,9]. Recent

investigation has focused on determining the factors that identify a group of patients at high-risk of the relapse, who might therefore benefit from an approach other than surveillance [10,11]. The utility of lymphovascular invasion (LVI) as a prognostic marker in testicular CSI NSGCTT was first recognized in the 1980s [12] and during the years, it has become the main predictor of relapse in CSI NSGCTT managed by surveillance only [13]. The importance of embryonal carcinoma as a prognostic factor in low stage NSGCTT was discovered when surveillance studies were analyzed for relapse factors. Peckham et al. [3] established the importance of embryonal carcinoma in their initial surveillance report. Wishnow et al. [11] were the first, who did a quantitative analysis of the percentage of the extent of embryonal carcinoma. So, the embryonal carcinoma is extremely important as a prognostic marker for occult disease in CSI NSGCTT. An experienced reference pathologist should do a careful assessment for embryonal carcinoma, including the percentage of embryonal carcinoma [14]. The presence of teratomatous elements in testicular germ cell tumors has been known to have a favorable impact on prognosis. Klepp et al. [10] found out that teratoma of any type (mature and immature) was a significant multivariate predictor of occult nodes. Overall, only 45.4% of patients without teratomatous elements had a true pathological stage I of the disease vs. 71.2% of those with teratoma. The importance of tumor size and pT stage has not been confirmed in most multivariate studies of CSI NSGCTT. Therefore, patients can be stratified according to risk factors into different prognostic groups with different recurrence rates. According to



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recent EAU Guidelines on TC, the risk-adapted treatment is recommended as a treatment of first choice in CSI NSGCTT patients [1]. High-risk patients with LVI are recommended to undergo adjuvant chemotherapy with two cycles of BEP regimen, intermediate risk patients are recommended to undergo primary RPLND and low-risk patients without LVI are recommended to undergo surveillance only.

Differentiated managements of CSI NSGCTT patients were studied since the late 1980s to early 90s [7,8,10,11,14] and was accepted later to several national and international guidelines [1,15]. All mentioned options provide cure rates of approximately 99% [13]. In the USA, a standard postorchiectomy approach has been nerve-sparing RPLND; mainly in Europe, primary surgical approaches have fallen out of favor and nonsurgical approaches now predominate.

Because only 30% of patients relapse during surveillance, 70% of patients who are cured by orchiectomy alone could be unnecessarily exposed to adjuvant treatment-related toxicity. To reduce this overtreatment, the EAU 2015 guidelines [1] advise a risk-adapted treatment approach recommending



adjuvant treatment only for high-risk cases. The guidelines [1] propose 1–2 cycles of adjuvant BEP chemotherapy to those high-risk patients with pT2 N0 M0 (with LVI) or pT3–4 N0 M0, while those low-risk cases (pT1 N0 M0, without LVI) are recommended to undergo active surveillance.

Given that all current strategies for CSI NSGCTT, when carried out well, lead to nearly uniform cure, diminishing treatment-related morbidity has become the primary concern.

Kollmannsberger et al. [16] reported results of the largest multicentric retrospective study to date as well as the experience of several high-volume European and North American testicular cancer centers. The relapse occurred in 221 of 1,139 (19%) patients with CSI NSGCTT following active surveillance as non-risk adapted therapeutic approach, median time to relapse was 6 months. Canadian study [17] using non-risk-adapted approach described two cohorts. In the initial cohort (1981–1992), 53 of 157 patients (33.8%) relapsed compared with 51 of 214 patients (23.8%) in the recent cohort (1993–2005). In the last non-risk-adapted Slovakian study [18], relapse rate for 52/145 (35.9%) was described, following surveillance used in all CSI NSGCTT patients. Nichols et al. [19] argue that adjuvant chemotherapy results in unnecessary treatment for approximately 50% of patients with increasing awareness of the long-term risk for cardiovascular diseases and second malignancies attributable to cisplatin-based chemotherapy. The results of large prospective SWE-NOTECA study [20] using risk-adapted approach described relapse rate 39/228 (13.5%) in patients without LVI who chose surveillance and relapse rate 5/157 (3.2%) in patients with LVI receiving one cycle of BEP regimen.

The recent Slovakian risk-adapted study [21] described relapse rate 46/276 (16.7%) in the group of patients without LVI following active surveillance and 2/155 (1.3%) in the group of patients with LVI after adjuvant chemotherapy (two cycles of BEP regimen). Albers et al. [22] reported results of the largest randomized trial (German Testicular

Cancer Study Group) investigating adjuvant treatment strategies in CSI NSGCTT which showed 2/174 (1.2%) relapses following one cycle of BEP chemotherapy. A pooled analysis of 13 studies involving 1,043 patients revealed a relapse rate of 1.6% in six patients (0.6%) dying of disease [23]. Given the two cycles of BEP, only 3% of patients relapsed; therefore, risk reduction of relapse is 90% [23]. The EAU Guidelines [1] and European Germ Cell Cancer Consensus Group (EGCCCG) [15] recommend active surveillance for low-risk CSI NSGCTT patients and 1–2 cycles of BEP chemotherapy for high-risk CSI NSGCTT patients, which are considered the standard treatment option.

Experiences of recent studies confirm that surveillance policy is recommended only in low-risk CSI NSGCTT patients (without LVI). Patients at high-risk of relapse (with LVI) may be cured with adjuvant chemotherapy. Pokrivcak et al. [24] reported in their review that all modalities are associated with adjuvant treatment-related toxicity with total cure around 99%. So, further studies with long-term follow-up are necessary, they will give answer for controversies between non-risk-adapted and risk-adapted treatment approach in the future with decrease of adverse effects occurrence without impact on relapse rate.

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