ALGORITHM FOR THE TREATMENT OF GERM-CELL TESTICULAR TUMOURS

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INTRODUCTION

The incidence of testicular tumours is not striking when defined as 2-3 in looooo. However, the affected group is the young men who had a long life expectancy with productivity before this disease and also current data indicate a steady increase in incidence (1, 2).

Nowadays, there is little problem in the diagnosis of a testicular tumour and the increasing sensitivity of scanning techniques offers a great accuracy in the staging of the diagnosed tumour. The application of immunohistochemical staining methods and determination of serum tumour markers greatly minimize error in histologic classification of testicular cancer. Hence, germ-cell tumours of the testis could finely be divided into seminoma and non-seminoma groups which in advance affect the modality of management.

Over 85 % of patients with testis cancer are expected to be cured of their disease and the 5-year survival rate is nearly 100 % in favorable or low volume disease (3). The success of management is still disturbed by two major problems one of which is the complications and morbidity due to the intensive treatment modalities and the other is the persistent poor prognosis of patients with bulky disease and/or very high serum tumour markers. So the beginning and a logical sequence of treatment modalities are of utmost importance for testicular tumours.

STAGING AND TUMOUR MARKERS

Since the basic staging procedure of Boden and Gibb who just defined three stages of disease as, I:Tumour confined to testis, II:Lymphatic involvement in the abdomen, and III:Lymphatic involvement above the diaphragm and/or extralymphatic metastases, more detailed staging classifications were made by several centres dealing with the particular subject (4). Two factors are known to affect the outcome of patients with testicular tumours. One is the volume of the disease and the other is the highness of serum tumour markers. The latter can always be determined with sensitive methods and added to final staging independantly. Then, the bulk of the disease needs to be delineated accurately. For this reason staging systems that finely defined the extent and volume of the disease are preferred in the assessment of the patients. In this regard, the Royal Marsden Hospital staging system for testis cancer gained wide acceptance in the field. We also use this classification in our department since 1985. The system has delicately been defined elsewhere and a brief definition is given in table I (5).

Seminomas are generally known to be negative in regard to production of the two outstanding tumour markers of testicular cancer, alpha fetoprotein (AFP) and beta subunit of human chorionic gonadotropin (B-HCG). This situation was disturbed by the gathering data that showed AFP and B-HCG producing seminoma. Today, it became clear that B-HCG production of seminomas in no way changes the outcome after treatments including radiotherapy, nevertheless AFP production by a seminoma causes it to be regarded in the non-seminoma group, treated and followed in such a way (6-9).

Tumour markers help to establish the stage and may sometimes indicate biochemical metastatic disease in the absence of computerized tomographic (CT) abnormalities, as in stage IM. One or both markers are raised in over 90 % of patients with advanced nonseminomatous disease (10). Investigations to find out a good marker for seminoma with the exception of placental alkaline phosphatase (PLAP) had been disappointing. PLAP can be used in the follow-up of some patients with seminoma although it is less reliable than AFP and B-HCG with high false positive and false negative results.

TREATMENT

Uro-oncologists do have a chance in the treatment of testicular tumours due to: 1.Germ cell origin and rapid growth rate of these tumours which render a great sensitivity to radiotherapy and chemotherapy as well, 2.The propensity of the tumours to differentiate into more benign counterparts either spontaneously or induced, 3.The predictable spread pattern of the disease, 4.Common production tumour markers, and 5.Occurrence in otherwise healthy young men (1).

The mainstay of the treatment of testicular cancer is a radical orchiectomy through a high inguinal incision. This surgery constitutes the beginning and sometimes the whole therapy for all histologic types of testis cancer. Scrotal surgery for testicular tumours should be condemned since it alters the predictable lymphatic spread pattern of the disease. On the other hand, it has been reported that the prognosis was not much changed solely due to scrotal violation (11, 12).

The management of testicular cancer is similar to other malignancies since the treatment consists of radiotherapy, chemotherapy and surgery applied in different sequences and combinations. The following algorithm for the treatment of testicular cancer reflects our experience in a twelve years period since 1978, during which 127 patients were diagnosed to have testis cancer. Among these 47 (37%) were seminomas.

THE MANAGEMENT OF SEMINOMA

Stage I : Is orchiectomy enough for the treatment of clinical stage I seminoma ? Collecting data indicated that the low metastatic potential of seminomas justifies the cessation of therapy after orchiectomy (13, 14). On the other hand, about 20% of patients with clinical stage I seminoma have retroperitoneal micrometastases undetectable during the initial evaluations and no satisfactory markers are available for a close follow-up. The safest method of sterilising all deposits in these patients is to give adjuvant radiotherapy (usually 30 Gy) to the retroperitoneal and ipsilateral pelvic nodes and the morbidity of irradiation in mentioned doses is almost negligible. