State-of-the-art approach in selective curable tumors: germ cell tumors

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introduction
This review covers the management of patients once they have been diagnosed with a germ cell tumor. We take note of the European Society for Medical Oncology (ESMO) guidelines [1, 2] and European Germ Cell Cancer Consensus Group report [3] and expand on controversial areas where more than one management option exists. Although we will only discuss testicular germ cell tumors, the same principles of management apply to extragonadal and ovarian germ cell tumors.

treatment
A radical inguinal orchidectomy remains the treatment of choice for patients presenting with a suspected testicular tumor. Patients with impending organ failure from advanced disease can be started on chemotherapy without a histological diagnosis if they have an elevated human chorionic gonadotropin (HCG) and or alpha-fetoprotein (AFP) and classical distribution of disease. Patients with bilateral tumors or those with only one testis can be considered for a partial orchidectomy.

Patients are placed into prognostic groups as per the International Germ Cell Consensus Classification [4] and staged by TNM (tumour–node–metastasis) staging.

management of stage I seminoma
The proportion of germ cell patients presenting with stage I disease appears to be increasing and now represents about 80% of all seminoma patients [5]. With no adjuvant treatment 15–20% of these patients will subsequently relapse due to the presence of occult metastatic disease. A retrospective analysis by Warde et al. [6], of 638 patients from four centres on surveillance, showed that most relapses (68.6%) occurred within 2 years of surgery. However, eight relapses (6.6%) occurred more than 6 years after diagnosis. Tumor size greater than 4 cm has consistently been shown to be associated with an increased risk of relapse, as has rete testis invasion. Although vascular invasion predicts relapse on surveillance in univariate analysis it is not significant on multivariate analysis. The risk of relapse on surveillance varies from 12% if there is no rete testis involvement and tumor size is less than 4 cm to 29% if both those factors are present.

adjuvant radiotherapy
Radiotherapy has been the standard therapy for many years with studies over the past 20 years attempting to reduce the dose, number of fractions and field size. Adjuvant radiotherapy consists of a total dose of 20 Gy given in 2 Gy fractions 5 days a week usually just to a para-aortic strip between T10 and L5 and including the ipsilateral renal pelvis. A Medical Research Council (MRC) trial comparing 20 Gy and 30 Gy found that 30 Gy was associated with higher morbidity without improved efficacy [7]. The relapse rate following adjuvant radiotherapy is reduced from approximately 15% to less than 4%. These relapses are nearly always outside of the radiation field.

pros.
- Immediate treatment reduces anxiety.
- Follow up can be less intensive.

cons.
- Acute morbidity includes fatigue and gastrointestinal upset with some patients having long-term gastrointestinal problems.
- Daily attendance for 2 weeks.
- Risk of a second malignant tumor. The largest study of second malignancies in long-term survivors of testicular cancer was conducted by Travis et al. [8] using data from 40 576 patients (>22 000 with seminoma), many followed up for more than 20 years. Overall, 2285 second cancers, excluding contralateral testis cancers, occurred such that among 10 year survivors diagnosed at age 35 years, the relative risk of developing a second solid tumor was 1.9. Significantly elevated risks were seen for cancers of the stomach, pancreas, pleura, bladder, colon, esophagus and lung. Statistically significantly increased risks of solid cancers were observed among patients treated with radiotherapy [relative risk (RR) = 2.0, 95% confidence interval (CI) = 1.9–2.2].

adjuvant carboplatin
The cure of advanced disease with chemotherapy led to studies investigating adjuvant chemotherapy. A large randomized European Organisation for Research and Treatment of Cancer (EORTC)/MRC trial compared 886 patients receiving adjuvant...
radiotherapy with 560 receiving single dose adjuvant carboplatin at AUC7. They found no significant difference in relapse-free survival rates between the two groups [radiotherapy 95.9% (94.4–97.1) versus carboplatin 94.8% (92.5–96.4)] at a median of 4 years [9]. A Spanish study offered surveillance to patients with no adverse risk factors and administered two courses of carboplatin to those with tumors larger than 4 cm or those with rete testis involvement. Relapses were observed in six patients (6.0%) on surveillance and seven (3.3%) after carboplatin, with 5 year overall survival at 100% [10].

pros.
- Immediate treatment reduces anxiety.
- Follow up can be less intensive.
- Reduction in the incidence of tumor in the contralateral testis was an unexpected finding in patients treated with carboplatin. These were reported in 10 patients allocated irradiation and two allocated carboplatin [9].

cons.
- Short/medium term toxicity of fatigue, nausea, neurotoxicity, nephrotoxicity but fewer acute side effects compared with radiotherapy. Patients are less lethargic and less likely to take time off work than those given radiotherapy [9].
- There is the potential risk of secondary leukaemia developing after platinum-based chemotherapy though the low total dose and absence of other carcinogenic drugs suggest that the relative risk is less than the 4.0 reported among women treated for ovarian cancer [11]. In a recent paper by Powles et al. [12] studying 191 men post adjuvant carboplatin with median follow up of 9.0 years there was no excess in overall mortality or the incidence of second non-testis cancers although small numbers limited the statistical significance of these results.

surveillance
The adverse events following radiotherapy or carboplatin, plus the use of surveillance for stage 1 non-seminomatous germ cell tumors, led to several large studies of surveillance for stage 1 seminomas [6, 10, 13].

pros.
- The biggest attraction of surveillance is that it potentially spares about 85% of patients from being unnecessarily treated with cytotoxic agents or radiotherapy, therefore eliminating anxiety about long-term sequelae.

cons.
- It requires motivation on behalf of the patients and treating physicians to work.
- Not suitable for some patients or parts of the world e.g. long distances from treating centre.
- A strict follow-up schedule may induce stress [14] and invite noncompliance.

- Cost effectiveness when compared to adjuvant treatments is difficult to ascertain. Some studies suggest it is cost effective [15] whereas others find it to be more expensive but point out the added cost of second malignancies post radiotherapy [16].

The optimum surveillance schedule is still uncertain but should consist of a combination of tumor marker measurement, clinical examination and computed tomography (CT) imaging of the retroperitoneum and thorax [by CT or chest X-ray (CXR)]. Scanning needs to continue longer for seminoma patients than for non-seminoma patients, as they can relapse late, and tumor markers are less frequently elevated. In view of the radiation exposure from CT scans (discussed later) low dose imaging or use of magnetic resonance imaging (MRI) are being explored. The MRC have just started the Trial of Imaging and Schedule in Seminoma Testis (TRISST) which randomizes patients on surveillance between three or seven MRI or CT scans.

Most patients relapse with low-volume good prognosis disease and overall survival for stage I patients is better than 99%, irrespective of which strategy is chosen. The three possible management options need to be explained to patients, but the option they choose is invariably influenced not just by practical aspects such as ability to attend for surveillance, but also by the opinions of their oncologist.

stage I NSGCT surveillance
There is now increasing consensus that surveillance should be part of a risk adapted option and the long-term survival of these patients should be over 99% [3]. Surveillance has become widespread with many publications demonstrating that on surveillance about 25% of patients relapse but that almost all these patients could be cured by subsequent therapy. The MRC retrospective study of surveillance in 259 cases defined four histological factors within the primary tumor that carry independent prognostic significance: tumor invasion of testicular veins, tumor invasion of testicular lymphatics, presence of undifferentiated cells and absence of yolk sac tumor elements. The presence of any three or all four of these factors identifies a high-risk group of stage I NSGCT patients with a chance of recurrence of approximately 50% [17, 18]. Vascular invasion, which was present in 47% of patients, was associated with a 35% chance of relapsing within 2 years. Those patients without vascular invasion had a 14% chance of relapsing within 2 years. Vascular invasion has become accepted as the single most important prognostic factor after its prognostic value has been confirmed in numerous publications [19]. Some centres use immunohistochemical staining with MIB-1 and a high percentage of embryonal carcinoma to select high-risk patients with a predicted >60% chance of relapse on surveillance.

follow up on surveillance
The ESMO recommendations for follow up are that patients should be followed with clinical review, CXR and tumor
markers monthly for 1 year, 2 monthly for second year, 4 monthly for third year and then 6 monthly for 5 years [1]. The impact of radiation exposure due to CT scans is of relevance during surveillance when routine CT scanning can add significant radiation exposure over time. Each CT thorax is associated with a radiation dose of 8 mSv, equivalent to 400 plain chest radiographs. Optimal routine scanning schedules are yet to be defined but efforts are underway to reduce the number of scans required. The TE08 trial of 414 patients randomized them to either two or five CT scans as part of their surveillance protocol. They found a <1.6% increase in proportion of patients relapsing with intermediate- or poor-prognosis disease if they have two rather than five CT scans, concluding that two CT scans is a reasonable surveillance option [20].

adjuvant chemotherapy
Risk stratified adjuvant treatment based on the risk factors detailed above was studied in 114 patients who received two courses of BEP chemotherapy (cisplatin 100 mg/m², etoposide 120 mg/m² i.v. and bleomycin 30 mg). Only those with three or four risk factors were treated. Median follow up was 4 years and the relapse-free rate at 2 years was 98% [21]. A recent report of 35 patients suggests that one course of BEP might be sufficient but one course has not yet become widely accepted [22]. Currently patients with high-risk features and those with low risk features who are unlikely to comply with surveillance should be offered two courses of adjuvant BEP chemotherapy. In view of the immediate and potential delayed toxicity and the fact that in about 50% chemotherapy is not necessary, they should also be given the alternative option of surveillance.

retroperitoneal lymph node dissection
Retroperitoneal lymph node dissection (RPLND) is still offered to some patients and, if they are proven to be pathological stage I, the risk of relapse is less than 10% [23]. Those with pathological stage II disease have about a 30% chance of relapse and are therefore offered adjuvant chemotherapy. The chance of finding tumor in resected nodes will obviously increase if RPLND is offered to those with high-risk disease. Although the RPLND can predict those who have a low risk of relapse, all of those with positive nodes end up having surgery followed by adjuvant chemotherapy. Thus, in low risk patients RPLND is unnecessary in 85% of cases and, as major complications occur in about 5% of patients after RPLND, an increasing proportion of these patients prefer surveillance [24].

management of stage IIA/IIB NSGCT
Traditionally, the exquisite radiosensitivity of seminomas has made radiotherapy standard care. A regimen using modern radiotherapy techniques was assessed prospectively in 94 stage IIA/IIB patients [25] revealing 6-year disease-free survival of 95% and 89% for stage IIA and IIB, respectively. Routine supradiaphragmatic radiotherapy to reduce relapse rates is no longer routinely used. As relapses are usually curable, the survival rate in these patients approaches 100% [25]. Most centres now only offer radiotherapy to stage Ila patients.

High relapse rates of 39% for stage IIC disease following para-aortic and ipsilateral pelvic radiotherapy have made chemotherapy standard for these patients. Efficacy of both three courses of BEP [26] and four courses of EP [27] chemotherapy has been proven in good prognosis metastatic seminoma making this an acceptable alternative to radiotherapy.

In an attempt to reduce toxicity either three or four cycles of single agent carboplatin (AUC7) was given to 108 patients with stage IIA or IIB seminoma. As 13% relapsed, all in the retroperitoneum, single agent carboplatin cannot be recommended [28]. In a small trial combining chemotherapy (mainly carboplatin AUC7) and radiotherapy, Patterson et al. [29] found that patients receiving combined treatment had reduced relapse rates at 5 years compared with those receiving carboplatin only (5-year relapse-free survival 97% versus 81%).

management of stage IIA/IIB NSGCT
The options of management for these patients are either three courses of BEP or four courses of EP chemotherapy or primary RPLND with postoperative chemotherapy given to those with adverse factors. The survival for these patients who are virtually all classified as good risk according to the International Germ Cell Cancer Collaborative Group (IGCCG) criteria is close to 100%.

BEP or EP chemotherapy
Three courses of BEP has become the standard of care for these patients in many countries [26]. If bleomycin is contraindicated, four courses of EP is equally satisfactory. Patients who have residual disease greater than 1 cm after chemotherapy should be considered for an RPLND as 5–10% of these masses contain viable tumor and 15–30% contain teratoma differentiated (TD) [30, 31].

retroperitoneal lymph node dissection
This surgery should be considered for those with a <2 cm solitary node that is within the primary landing site and who have normal tumor markers [30]. Using such selection criteria led to initial RPLND in 32% of stage IIA and IIB patients, with the remainder having induction chemotherapy. About 35% of those who have primary RPLND will require postoperative chemotherapy, which could be just two courses of EP, whilst 65% of these selected stage IIA patients will not require chemotherapy.

The advantages of primary RPLND is that approximately 36% of all stage IIA patients will avoid chemotherapy; although they will all have surgery. However, 35% of patients who have an RPLND for clinical stage II disease have no histological evidence of tumor at surgery. It would therefore seem sensible that patients with indeterminately enlarged nodes around 1 cm are not immediately subjected to either chemotherapy or surgery but, if their tumor markers are normal, have a repeat CT scan 6–8 weeks later to decide if they require therapy. Although some advocate post-chemotherapy RPLND for all patients following induction chemotherapy because of the risk
of viable tumor or TD, this is not common practice in most centres. The relapse rate is incredibly low in patients with <1 cm residual lymphadenopathy. This suggests that small volume residual nodes that appear to contain viable tumor or TD following chemotherapy in good risk stage II patients may not have malignant potential.

management of good prognosis metastatic disease

The standard treatment is three cycles of BEP (bleomycin, etoposide and cisplatin) chemotherapy. This can be given over 5 days (etoposide 100 mg/m² and cisplatin 20 mg/m² daily) or over 3 days (etoposide 165 mg/m² days 1–3 and cisplatin 50 mg/m² over 2 days) with equivalent results [26] but possibly more long-term toxicity with the 3-day schedule when four cycles are used.

In cases where bleomycin is contraindicated, especially due to concern regarding pulmonary toxicity, four cycles of etoposide and cisplatin can be used [32].

management of intermediate and poor prognosis metastatic disease

The most common treatment choice is four cycles of BEP. Four cycles of VIP chemotherapy (etoposide, ifosfamide, cisplatin) offer similar results to 4×BEP with 2-year overall survival rates of 74% versus 71%, respectively, but with increased toxicity in patients receiving VIP [33].

Strategies aimed at improving results include the use of multi-agent regimens (e.g. POMB/ACE [34]), intensive induction chemotherapy (e.g. CBOP/BEP [35]), the use of alternative chemotherapy drugs, such as ifosfamide, gemcitabine, oxaliplatin, paclitaxel, and high-dose chemotherapy followed by autograft. Treatment of these patients in specialist centres with appropriate use of surgery should lead to 5-year survival rates of >80%.

late side effects of treatment

As detailed for radiotherapy, second malignancies following treatment with chemotherapy are described, often leukemias [36]. This seems to be related to etoposide and is largely confined to patients receiving total etoposide doses of more than 2000 mg/m² [37]. In a report of 536 patients treated with standard etoposide doses (1500–2000 mg/m²) at Indiana University, two cases of secondary acute myeloid leukemia were found [38] and in 293 cases treated with similar doses in Hanover, Germany, there was one case of lymphoblastic leukemia [39].

Chemotherapy also increases the risks of hypertension and cardiovascular disease [40] so this must be monitored at post-chemotherapy follow up when late sequelae of treatment may represent a significant threat to patients’ long-term health.

disclosures

No significant relationships


