Stage I nonseminomatous germ cell tumors: the case for management by risk stratification

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For patients with clinical stage I nonseminomatous germ cell tumor (NSGCT), the therapeutic options after orchiectomy are retroperitoneal lymphadenectomy, surveillance, and chemotherapy. Ideally the option selected will be based on an individualized assessment of the estimated risk of progression based on prognostic factors, so called risk-adapted treatment, to reduce overall burden of therapy while maintaining survival. It is possible to identify patients at low risk of progression who can be followed by active surveillance initially. Prognostic factors for high risk, while well defined, do not identify all patients at risk and those that are destined to progress, can usually be salvaged with delayed therapy. Most centres recommend either surgery or primary chemotherapy for those defined as being at high risk for progression. Prognostic factors for high risk however, while well defined, do not identify all patients at risk and those that are destined to progress, can usually be salvaged with delayed therapy.

Key Words: clincal stage I, surveillance, NSGCT

Introduction

For patients with clinical stage I nonseminomatous germ cell tumor (NSGCT), the therapeutic options after orchiectomy are retroperitoneal lymphadenectomy (RPL), surveillance, chemotherapy. Ideally the option selected will be based on an individualized assessment of the estimated risk of progression based on prognostic factors, so called risk-adapted treatment, to reduce overall burden of therapy while maintaining survival.

Estimation of risk of progression in clinical stage I

After orchiectomy, staging studies including history and physical, imaging of the chest, retroperitoneum and pelvis plus tumor markers are performed and if negative, patients are clinically disease free and defined as clinical stage I. Prognostic factors for progression have been extensively reported and analyzed in various ways. Some report the pathological findings at RPL and have correlated the primary tumor characteristics with the presence of nodal metastases.[1] The risk of progression in those with negative nodes is approximately 10% overall but as high as 20% in those considered at high risk.[2] Furthermore, the thoroughness of RPL may vary between centres so that multicentre data may not be as rigorous and single centre experience.[3]

The most reliable data has been generated from the natural history of cohorts of patients managed by initial active surveillance with subsequent salvage therapy for relapse. The largest experience is the British Medical Research Council study of 259 men managed by active surveillance which correlated the primary tumor histology and characteristics with progression.[4] The presence of vascular invasion, embryonal carcinoma (EC), and the absence yolk sac

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elements were initially identified by the MRC to establish relative risk groups but further reports have identified the presence of mature teratoma, the extent of EC, the level of AFP preorchiectomy, and the level of proliferative markers (MIB) as potentially important. Our local experience supports the observation that the presence of vascular invasion and the extent of embryonal carcinoma (but only pure or 100%) predicted a higher risk of progression.[5] A recent systematic review of reports of risk factors has identified lymphatic and/or vascular invasion (the distinction does not appear to add additional information and may be difficult for the pathologist to report accurately) as the strongest risk factor.[6] The presence/absence (+/-) and percentage (%) of embryonal carcinoma (EC) as a continuous variable or expressed in ranges are associated with increased risk of occult metastases. There are considerable differences between reports as to the relative importance of these variables. Vergouwe et al have considered these differences and conclude that % EC is probably the most useful but investigators, perhaps because of varying local pathology reporting practices, differ in their opinion as to the thresholds for defining low, intermediate and high risk.[1,7]

In summary, in clinical practice, it is possible to identify patients at low risk of progression who can be followed by active surveillance initially.[8] The rate of relapse can be safely predicted in the range 8%-19% for patients with no LVI, absent or low % EC, and the presence of teratoma or yolk sac tumor.[6] The controversy is in the reliability of individualizing high risk assignment. At present, it appears that we can predict a risk of at least 50% with some reliability in patients with LVI and pure or high % EC (at least 50% and probably 80%). Definition of an intermediate risk group is much more difficult.

Experience with surveillance in clinical stage I

From the time of the original report of initial active surveillance in stage I nonseminoma germ cell tumor of the testis, there have been a number of reports of experience elsewhere and a recent consensus statement recommends this approach for low risk patients.[9,10] Overall, approximately 30% of patients will relapse and require chemotherapy with three cycles of bleomycin, etoposide and cisplatinum (BEP).[4,11] The rationale for the surveillance approach is an overall reduction in treatment burden as approximately 70% are spared further therapy and remain relapse free.[12,13] This is effective treatment so that delaying treatment to the time of clinical progression does not affect survival.

We have reported that over a 15-year period, 170 clinical stage I patients with a median age was 26.5 years (range 14 to 44 years) were placed on surveillance.[14] The median follow-up time for these patients was 6.3 years (range 0.7 months to 14.4 years). One hundred and forty-eight patients (87.1%) had been followed for at least 2 years, 105 (61.8%) for more than 5 years, and 34 (20.0%) for more than 10 years.

Of the 170 patients, 48 (28.2%) progressed. The median time to progression was 6.9 months (range 2.4 to 20.8 months). Of these 48 patients, 38 (79.2%) had recurrences within 1 year of orchiectomy. All patients who suffered relapses did so within 2 years of surgery. Of interest, metachronous second primaries were detected in the contralateral testis in five of the 170 surveillance patients (2.9%). This occurred at a mean time of 8.1 years following orchiectomy (range 4.9 to 10.3 years). Pathology was seminoma in three, nonseminoma in one, and Sertoli cell tumor in one. In clinical stage I testis cancer patients on surveillance, previous studies have demonstrated that the pattern of metastasis involves retroperitoneal lymph nodes most commonly (45%), lung only in 17%-20%, both the retroperitoneum and lung in 10%, and marker elevation without radiological evidence of progression in 15%-20%. Because of this anatomic pattern of failure, surveillance protocols mandate marker determination and radiological investigations of the chest, abdomen, and pelvis in addition to history and physical. The length of time for which surveillance should be continued is still controversial. In our series we found no late relapses despite over 5 years of follow-up for 105 patients. However, other centres have experienced relapses after 24 months and there are published reports of late relapses noted 12 years after orchiectomy alone for NSGCT.[15] Because there remains a potential for late progression (defined as relapse after 2 years from initial successful therapy) and there is an increased risk of a second primary, we currently recommend that follow-up be continued to 5 years.

Close follow-up for early detection of progression is generally considered critical for surveillance because NSGCT is known to have a short doubling time and treatment of smaller volume disease will produce better cure rates.[16] However, the desire for frequent follow-up must be balanced by the additional inconvenience to the patient and the risk of noncompliance with possibly increased costs and the toxicity of salvage chemotherapy.

There are a number of surveillance protocols in use

at various institutions.[9] They differ to some extent in the types of surveillance methods used and the timing of follow-up visits. There is currently no consensus on the optimal protocol.

Previous studies have usually examined the pattern of progression based on the anatomic sites where failure occurs.[3-6] An analysis of the investigations used to detect these progressions was often not reported in a systematic fashion. This latter approach is more useful when attempting to optimize the surveillance protocol. The cost efficiency of surveillance compared to alternative therapy is controversial.[17,18] Some studies have used charges and most studies have not captured the indirect costs or opportunity costs to the patients and their employers. As well, there are great variations between jurisdictions, which make comparison difficult.

The potential for poor compliance with follow-up protocols resulting in late relapse at an advanced stage with poor outcome has been identified as a weakness of the surveillance option. However, the definition of compliance failure will influence its rate of occurrence so that some report a very high rate of noncompliance.[19] Furthermore, noncompliance does not appear to adversely effect overall survival.[20]

Overall the benefit of surveillance is that at least 70% of patients are spared further therapy after orchiectomy. However, the patients who relapse usually require 3-4 courses of chemotherapy, all need close follow-up with exposure to diagnostic imaging, and there is a small risk of late relapse.

Experience with initial retroperitoneal lymphadenectomy in clinical stage I

Initial surgery by retroperitoneal lymphadenectomy is widely practiced in North America, particularly if the patient is perceived to have risk factors. The primary rationales are the therapeutic role of surgery in the presence of small volume nodal disease which can be cured without further chemotherapy in a high percentage of cases.[3] Furthermore, the retroperitoneum is rarely a site of subsequent relapse and abdominal imaging can be omitted in follow-up. The risk of infertility due to the loss of seminal emission and antegrade ejaculation is now very low.[21] Other complications of surgery are infrequent and usually minor. Mortality is virtually unknown in current experience. However, at least 70% of patients undergo unnecessary surgery if all stage I patients are managed by primary RPL and the thoroughness of surgery will vary between surgeons and centres with varying volumes. Close follow-up is still required after surgery. Cost can be significant in some countries. Much has been made of elimination of the risk of poor compliance with surveillance and reduced patient anxiety but this has been addressed elsewhere in this review. If reserved for patients at higher risk, e.g., pure EC, some of those with negative nodes are still destined to progress with pulmonary and other systemic sites of metastases. However, this has not been the universal experience and the Memorial Sloan Kettering Cancer Center group led by Sheinfeld has excellent results although in small numbers.[22] Finally, there may be a role for resecting microscopic teratoma that might be chemoresistant at later relapse.[23] At this time, there is no clear survival advantage with initial RPL compared to the other modalities so the final decision will be taken by the patient after informed consent based on his preference. A major concern at the community level is that patients with positive nodes usually receive adjuvant chemotherapy, even those with small volume disease. The total burden of therapy is therefore increased in the population of men managed with initial surgery compared to initial surveillance or risk adapted therapy.

Experience with primary chemotherapy in clinical stage I

Primary chemotherapy is rarely used in North America. There has been extensive experience elsewhere although in general, limited compared to experience with the other modalities used in stage I. First described by Oliver, there are a number of reports in the literature.[18] Experience has been limited to those patients determined to be at high risk of relapse, so called risk adapted therapy.[6,24,25] Results are therefore determined in part by the rate of occult metastases in the selected cohorts as well as drug sensitivity. This is exemplified by the experience of Amato and colleagues with a small number of patients who refused therapy and who all remained disease free. The treatment protocols usually include two cycles of BEP with a relapse rate of 0-7%.[6] Notably, of those that relapse after chemotherapy, approximately 50% are chemoresistant and die of disease. With small numbers, it is difficult to determine if these are the same population of stage I patients destined to die of disease if managed with alternative initial treatment, but this observation has discouraged many from this approach. In addition, late complications of chemotherapy have been described including second malignancy.[3,26] Despite these observations, the European consensus has recommended primary chemotherapy.[10]

Risk adapted therapy in clinical stage I

For the past 15 years there has been interest in stratifying patients on the basis of risk as defined above. This approach now widely determines initial therapy despite the inaccuracy of risk assignment for individual patients. There is no international agreement as to the appropriate initial therapy for high risk patients, however defined. Chemotherapy is usually recommended in Europe but RPL is a frequent approach in North America. Low risk patients are increasingly managed by initial active surveillance worldwide. Randomized trials of the alternatives have not been done and probably will never be done for this rare tumor. All treatments have similar survival outcomes so morbidity of treatment, particularly due to multiple modality therapy, determines the selection of initial therapy. We have addressed the principal problems with risk adapted therapy. Prognostic factors for high risk, while well defined, do not identify all patients at risk and those that are destined to progress, can usually be salvaged with delayed therapy. □

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