Pergamon

European Journal of Cancer Vol. 32A, No. 10, pp. 1641–1644, 1996

Printed in Great Britain
0959–8049/96 $15.00+0.00

PII: S0959-8049(96)00163-3

Point of View

Primary Treatment in Stage II Non-seminomatous Germ Cell Tumours of the Testis: a Matter of Scalpel or Drug Infusion?

S. Culine[1] and J.-P. Droz[2]

[1]Department of Medicine, C.R.L.C. Val d'Aurelle, Rue de la Croix Verte, 34298 Montpellier; and [2]Department of Medical Oncology, Centre Léon Bérard, Lyon, France

The optimal primary treatment of patients with low volume (≤5 cm) retroperitoneal metastases remains a matter of debate. Retroperitoneal lymph node dissection (RPLND) is a common practice in North America whereas chemotherapy is a prevailing approach in Europe. In patients with normal serum tumour markers after orchiectomy, primary RPLND appears to be the most appropriate way of staging. In other patients, neither surgery nor chemotherapy are entirely sufficient as monotherapy since approximately one-third of cases for each approach will need the other for achieving optimal results. Treatment decisions are based on cost/benefit and risk/benefit considerations, including relative toxicity and individual patient preference. The treatment of low volume stage II non-seminomatous germ cell tumours (NSGCT) clearly is a matter of scalpel and drug infusion. Copyright © 1996 Elsevier Science Ltd

Key words: testicular cancer, retroperitoneal metastases, stage II, chemotherapy, retroperitoneal lymph node dissection

Eur J Cancer, Vol. 32A, No. 10, pp. 1641–1644, 1996

INTRODUCTION

SINCE THE successful introduction of cisplatin in chemotherapy regimens, metastatic non-seminomatous germ cell tumours (NSGCT) of the testis have become a model for all curable neoplasms [1]. Stage II disease is defined as a metastatic disease limited to the retroperitoneal lymph nodes. The maximum transverse diameter of retroperitoneal lymph nodes allows patients with stage IIA (<2 cm), IIB (2–5 cm) and IIC (>5 cm) to be distinguished. Stage II disease accounts for 25–40% of all patients presenting with NSGCT of the testis [2]. If chemotherapy is recognised as the standard primary modality after orchiectomy for patients with visceral metastases or stage IIC disease, the optimal management of patients with low volume retroperitoneal metastases (stages IIA and IIB) remains a matter of debate. Primary retroperitoneal lymph node dissection (RPLND) is a common practice in North America and certain European countries. Such an attitude is regarded as having diagnostic as well as therapeutic value [2–4]. Another possible approach is primary chemotherapy with subsequent RPLND limited to patients with residual disease [5, 6].

Correspondence to S. Culine.
Received 26 Oct. 1995; revised 11 Mar. 1996; accepted 23 Apr. 1996.

EJC(A) 32-10-C

PRIMARY RETROPERITONEAL LYMPH NODE DISSECTION

The Indiana University experience

The largest experience with primary RPLND was recently reported by investigators at Indiana University [2, 3]. Among 174 patients who underwent primary RPLND, 145 (83%) had a full bilateral RPLND below the level of the renal vessels. Sixty-three per cent of patients had their dissection extended into the suprahilar region either unilaterally or bilaterally. Therefore, only 29 (17%) had a modified unilateral RPLND. Most importantly, surgery revealed that 41 (23%) patients had no metastatic deposits in retroperitoneal lymph nodes. Only two relapses (one pulmonary and one pulmonary plus mediastinum) were subsequently observed in this group of patients with pathological stage I disease. These 2 patients were rendered free of disease by salvage cisplatin-based chemotherapy. Among 133 patients with pathological stage II disease, 54 (41%) had no further therapy. 19 (35%) patients relapsed, 2 of whom died. 79 patients received postoperative adjuvant treatment. 11 relapses occurred before the cisplatin era. 4 deaths related to progressive disease were registered. No relapse was observed in 59 patients who were treated with adjuvant cisplatin-based chemotherapy. Overall, 7 (5%) patients died out of 133 pathological stage II. There were 5

cancer-related deaths (4 before the cisplatin era), 1 postoperative death and 1 death related to complications of chemotherapy. Eighty-six per cent of patients who underwent full bilateral dissection had definitive retrograde ejaculation [2, 3].

