State-of-the-art and controversies in germ-cell cancer

Many different, intersecting strategies are available for managing germ-cell cancers, particularly in early-stage disease. Which is 'right' remains a matter of debate, and requires balancing efficacy against late effects, bearing in mind the complexity of treatment strategies and the available expertise.

The treatment of germ-cell tumours represents a model of cure for cancer. The key to this success relies on the quality and adequacy of care.

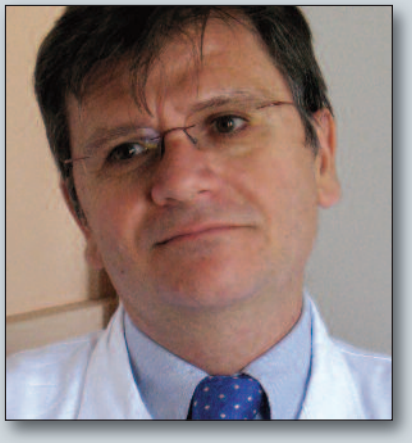
The European Germ Cell Cancer Consensus Group (EGCCCG) met in 2006 to review new data and form an international consensus on the treatment of this disease (Krege, *Eur Urol* 2008). National groups have also developed guidelines on germ-cell cancer (De Giorgi, *Tumori* 2008).

The current strategy for the management of germ-cell tumour is extremely complex. Advanced diagnostics, high-tech surgery, medical oncology and radiation oncology are all involved.

Key issues include staging, the role of positron emission tomography (PET), treatment of early disease, the role of laparoscopy, treatment of clinical stage IIA disease, residual mass left after chemotherapy, long-term toxicities, and treatment options for advanced disease.

The role of PET as a staging tool in early-stage non-seminomatous germ-cell tumours has been examined in two clinical research trials (Huddart, *JCO* 2007;

European School of Oncology
e-grandround



The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these will be selected for publication in each issue of *Cancer World*.
In this issue, Nicola Nicolai, from the surgical department of the urologic oncology unit at Fondazione IRCCS National Cancer Institute, Milan, Italy, reviews the pros and cons of treatment options for early-stage and advanced germ-cell carcinomas – both non-seminomatous and seminomatous.
His presentation is summarised here by Paula Gould.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

De Wit, *Ann Oncol* 2008). Both studies failed in their goal of demonstrating an improvement in negative predictive value when PET was used to assess the extent of disease. The studies were also closed early because they did not recruit an adequate number of patients. At the moment we have to conclude that PET is not advisable when staging early disease.

Early-stage non-seminoma

Efficacy is probably not the most essential issue to consider in the management of early-stage non-seminomatous germ-cell tumours, assuming treatment is delivered properly. Three other aspects to consider when deciding on a management plan are: ease of use, complexity of follow-up and late adverse events.

There are three options for initial management: surveillance, chemotherapy with two or one cycles of PEB (cisplatin, etoposide and bleomycin) and retroperitoneal lymph node dissection. All of these options can lead to a cure rate of approximately 100%. Every one of these management pathways may intersect with another when relapse occurs. Patients may have to undergo a second or third therapy – chemotherapy, surgery of the residual mass or nodal dissection, depending on their previous treatment, clinical stage and the site of disease. This should be considered when evaluating the optimum treatment plan.

Vascular invasion is currently accepted as the most important prognostic factor for this kind of disease. Recent guidelines recommend therapy options according to a risk-adaptive strategy based on vascular invasion. In low-risk patients (no vascular invasion observed), surveillance is preferred to other options, whereas in high-risk patients (evidence of vascular invasion), adjuvant chemotherapy has to be preferred to other options. All guidelines advise lymphadenectomy when the patient has access to a surgeon with relevant expertise.

Pros and cons

Each of the possibilities for treating patients with clinical stage I germ-cell carcinoma has pros and cons.

Surveillance is clearly the simplest strategy, since it relies on just orchiectomy and a follow-up programme. The main disadvantage is intensity of the follow-up schedule and patient anxiety. Patient adherence to the follow-up schedule is essential. Patients treated in this way may still need to undergo lymphadenectomy, and the risk of late relapse cannot be ruled out.

Lymphadenectomy can cure patients with nodal metastases and remove disease that may be resistant or refractory to chemotherapy, preventing later relapses. Late toxicity is not an issue. Loss of ejaculation can occur, but this is rare, particularly if the treatment is done at a specialist (high-volume) centre. First-line lymphadenectomy does not necessarily spare patients from further chemotherapy.

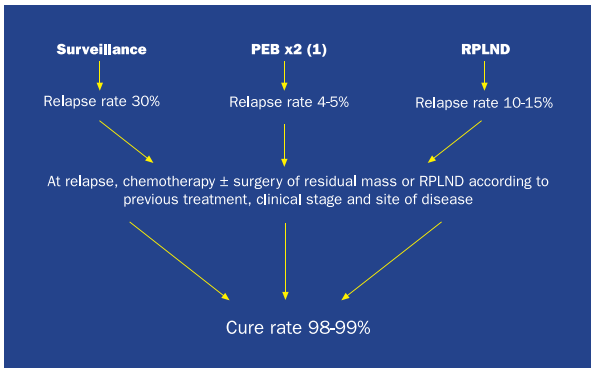
Chemotherapy is a short treatment, particularly if only one PEB cycle is required, and further treatment is unnecessary in the vast majority of patients. This is probably the best community-based treatment option available. However, further surgery cannot always be ruled out in patients who have undergone chemotherapy. Almost all relapses are retroperitoneal and there is also a risk of chemo-insensitive relapse, though the extent of this risk has not yet been defined. A link between chemotherapy and late toxicity is still being explored.

A well-known multicentre, randomised phase III trial from Germany compared retroperitoneal lymph node dissection with adjuvant chemotherapy treatment of clinical stage I disease (Albers, *JCO* 2008). The authors found a difference of 7% in favour of PEB chemotherapy in terms of relapse over two years. But all this study really shows is that, at two-years follow-up, in a series of patients of whom 70% would never relapse anyway, one cycle of PEB chemotherapy is 7% more effective at preventing recurrence than sub-optimal surgery – over half the relapses in the dissection arm of the study (54%) occurred in the retroperitoneum.

A policy of medical treatment rather than intervention is usually accepted as a community-based approach to treating early-stage non-seminomatous germ-cell tumours. Such an approach was adopted by the Swedish and Norwegian Testicular Cancer Project (SWENOTECA) management programme.

From a physician's point of view,

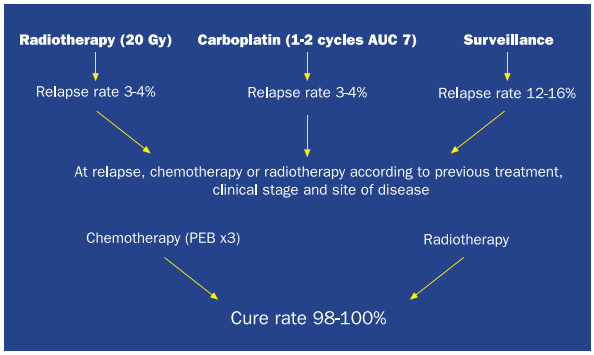
MANAGEMENT OF EARLY NON-SEMINOMAS



All three options for treating stage I non-seminomatous germ-cell tumours lead to a cure rate close to 100%, each has its own pros and cons

PEB = cisplatin, etoposide and bleomycin, RPLND = retroperitoneal lymph node dissection

MANAGEMENT OF EARLY SEMINOMAS



Like non-seminomas, stage I seminomatous germ-cell tumours have three treatment options, all associated with a near-100% cure rate
AUC = area under curve, PEB = cisplatin, etoposide and bleomycin

chemotherapy is probably preferable as the first-line treatment option for stage I non-seminomatous germ-cell tumours. However, from the patient's point of view, if the patient wants to avoid long-term consequences from their therapy, then lymphadenectomy is probably the best choice. This is the policy followed at our institution.

Early-stage seminoma

Three options are available for the treatment of early-stage seminoma: radiotherapy, carboplatin chemotherapy and surveillance. The success rate is close to 100% whichever option is chosen. As with early-stage non-seminomas, each first choice can be followed by any other of the treatment options when relapse occurs.

The risk factors for relapse in stage I seminoma have not been explored as deeply as those for non-seminomatous germ-cell cancers. Tumour size > 4 cm and invasion of the rete testis were identified as prognostic factors for relapse by Warde et al in a pooled analysis of data (*JCO* 2002). However, these findings have not been independently validated.

An important contribution to evaluating the management of stage I seminoma comes from the Medical Research Council Cornerstone trials. The first trial compared relapse rates and toxicity associated with para-aortic strip versus ipsilateral iliac lymph node irradiation – known as the 'dog-leg' field (Fosså, *JCO* 1999). Acute toxicity was less frequent and less pronounced in the arm with reduced-field (para-aortic strip) irradiation. Sperm counts in patients randomised to this arm of the study also recovered more quickly.

The second study (Jones, *JCO* 2005) compared treatment with 30 Gy radiotherapy (15 fractions) against 20 Gy (10 fractions). Once again, patient tolerance was better in the lower-dose treatment arm.

The third of these trials looked at single-dose carboplatin versus radiotherapy (Oliver, *Lancet* 2005). Acute toxicity was lower in the carboplatin group than the radiotherapy group. However, this trial did not adequately demonstrate that chemotherapy is equivalent to radiotherapy (Oliver, ASCO 2008).

Pros and cons

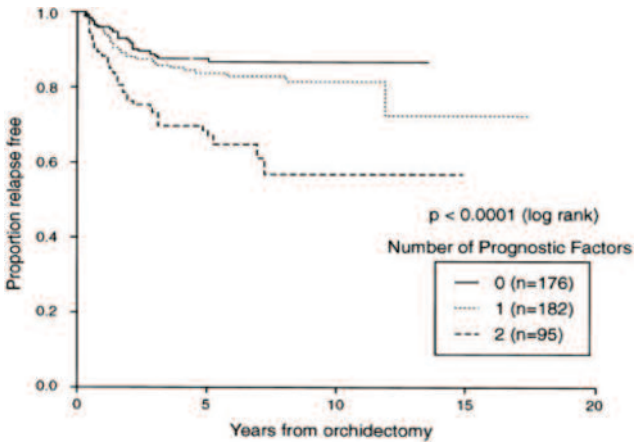
The main advantage with surveillance is the avoidance of unnecessary treatment. Between 80% and 85% of patients do not have distant metastases. As with non-seminomas, long-term follow-up – up to 10 years – is required, and adherence to the follow-up schedule is essential. Late relapses are possible, but there are few devices or biomarkers that can identify disease recurrence at an early stage.

Adjuvant carboplatin is probably less toxic than radiotherapy, especially regarding gastrointestinal toxicity, allowing patients to return to work sooner. However, as yet no single trial has shown clear equivalence with radiotherapy.

Modern radiotherapy techniques, including reduced-field radiotherapy and reduced-dose radiotherapy, have probably reduced the toxicity of radiation treatment. However, concerns remain regarding late toxicity, as with all forms of modern radiotherapy.

Risk-adapted management can be

PROGNOSTIC FACTORS FOR RELAPSE IN EARLY SEMINOMAS



This study looked at tumour size >4 cm and rete testis invasion as prognostic factors in seminomatous germ-cell tumours. Patients with one or other had a higher relapse rate than those with neither. Patients with both prognostic factors had the worst relapse rates

Source: Warde, *JCO* 2002

used in clinical stage I seminoma, according to Spanish authors Aparicio et al (*JCO* 2005). There are advantages and disadvantages to this type of strategy. Treatment choice should take into account information regarding the disease, the patient's environment and the experience of each centre/physician.

A deeper knowledge of the biology of germ-cell carcinoma should ideally lead to a better understanding of the disease and help inform decisions on treatment. Studies investigating the potential of molecular profiling for patient management are underway (Korkola, ASCO 2008).

CHEMOTHERAPY VS RADIOTHERAPY IN EARLY SEMINOMA

Results: event rates at 6.5 years median follow-up

	Carboplatin n=573	RT n=904
Total relapses	29 (5%)	37 (4%)
New primary cancers	7 (1.1%)	25 (2.8%)
GCT	2 (0.3%)	15 (1.7%)
Other	5 (0.8%)	10 (1.1%)
Total deaths	6 (1.0%)	10 (1.1%)
death from seminoma	0	1
death from other cause	6	9

This non-inferiority trial showed toxicity is lower using carboplatin, but chemotherapy has still not been shown to be equivalent to radiotherapy (see rebuttal by Bosl, ASCO 2008)

GCT = germ-cell tumour *Source:* Oliver, ASCO 2008

The relative merits of radiotherapy and chemotherapy for treating early-stage metastatic seminoma remain a matter for debate. The current trend favours radiotherapy for small-volume seminomas (≤3cm diameter), while for larger masses, chemotherapy should be the first choice.

ADVANCED DISEASE

Non-seminomas

The standard treatment choice for patients with advanced non-seminomatous germ-cell tumours is PEB chemotherapy.

Post-chemotherapy resection plays an important role in the overall management of the disease. All masses that still remain after treatment with chemotherapy should be removed.

The rationale for performing retroperitoneal lymph node dissection is as follows:

- The retroperitoneal nodes are usually the first – and often the only – site of disease.
- Surgical resection of non-germ-cell cancer, for example sarcoma, is known to be therapeutic, but the histology is not chemo-responsive.
- Any residual teratoma (a chemo-insensitive tumour) left in the retroperitoneum may grow until it is unresectable and becomes malignant.
- Unresected retroperitoneal metastases can potentially result in repeat surgery or late relapse and decreased survival.
- Complete surgical resection of metastatic disease has been shown to be a significant and independent predictor of relapse-free survival in advanced non-seminomatous disease.

Can surgery ever be avoided?

The goal of post-chemotherapy surgery in advanced non-seminomatous disease is to radically resect the mature teratoma (50%) and/or viable carcinoma (10%). It is very difficult to predict the histology of residual masses following chemotherapy. Modern staging devices such as CT scanning, MRI and PET are used to do this. However, research from the German multicentre PET study group showed that PET was unable to give a clear additional clinical benefit to a diagnostic protocol combining CT scanning and serum tumour markers (Oechsle, *JCO* 2008).

The only patients who should not undergo post-chemotherapy surgery are those with complete serologic and radiographic remission after the drug treatment. We sometimes also choose not to perform surgery in cases where there is no teratoma in the primary tumour, complete serologic remission and radiographic regression is greater than 90%.

Surgery in advanced seminomas

Residual mass is left in up to 25% of advanced seminomas following chemotherapy. The histology of these masses cannot be predicted reliably from factors such as shrinkage and initial size. We know that very few masses (~10%) contain viable cancer. The size of the residual mass (>3 cm) and positive PET scans with the radioisotope tracer fluorodeoxyglucose (FDG) have a role in determining which kind of masses may contain persistent or viable cancer. A review of published data by Heidenrich et al showed that no cancer was found during post-chemotherapy retroperitoneal lymph node dissection when the residual mass was smaller than 3 cm (*Eur Urol* 2008).

We also know that surgery for seminoma is associated with high complication rates (up to 10% mortality). Given the high risk of complications, this type of surgery should only be performed in high-volume centres.

According to Italian guidelines on germ-cell cancer (De Giorgi, *Tumori* 2008), residual mass after chemotherapy

(PEB) treatment for seminoma is considered suspicious if there is persistent elevation of the serum tumour marker hCG or a positive PET scan. We would then suggest further treatment with second-line chemotherapy, surgery (in some specific cases) or radiotherapy.

Laparoscopic lymphadenectomy

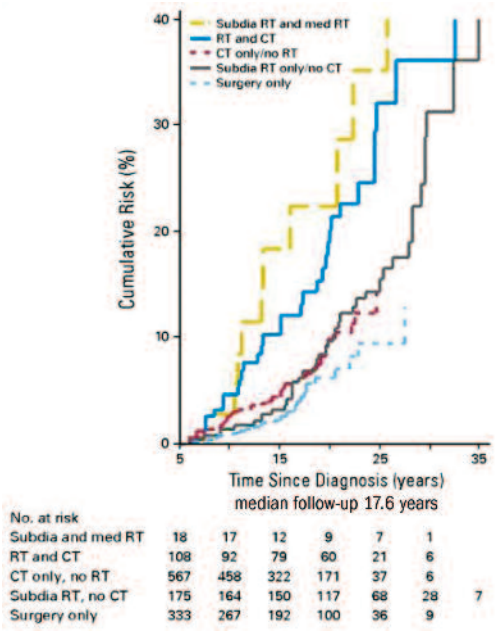
Laparoscopic retroperitoneal lymph node dissection (RPLND) is emerging as a possibility for treating germ-cell cancer. The recent EGCCCG guidelines (Krege, *Eur Urol* 2008) do not include laparoscopic RPLND as a recommended option for treating clinical stage I disease. Nevertheless, some centres do currently perform this intervention in clinical stage I non-seminoma patients.

The main advantage of this type of surgery is its low morbidity when compared with open procedures and with other options such as surveillance or adjuvant chemotherapy. The main disadvantages are that the curative efficacy has not been explored and patients who have nodal metastases must usually undergo adjuvant chemotherapy (Nielsen, *Urology* 2007; Cresswell, *BJU Int* 2008; Rassweiler, *Eur Urol* 2008; Steiner, *J Urol* 2008).

Our current policy is to suggest lymphadenectomy for most cases of stage I non-seminomatous disease. Current data suggest that laparoscopic RPLND is as effective as open RPLND in staging retroperitoneal nodes. In our experience, we have not found an excess of retroperitoneal recurrences following laparoscopic RPLND in patients with no nodal metastases. There are no consistent and reliable data about the omission of adjuvant chemotherapy in cases of nodal metastases following laparoscopic RPLND. We have found that the safety and efficiency of laparoscopic RPLND improved with time, leading to a reduction in morbidity, reduced operative time and an increased number of nodes removed. So after counselling, we currently offer open and laparoscopic RPLND independently of risk category, according to the patient's preference.

Post-chemotherapy laparoscopic RPLND is a technically demanding surgical procedure. It should be considered only as an experimental option or in a very selected group of patients (small-volume residual masses with a cystic appearance), and only performed in high-volume centres that have adequate expertise.

LATE TOXICITIES AND TREATMENT CHOICE



The risk of a second cancer or cardiovascular disease rises after radiotherapy and/or chemotherapy

Source: Van Den Belt-Dusebout, *JCO* 2007

Late toxicities

An analysis by Van den Belt-Dusebout et al (*JCO* 2007) has shown that patients with testicular cancer treated with radiotherapy and/or chemotherapy had a higher risk of second malignant neoplasms and cardiovascular disease than patients whose treatment did not include these types of options.

The risk of cardiovascular events has been shown to be two to three times greater in patients who received chemotherapy or radiotherapy or both, when compared with a strategy that did not include these type of therapies (Huddart, *JCO* 2003).

The risk of a second cancer is greater for younger patients (Travis, *J Nat Cancer Inst* 2005).

Risk of late toxicity should be considered when we face patients who have to undergo treatment for a germ-cell tumour.

Prognostic markers

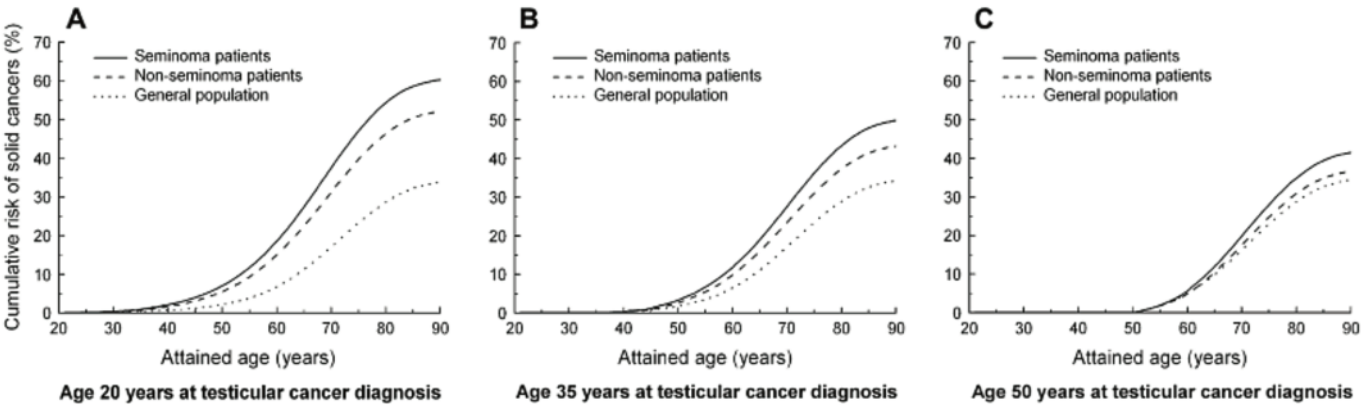
Certain clinical prognostic factors are known to predict outcome. Patients are likely to have a poor outcome if:

- The primary tumour is mediastinal
- The histology indicates non-seminomatous disease
- The disease is absolutely refractory to cisplatin
- There is no response to first-line chemotherapy, and the response to second or subsequent salvage is short
- Serum tumour marker levels are high
- There are metastases in the brain, bones and/or liver.

A good outcome is likely if:

- The primary tumour is gonadal
- The histology indicates seminomatous disease
- The disease is sensitive to cisplatin
- It responds completely to first-line chemotherapy, only one salvage attempt is needed, response is long
- Serum marker levels are low
- Metastases are in the lymph nodes or lung only.

LATE TOXICITIES BY PATIENT AGE



The younger the patient, the greater the risk of a secondary cancer

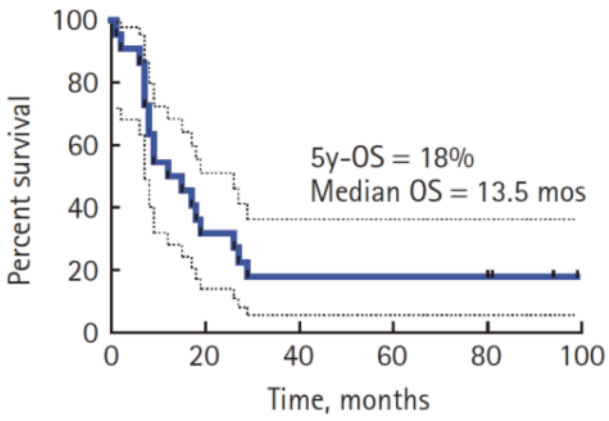
Source: Travis, *J Nat Cancer Inst* 2005

SALVAGE REGIMENS

Historically, conventional-dose salvage regimens have been a combination of cisplatin with iphosphamide and etoposide/vinblastine. Response rates have ranged from 30% to 80%, with the best results coming from more recent drug combinations incorporating taxanes.

In high-dose chemotherapy trials, the story dates back to about 20 years ago. Various drug combinations have been tested in clinical trials. Importantly, the only two clinical trials that were randomised were the IT94 study by the European Group for Blood and Marrow Transplantation (Pico, *Ann Oncol* 2005) and the study by the German Testicular Cancer Study Group (Lorch, *JCO* 2007). Pico et al found that delivering a high dose of carboplatin, etoposide and cyclophosphamide (CarboPEC) after three doses of standard chemotherapy (cisplatin, iphosphamide and etoposide/vinblastine) did not meet the primary endpoint of improvement in overall survival and progression-free survival when compared with four cycles of standard chemotherapy. These negative results from randomised studies have, until recently, limited the use of high-dose chemotherapy.

SALVAGE THERAPY RESULTS



Salvage treatment with a combination of paclitaxel, cisplatin and gemcitabine has shown long-term response rates of around 20%

OS = overall survival, dotted line shows 95% confidence interval

Source: Nicolai, *BJU Int* 2009

Third-line options and beyond

A number of new drugs have been tested as third-line options; for example, oxaliplatin, gemcitabine and paclitaxel. These have led to a response rate of 20%, 30% or, at best, 50%, but few long-term responses have been recorded.

We have recently published our experience of salvage therapy with the combination of paclitaxel, cisplatin and gemcitabine (Nicolai, *BJU Int* 2009). We achieved interesting results – in particular, long-term, maintained responses were seen in approximately 20% of patients.

Also published recently is the Indianapolis series from Einhorn et al (*NEJM* 2007), in which a large number

of patients underwent a double cycle of chemotherapy with carboplatin and etoposide followed by stem cell transplantation.

Very good results were obtained in cisplatin-refractory patients and beyond the second-line setting. In the light of these results, high-dose chemotherapy with tandem transplantation is now seen as a reasonable option in all patients in the third- or fourth-line setting.

New prognostic factors derived from an international appraisal have been described (Lorch and Beyer, ASCO 2009), and these could be used in future to indicate when high-dose chemotherapy should be used as a salvage treatment. Based on these prognostic factors, 'good' relapsers might receive conventional-dose treatment and 'poor' relapsers could undergo a high-dose chemotherapy programme incorporating tandem cell transplantation.

Thanks to salvage treatments, the overall prognosis of patients has improved. In particular, the long-term survival of patients with a poor prognosis has improved by approximately 20% (Van Dijk, *Eur J Cancer* 2006).

In conclusion, integration between surgery and medical treatment is important in salvage strategies and even crucial in this setting. More importantly, there is a need for a better understanding of disease biology so that the right treatment can be delivered to the right patient.

Q&A

Andrea Necchi (AN), from the Department of Medical Oncology at the Istituto Tumori in Milan, hosted a question and answer session with Nicola Nicolai (NN) on the controversial issues in management of germ-cell cancer.

AN: In the light of the recent publication by Albers et al (*JCO* 2008), which discussed the role of medical treatment versus surgery in stage I germ-cell cancer, what is your view on the role of retroperitoneal lymph-node dissection in these patients?

NN: These trials, comparing treatment options for patients with stage I disease, are really important. The question we must ask is: do we have to treat this kind of disease on a community basis or not? If the answer is yes, then adjuvant chemotherapy is an optimal option. Treatment can be standardised because chemotherapy can be delivered anywhere. However, I am not entirely convinced that germ-cell tumours should be cured on a community basis. We are now sensitive to the late events that can occur following treatment for this type of disease, in particular the possibility that chemotherapy and radiotherapy can be associated with, for example, cardiovascular disease and secondary cancer. With this in mind, a solution that includes referral centres that can offer retroperitoneal lymph node dissection is probably a better option. So lymphadenectomy probably still has a role if you consider that the treatment policy should be on a referral basis.

AN: What about laparoscopic dissection? Do you think that in the future this will be equivalent to the open technique?

NN: We do not have enough data at the moment to say that laparoscopic lymphadenectomy in stage I germ-cell non-seminoma is equivalent to the open procedure. The vast majority of patients with nodal metastases received adjuvant chemotherapy following laparoscopic retroperitoneal lymph node dissection. But some centres do not administer chemotherapy in this patient group, and we have started to take this approach too. Based on our experience, we are confident that laparoscopic resection is very close to the open procedure in terms of the ability to resect the nodes and be able to clean the retroperitoneal space. When we have more data, then I think that we will be able to replace the open procedure with laparoscopic dissection. It is incontrovertible that the morbidity of laparoscopic procedures is lower than that of open procedures.

NN to AN: Recent evidence has re-highlighted the role of a dose-intensification strategy in germ-cell tumours. Is there now a particular setting in which high-dose chemotherapy should be recommended?

AN: High-dose chemotherapy is equivalent to or better than conventional dose chemotherapy in the third-line or fourth-line setting. We are now thinking about putting high-dose chemotherapy with tandem carboplatin and etoposide in an earlier setting. But more important is the selection of patients for dose intensification. It is a paradox that high-dose chemotherapy is functional in the third- or fourth-line setting, but we cannot demonstrate equivalence or better in the second-line or first-line setting. At the moment, we are not able to select which patients should move from a conventional dose to a higher dose. By incorporating results from the ongoing international project on prognostic factors at first salvage, we would be able to investigate the role of dose intensification by administering tandem carboplatin and etoposide (CBDCA-VP16) to relapsing patients classified as 'high-risk'.