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Rationale for Lymph Node Dissection in Testis Cancer

N. W. Clarke

Post-Orchidectomy Lymph Node Management in Stage-1 Testis Cancer

Clinical management after primary surgery for testis cancer is predicated on its outcome. Patients with stage-1 seminoma and NSGCT have traditionally been managed by very different strategies but there has been a change in recent years, with options for radiation, low-dose chemotherapy or surveillance and salvage emerging for seminoma and observation, low dose chemotherapy or primary RPLND for non-seminoma, depending on specific risk characteristics for non-seminoma. If the disease is stage 2 or more, the standard treatment for most tumours is a combination of platinum-based chemotherapy with subsequent surgical removal of post-chemotherapy residual masses when the histology is consistent with NSGCT or „mixed" tumours.

Staging usually comprises CT-scanning of the chest, abdomen and pelvis and assay of tumour markers as a minimum. The first order lymph nodes in the retroperiteoneum are usually the initial site of metastatic spread although distal haematogenous dissemination can occur in up to 15 % of men. CT-scanning has its limitations: up to 30 % of patients with negative CT-scans will have positive lymph nodes detected subsequently at surgical staging. By contrast, up to 25 % of patients may be radiologically overstaged, having abnormal nodes on CT-staging, which are subsequently shown to be negative following surgical exploration. MRI and PET imaging have been used in this scenario although neither has proved to be more effective or reliable than CT-scanning.

Risk Stratification

Clinical Stage-1 NSGCT and Stratification of Risk

Data from large multicentre studies correlating tumour related factors with disease outcome has enabled stratification of stage-1 NSGCT for risk. The rationale for this is the identification of men who truly have stage-1 disease and to separate these from cases who are clinically stage 1 but have risk characteristics associated with the presence occult microscopic metastases (pathological stage 2+). In this way, aggressive and potentially toxic treatments can be reserved only for those patients who truly need them. Four specific primary pathological findings are known to be associated with a high risk of occult metastatic spread in clinical stage-1 disease:

- vascular invasion
- lymphatic invasion
- absence of the yoke sac elements
- presence of embryonal carcinoma

Patients with these primary characteristics are usually treated with a more aggressive therapeutic regimen following initial orchidectomy to optimise outcome. In Europe this usually involves the use of adjuvant chemotherapy, whilst in the US some centres elect to use primary retroperitoneal lymph node dissection (Primary RPLND). The evidence for this latter approach is however becoming more difficult to justify in light of the evidence currently available for the safety and efficacy of low dose chemotherapy or surveillance and salvage chemotherapy approaches (see below). A third approach, adopted by a number of high-volume departments is to identify high-risk patients and to follow them more intensively, treating early with combination chemotherapy in the event of failure and avoiding unnecessary treatment in those who remain disease-free.

NSGCT: Surveillance vs Primary Retroperitoneal Lymph Node Dissection (RPLND)

Treatment strategies for stage 1 have varied in Europe and the United States of America, with surgery traditionally prevailing in the US and surveillance in Europe. The rationale for the RPLND approach is that up to 30 % of patients will have microscopic evidence of disease in the retroperitoneal nodes. However, using risk stratification profiles based on histology, it is possible to predict with accuracy of approximately 80 % that low-risk cases will not relapse and furthermore, if they do, they can then undergo systemic treatment with chemotherapy with excellent results. Patients relapsing on surveillance are successfully treated with standard chemotherapy. Their long-term outcome shows remission of 98 %, which is the same as that for primary surgery. In addition, over 95 % of patients who are going to relapse will do so within the first 2 years of diagnosis of their original cancer. Prolonged and intensive follow-up over many years is therefore not required although a degree of follow-up is needed because of the risk of late relapse. Surveillance is now the preferred option in most European and many US centres.

Primary RPLND

Existing non-invasive staging techniques fail to identify up to 30 % of patients with positive nodes. This fact has provided a rationale for a surgical approach in stage-1 testicular cancer in the USA and in some centres in Europe. The procedure is usually carried out through a midline abdominal incision although an increasing number of reports are emerging relating to the use of laparoscopic techniques [1]. This latter approach has lead to some surgeons suggesting that laparoscopic primary RPLND should be used more often. The recent results of the German Testis Study Group however confirm that low intensity single cycle BEP is significantly superior to surgery, no matter what surgical technique is used [2].

Surgery also has a significant complication rate, even in expert centres. The traditional approach of standard bilateral lymphadenectomy is associated with loss of ejaculatory function in most pa-

tients. Use of „template"-based nerve sparing techniques, utilising knowledge relating to the course of ejaculatory nerves and the likely site of metastatic deposits has resulted in > 75 % of patients preserving ejaculatory function postoperatively. Whether open or laparoscopic, the surgery required is major and there are potential complications (adhesion obstruction, wound infection, leg oedema etc), which can occur in up to one third of patients. A further issue is the outcome relating to surgery; 70 % will have no evidence of disease at lymphadenectomy and up to 10 % will have post-RPLND recurrence in the retroperitoneum or elsewhere [3]. In recent years, the use of primary RPLND-surgery has diminished but there has been a rekindling of interest with the use of laparoscopic techniques.

One potential advantage of RPLND is in relation to patient compliance. The requirement for repeated CT-scans inherent in a surveillance protocol requires that patients will attend for repeated follow-up appointments. This is known to present problems in certain circumstances, particularly when the distance to referral centres is large.

Chemotherapy for High-Risk Stage-1 Disease

Most departments will now use standard or reduced intensity chemotherapy for high-risk NSGCT cases, most commonly using Bleomycin, Etoposide and Cisplatin (BEP). Disease-free survival in the region of 98 % is expected in the long term with the adoption of this therapy. Studies evaluating „single-shot" chemotherapy as a means of reducing the overall toxicity of treatment are ongoing.

Another approach, which is used commonly in some centres is to identify high-risk cases and follow them intensively for the first 2 years. This is on the basis that a significant number of patients can be spared the potential long term effects of chemotherapy, whilst patients relapsing can be identified quickly and treated with standard BEP, with excellent outcome.

The use of risk stratification in clinical stage-1 seminoma has been less widely used than in NSGCT, although anaplastic morphology, tumour size and a high local stage are predictors of relapse. This scenario is now changing and this approach has become a genuine option for many patients (see below).

Risk Stratification in Clinical Stage-1 Seminoma

Because of the retroperitoneal relapse rate of 15–19 % and the exquisite radiosensitivity of seminoma, adjuvant low-dose abdominal radiotherapy has been used widely in the treatment of this condition. This has been the standard adjuvant treatment in many countries. However, more recent strategies involving the use of single agent chemotherapy with Carboplatin, or surveillance are being used more commonly.

Adjuvant Radiotherapy

Irradiation of the paraaortic and pelvic lymph nodes has been the most favoured adjuvant treatment in Europe. The standard approach traditionally involved irradiation of the paraaortic nodes. Inclusion of the ipsilateral inguinal nodes („dog-leg" radiotherapy) is still used in some circumstances, but it has been shown that there are no differences in survival and recurrence rates if the radiation field is limited to the paraaortic lymph nodes only and toxicity of the „dog leg"-scheme is greater. Grade-1-complications such as nausea, vomiting, GI ulceration are often seen with paraaortic XRT and a transient drop in sperm count can occur in a proportion. The decrease in sperm count will usually recover within one year. Using the paraaortic low-dose regimen the acute toxicity is reduced and the effect on sperm count within the first 18 months is less profound [4].

Regarding the dose of radiation, the UK MRC randomised trial of 20 Gy versus 30 Gy paraaortic radiation in stage-1 seminoma showed equivalence for both doses in relation to recurrence rates, with severe radiation-induced long-term toxicity occurring in less than 2 %. Moderate chronic gastrointestinal (GI) side-effects were seen in about 5 % of patients and moderate and acute GI toxicity in about 60 % [5].

The main concern surrounding adjuvant radiotherapy is the potentially increased risk of radiation induced secondary non-germ cell malignancies. This represents a small but significant risk. In light of this many centres have discontinued the use of radiotherapy in this setting, although audit data suggests that the treatment options offered to patients still depend on whether the patient sees a radiotherapist, a medical oncologist or a surgeon for their consultation.

Adjuvant Low-Dose Chemotherapy

Studies assessing the use of single agent chemotherapy as an alternative to radiotherapy have recently been completed. This therapeutic strategy has recently been proven to be an effective treatment for this type of disease. Oliver et al. [6] reported on a series of patients treated with single agent carboplatin: The relapse rate of the whole group was 4 % (median follow-up of 51 months) and 99 % of patients were disease-free. These results have been repeated in other studies such as the MRC phase III trial of carboplatin-monotherapy versus radiotherapy as adjuvant treatment in clinical stage-1 seminoma. In this study there was no statistical difference in recurrence rates. After a mean follow-up of more than 4 years the relapse rate with one single course of carboplatin at 3 years was 5.2 % [7]. There were however a number of the relapses occurring after more than 2 years. Caution is therefore still required in interpreting these results.

A further potential concern with this therapeutic approach is the development of late sequelae, particularly the induction of second malignancy, induction of drug resistance in recurrences, the effect on fertility and the impact on quality of life. Thus, the long-term results of the published trials using single agent adjuvant chemotherapy are awaited.

Surveillance and Salvage in Clinical Stage-1 Seminoma

Surveillance strategies have been pioneered by Canadian researchers [8] and they are being used in a manner similar to those which have been used for many

years in non-seminoma. In patients with clinical stage-1 seminoma, observation studies have shown that about 16 % of patients are at risk for recurrent disease. The median time to relapse is 12–15 months with 96 % of relapses occurring in the retroperitoneum or inguinal region. In a multivariate analysis of several retrospective observation studies a tumor size > 4 cm and the presence of rete testis invasion remain adverse prognostic signs and these define a high-risk group for relapse. If both factors are present, patients have a risk of relapse during surveillance of 32 %. If both factors are absent, a low-risk group can be defined with a relapse risk of only 12 %. Prospective studies using risk factors had been now performed by other groups e.g. by the Spanish Testicular Cancer Group. One third of the patients in this group's study had neither of the defined risk factors (rete testis invasion or a tumor size > 4 cm): They received surveillance only following orchiectomy. Only 6 % of these patients relapsed with a median follow-up of about 3 years. The remaining patients, with one or both risk factors, were treated with adjuvant carboplatin, and showed a relapse rate of just 3.3 % [9]. Studies of this type represent a significant way forward in targeting post-orchidectomy treatment for those patients who have a high risk of occult metastatic disease at the time of orchidectomy. Strategies to reduce immediate adjuvant treatment in as many patients as possible will confine treatment and treatment risk to those who need it most. This approach has been used to show that if the risk of relapse in patients managed with surveillance is under 10 %, the number of follow-up investigations can be reduced. It is, however notable that in the Canadian surveillance series, relapses have occurred after more than 5 years of follow-up. Therefore, surveillance strategies even with a very low risk of recurrence need coordinated and careful follow-up. This engenders one of the main problems with this approach i.e. the determination of the best surveillance strategy with the minimum of radiation exposure from repeated CT-scanning. The Canadian study [8] used an average of 20 CT-scans per patient, a significant amount of radiation to young men often with long-life expectancy. Strategies are currently underway utilising MR-based methods to address this problem.

Post-Chemotherapy Salvage RPLND

A key component of treatment of metastatic testis cancer is the surgical resection of the post-chemotherapy residual mass. The decision to operate, the determination of the extent of the surgery and the technical aspects of the procedure itself present particular challenges, which dictate that surgery of this type should only be undertaken in specialised multidisciplinary centres.

Post-chemotherapy resection is not usually undertaken for residual masses in pure seminoma unless there is definite evidence of residual and active chemorefractory disease which is amenable to excision. Residual mass size and FDG PET-scanning can be helpful in the clinical decision making process. In the event of surgery, such masses are associated with intense post-treatment fibrosis and they present an augmented degree of difficulty in excision.

In NSGCT it is usual to consider surgery 4–6 weeks after cessation of chemotherapy although this decision may be deferred in some circumstances such as post-treatment complication or major disease regression. The clinical preoperative prediction of the final histology is inaccurate but the rate of marker normalisation and the extent of tumour regression can facilitate better prediction of the presence of post-treatment fibrosis or mature teratoma. The surgical approach and extent of dissection are predicated on the size and distribution of the mass and the anatomical location of the primary. For discrete lesions < 3 cm it is usually possible to consider a template based resection with a low rate of „out of field" abdominal recurrence. This approach, usually undertaken through a midline incision, reduces the rate of surgical complications and improves the chance of preserving ejaculation significantly. Larger and/or bilaterally distributed tumours usually require a full RPLND, with mobilisation of the IVC and aorta and where necessary, resection of associated structures. These may include the ipsilateral kidney/ureter, affected bowel, the IVC and occasionally, the aorta. Large volume tumours, particularly those with augmented upper abdominal and/or retro-crural deposits will require a thoraco-abdominal or „roof-top" approach.

Major post-surgical complications are to be expected in up to 5 % of cases, even in expert centres and it is also important to recognise the added risk of surgical infection and compromised marrow reserve secondary to chemotherapy, and pulmonary insufficiency as a consequence of Bleomycin toxicity.

Pulmonary, mediastinal and cervical deposits will need resection at a later stage. The final pathology from abdominal resection doesn't always predict that elsewhere. Differences in abdominal and thoracic pathology may occur in at least 30 % of patients but in circumstances where resection of abdominal disease reveals „fibrosis only", it is reasonable to observe thoracic lesions as 90 % will have a similar pathology.

In the presence of active disease despite adequate chemotherapy, surgical resection may be considered as a last chance of cure. This should only be undertaken when there is a realistic expectation of complete and safe tumour removal.

Staging according to IGCCCG.

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