The Indiana experience highlights three major points. First, an estimated 20% of patients with clinical stage II have pathologically proven stage I disease. Although unspecified, it can be supposed that these patients had normal serum tumour markers at the time of RPLND. The staging error is due to the inability of computerised tomography to detect abnormalities in internal nodal architecture whereas enlargement in nodal size is readily detected. It is not clear how much lymphangiography adds to the CT scan, but it is widely acknowledged that the false negative and false positive rates of lymphangiography range from 20 to 40% [7]. This false positive staging error is important when considering primary chemotherapy since it would be particularly inappropriate for patients with stage I disease to suffer long-term toxicity of cytotoxic drugs. Second, the relapse rate in patients with pathological stage II disease was 35% when no further treatment was delivered. These results indicate that 65% of patients with stage II disease are expected to be cured by RPLND alone. Other groups have confirmed the therapeutic value of primary RPLND without postoperative treatment [8, 9].

Finally, the main perceived disadvantage of primary RPLND is the loss of ejaculatory function, the incidence of which is strongly related to the surgical technique. The loss of ejaculatory function is 100% with traditional bilateral suprahilar RPLND and 90% with modified infrahilar bilateral RPLND [2, 3]. However the development of modified templates of dissection has lowered the anejaculation rate from 30 to 40% with modified unilateral RPLND to 10% with nerve-sparing modified RPLND [10, 11]. However, application of latter techniques remains a matter of operator experience. Modified unilateral RPLND should be considered as the minimal appropriate approach for stage II disease [2, 3]. This statement implies that an incompressible rate of anejaculation is expected with standard primary RPLND.

Postoperative chemotherapy: when? how?

The investigations of prognostic factors that predict relapse after primary RPLND alone have focused on the degree of tumour bulk. Several reports have suggested that patients with minimal nodal involvement (fewer than six positive nodes located in the primary landing site, no node larger than 2 cm, no extranodal extension) have a low risk (0–30%) of relapse. In contrast, patients with higher volume nodal involvement have a relapse rate of 50–80% when no adjuvant cisplatin-based chemotherapy is given [12, 13]. A randomised trial was conducted by the Testicular Cancer Intergroup to determine whether close observation, with chemotherapy reserved for those patients who experienced a subsequent relapse, resulted in a survival rate equivalent to that observed with systematic adjuvant chemotherapy [14]. 48 (49%) of the 98 patients in the observation arm developed a relapse and received 3–4 cycles of cisplatin-based chemotherapy. Only 1 of the 97 patients who were treated by two cycles of adjuvant cisplatin-based chemotherapy had a relapse. After a median follow-up of more than 4 years, no difference was observed in the 96% overall survival in both groups. Moreover, no identifiable factor was strongly associated with the risk of subsequent relapse in the observation group.

Therefore, the following guidelines for adjuvant chemotherapy can be suggested. Patients with minimal volume retroperitoneal nodal involvement can be followed closely and treated with 3–4 cycles of cisplatin-based chemotherapy at relapse. Most importantly, this option is commendable if the surgical resection is complete and compliance is ensured. This would spare the patients, who do not have microscopic residual disease after RPLND, the morbidity of adjuvant chemotherapy. Patients with high volume nodal involvement may be treated with systematic adjuvant chemotherapy, which nearly guarantees the absence of subsequent relapse.

Which type of chemotherapy should be given when the option of adjuvant treatment is chosen? One randomised study attempted to evaluate the efficacy of two versus four courses of PVB (cisplatin, vinblastine, bleomycin) following a complete bilateral RPLND [15]. After a median follow-up of 43 months, relapses occurred in 6 of 114 patients who had received two courses and in 1 of 111 patients who had received four cycles. These results were not statistically different. Moreover, patient compliance differed. In the two-course regimen, 108 patients (96%) finished treatment as scheduled, whereas 77 (71%) patients receiving the four-course regimen completed therapy, largely because of toxicity. The authors concluded that two courses of PVB were sufficient in the adjuvant setting after complete bilateral RPLND. At the Memorial Sloan Kettering Cancer Center (New York, U.S.A.), two cycles of the two-drug programme EP (etoposide, cisplatin) were delivered in 50 patients with high-volume nodal metastases, 35 and 15 of whom had undergone a full bilateral and modified unilateral RPLND, respectively. All patients are free of disease after a median follow-up of 3.5 years [16]. Therefore, it could be concluded that two cycles of cisplatin-based chemotherapy is an adequate treatment after bilateral RPLND.

However, we feel that the optimal number of chemotherapy cycles that should be administered in the adjuvant setting is related to the quality of the primary surgical resection. At Institut Gustave Roussy (Villejuif, France), 44 patients received adjuvant chemotherapy over a 7-year period, 31 of whom were referred from 21 different surgeons. 9 patients had undergone a complete bilateral RPLND whereas 35 were offered the option of a modified unilateral dissection. The large range of surgeons who were involved in the management of our patients and the heterogeneity in the surgical procedures prompted us to deliver four cycles of chemotherapy. All patients remain free of disease with minimal toxicity after a median follow-up of 6 years [17]. It is important to note that no report in the literature provides evidence that two cycles of cisplatin-based chemotherapy is able to reliably salvage incomplete surgery. Prospective studies will be necessary in patients with high-volume nodal metastases who undergo a modified unilateral RPLND.

PRIMARY CHEMOTHERAPY

Worldwide experience

The other option in the treatment of stage II disease is to deliver primarily chemotherapy with subsequent RPLND in patients with residual disease. Few studies have reported the results of primary chemotherapy in clinical stage II NSGCT of the testis so far [5, 6]. Logothetis and colleagues treated 39 patients with radiological evidence of stage II testicular NSGCT, 31 of whom achieved a cCR. 8 (26%) of these patients required surgical exploration for a persistent tumour mass with normal serum marker levels after chemotherapy. 23

(78%) patients were spared RPLND. The relapse-free survival rate was 96% with a median follow-up of 2.5 years [5]. The largest experience with primary cisplatin-based chemotherapy has been recently reported by Horwich and colleagues in 122 patients with retroperitoneal lymph nodes of less than 5 cm diameter. Postchemotherapy RPLND was performed in 10 (17%) of 58 patients with stage IIA and 25 (39%) of 64 patients with stage IIB disease. After a median follow-up of 5.5 years, 118 (97%) patients were disease-free [6]. In the Institut Gustave Roussy experience, 45 patients with clinical stage IIA or IIB testicular cancer were referred for primary chemotherapy with conventional doses of cisplatin. 16 (36%) patients achieved a sustained complete remission after chemotherapy only, while 22 (49%) patients (6 patients with stage IIA and 16 patients with stage IIB) required subsequent RPLND for persistent residual tumour masses. 4 patients with stage IIB disease subsequently relapsed. Overall, 44 (98%) of 45 patients remained free of disease 27 to 105 months after the end of treatment [18]. These results argue for the excellent efficacy of chemotherapy as primary therapy for stage IIA and IIB disease.

The perceived disadvantages of primary chemotherapy relate first to the reliability of initial staging as discussed before and second to the acute and long-term side-effects of chemotherapy. There have been many recent studies aiming to define protocols of decreased toxicity in good prognosis metastatic patients [19–21]. Deleting bleomycin in patients receiving four cycles of EP or limiting the cumulative dose of bleomycin to three cycles of BEP (bleomycin, etoposide, cisplatin) currently represent two equivalent optimal alternatives in patients who received primary chemotherapy for clinical stage II disease. However, recent reports have implied etoposide as the cause of secondary leukaemia in patients treated for germ cell cancer. The risk appears to be related to the cumulative dose of etoposide and is significantly higher in patients treated with greater than 2 g/m^2, i.e. four cycles of EP or BEP [22]. In this context, some authors have claimed that non-etoposide-containing protocols should be explored in patients with good-risk disease [23]. Reports evaluating the long-term reproductive capacity of patients following cisplatin-based chemotherapy are scarce. A high incidence of persistent semen abnormalities has been suggested. However, some patients are still capable of reproductive capacity despite continued oligospermia [24].

Postchemotherapy surgery: when?

Besides a high efficacy, primary chemotherapy is supposed to decrease the number of patients who require RPLND. From the reported experience with this approach, 60–80% of patients are expected to be cured without postchemotherapy surgery [5, 6]. Therefore, the side-effects of RPLND are expected to be decreased. However, in reviewing their experience with postchemotherapy RPLND, investigators at the Indiana University reported an increased incidence of major complications as compared to primary RPLND [25]. Regarding the role of postchemotherapy surgery, two important points should be considered: (i) in which patients should an RPLND be performed? (ii) which areas should be affected by the dissection?

The nature of postchemotherapy tumour residuals can be determined only by excision and histological examination. Histological findings are defined as necrosis/fibrosis, mature teratoma or viable tumour. In patients with necrosis/fibrosis, the RPLND is only of diagnostic value whereas an additional therapeutic benefit is gained when mature teratoma or viable tumour is resected. Therefore RPLND should be omitted in patients with necrosis/fibrosis. However there is no factor to accurately predict which patients can be spared postchemotherapy surgery and its associated morbidity. Recommendations for resection of residual masses vary to a considerable extent. In this setting, a very sophisticated model that could predict the histology of tumour residuals was recently published [26]. Predictors of necrosis were the absence of teratoma elements in the primary tumour, prechemotherapy normal alfafetoprotein, normal human chorionic gonadotrophin, elevated lactate dehydrogenase levels, a small prechemotherapy or postchemotherapy tumour mass, and a large shrinkage of tumour mass during chemotherapy. Multivariate combination of these predictors yielded reliable models that discriminated necrosis from other histologies. Easier to apply in standard practice are the recommendations that emerged from studies at the Memorial Sloan Kettering Cancer Center [27]. RPLND was recommended for all patients with initial bulky metastases ($\geq$3 cm in diameter), irrespective of postchemotherapy-computed tomography findings. RPLND could be omitted when a large shrinkage (>90%) was observed in patients with initial tumour size <3 cm.

The extent of RPLND is related to the distribution of initial metastatic deposits in retroperitoneal lymph nodes. Bilateral RPLND has been recommended because lymph node metastases may be widespread. In studying patients with low- and high-volume nodal metastases, Donohue and colleagues demonstrated that left pre-aortic and left para-aortic lymph nodes are involved in 23–88% and 4–13% of cases, respectively, when right testicular primaries are considered whereas interaortocaval, right paracaval and right precaval lymph nodes are involved in 29–100%, 0–47% and 0–5%, respectively, when left testicular primaries are considered [28]. In contrast, investigators at the Memorial Sloan Kettering Cancer Center recently showed that the distribution of retroperitoneal metastases after chemotherapy was predictable and largely limited to the primary landing sites for right- and left-sided tumours [29]. These findings were validated in a prospective study with frozen section analysis [30]. Therefore, until we are able to accurately predict those patients that do not require adjunctive surgery, postchemotherapy resection of residual masses followed by a limited RPLND appears to be a safe alternative to bilateral dissection.

CONCLUSION

There is no doubt that primary RPLND or primary chemotherapy yield excellent results in terms of tumour cure in stage II NSGCT of the testis. However, neither surgery nor chemotherapy are entirely sufficient as monotherapy since approximately one-third of cases for each approach will need the other for achieving optimal results. In patients with normal serum tumour markers after orchiectomy, primary RPLND appears to be the most appropriate way of staging. In other cases, treatment decisions are based on cost/benefit and risk/benefit considerations, including relative toxicity and individual patient preference. Improvement in standard surgical dissection with reduction of the anejaculation rate and reduction of chemotherapy-induced acute and long-term toxicity would be important objectives to reach in the near future. A recent report from Indiana University suggested an advantage for RPLND in terms of costs and fertility as com-

pared with chemotherapy [31]. A comparative report from medical oncologists will be welcome. The treatment of low-volume stage II NSGCT clearly is a matter of scalpel and drug infusion.

1. Einhorn LH. Treatment of testicular cancer: a new and improved model. *J Clin Oncol* 1990, **8**, 1777–1781.
2. Donohue JP, Thornhill JA, Foster RS, Rowland RG, Bihrle R. Clinical stage B nonseminomatous germ cell testis cancer: the Indiana University experience (1965–1989) using routine primary retroperitoneal lymph node dissection. *Eur J Cancer* 1995, **31A**, 1599–1604.
3. Donohue JP, Thornhill JA, Foster RS, Bihrle R, Rowland RG, Einhorn LH. The role of retroperitoneal lymphadenectomy in clinical stage B testis cancer: the Indiana University experience (1965 to 1989). *J Urol* 1995, **153**, 85–89.
4. Pizzocaro G, Monfardini S. No adjuvant chemotherapy in selected patients with pathologic stage II nonseminomatous germ cell tumors of the testis. *J Urol* 1984, **131**, 677–680.
5. Logothetis CJ, Swanson DA, Dexeus F, *et al.* Primary chemotherapy for clinical stage II nonseminomatous germ cell tumors of the testis: a follow-up of 50 patients. *J Clin Oncol* 1987, **5**, 906–911.
6. Horwich A, Norman A, Fisher C, Hendry WF, Nicholls J, Dearnaley DP. Primary chemotherapy for stage II nonseminomatous germ cell tumors of the testis. *J Urol* 1994, **15**, 72–78.
7. McLeod DG, Weiss RB, Stablein DM, *et al.* Staging relationships and outcome in early stage testicular cancer: a report from the testicular cancer intergroup study. *J Urol* 1991, **145**, 1178–1183.
8. Pizzocaro G, Piva L, Salvioni R, *et al.* Adjuvant chemotherapy in resected stage II nonseminomatous germ cell tumors of the testis. In which cases is it necessary? *Eur Urol* 1984, **10**, 151–158.
9. Richie JP, Kantoff PW. Is adjuvant chemotherapy necessary for patients with stage B1 testicular cancer? *J Clin Oncol* 1991, **9**, 1393–1396.
10. Donohue JP, Thornhill JA, Foster RS, Rowland RG, Birhle R. Retroperitoneal lymphadenectomy for clinical stage A testis cancer (1965–1989): modifications of technique and impact on ejaculation. *J Urol* 1993, **149**, 237–243.
11. Donohue JP, Foster RS, Rowland RG, Birhle R, Jones J, Geier G. Nerve-sparing retroperitoneal lymphadenectomy with preservation of ejaculation. *J Urol* 1990, **144**, 287–292.
12. Javadpour N. Predictors of recurrence in stage II nonseminomatous testicular cancer after lymphadenectomy: implications for adjuvant chemotherapy. *J Urol* 1984, **135**, 629.
13. Vogelzang NJ, Fraley EE, Lange PH, Torkelson J, Levitt S, Kennedy BJ. Stage II nonseminomatous testicular cancer: a 10-year experience. *J Clin Oncol* 1983, **1**, 171–178.
14. Williams SD, Stablein DM, Einhorn LH, *et al.* Immediate adjuvant chemotherapy versus observation with treatment at relapse in pathological stage II testicular at relapse in pathological stage II testicular cancer. *N Engl J Med* 1987, **317**, 1433–1438.
15. Weissbach L, Hartlapp JH. Adjuvant chemotherapy of metastatic stage II nonseminomatous testis tumor. *J Urol* 1991, **146**, 1295–1298.
16. Motzer RJ, Sheinfeld J, Mazumdar M, *et al.* Etoposide and cisplatin adjuvant therapy for patients with pathologic stage II germ cell tumors. *J Clin Oncol* 1995, **13**, 2700–2704.
17. Culine S, Théodore C, Farhat F, Bekradda M, Terrier-Lacombe MJ, Droz JP. Cisplatin-based chemotherapy after retroperitoneal lymph node dissection in patients with pathological stage II nonseminomatous germ cell tumors. *J Surg Oncol* 1996, **61**, 195–198.
18. Culine S, Théodore C, Terrier-Lacombe MJ, Droz JP. Chemotherapy in stage II nonseminomatous germ cell tumors of the testis: the Institut Gustave Roussy experience. *Urol Oncol* 1996, **1**, 175–183.
19. Bosl GJ, Geller NL, Bajorin D, *et al.* A randomized trial of etoposide + cisplatin versus vinblastine + bleomycin + cisplatin + cyclophosphamide + dactinomycin in patients with good-prognosis germ cell tumors. *J Clin Oncol* 1988, **6**, 1231–1238.
20. Einhorn LH, Williams SD, Loehrer PJ, *et al.* Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. *J Clin Oncol* 1989, 7, 387–391.
21. Loehrer PJ, Johnson DH, Elson P, Einhorn LH, Trump D. Importance of bleomycin in favorable-prognosis disseminated germ cell tumors: an Eastern Cooperative Oncology Group trial. *J Clin Oncol* 1995, **13**, 470–476.
22. Bokemeyer C, Schmoll HJ. Treatment of testicular cancer and the development of secondary malignancies. *J Clin Oncol* 1995, **13**, 283–292.
23. Boshoff C, Begent RHJ, Oliver RTD. Secondary tumours following etoposide containing therapy for germ cell cancer. *Ann Oncol* 1995, **6**, 35–40.
24. Stephenson WT, Poirier SM, Rubin L, Einhorn LH. Evaluation of reproductive capacity in germ cell tumor patients following treatment with cisplatin, etoposide, and bleomycin. *J Clin Oncol* 1995, **13**, 2278–2280.
25. Baniel J, Foster RS, Rowland RG, Bihrle R, Donohue JP. Complications of post-chemotherapy retroperitoneal lymph node dissection. *J Urol* 1995, **153**, 976–980.
26. Steyerberg EW, Keiser HJ, Fossa SD, *et al.* Prediction of residual retroperitoneal mass histology after chemotherapy for metastatic nonseminomatous germ cell tumor: multivariate analysis of individual patient data from six study groups. *J Clin Oncol* 1995, **13**, 1177–1187.
27. Toner GC, Panicek DM, Heelan RT, *et al.* Adjunctive surgery after chemotherapy for nonseminomatous germ cell tumors: recommendations for patient selection. *J Clin Oncol* 1990, **8**, 1683–1694.
28. Donohue JP, Zachary JM, Maynard BR. Distribution of nodal metastases in nonseminomatous testis cancer. *J Urol* 1982, **128**, 315–320.
29. Wood DP, Herr HW, Heller G, *et al.* Distribution of retroperitoneal metastases after chemotherapy in patients with nonseminomatous germ cell tumors. *J Urol* 1992, **148**, 1812–1816.
30. Aprikian AG, Herr HW, Bajorin D, Bosl GJ. Resection of post-chemotherapy residual masses and limited retroperitoneal lymphadenectomy in patients with metastatic testicular nonseminomatous germ cell tumors. *Cancer* 1994, **74**, 1329–1334.
31. Baniel J, Roth BJ, Foster RS, Donohue JP. Cost and risk benefit in the management of clinical stage II nonseminomatous testicular tumors. *Cancer* 1995, 75, 2897–2903.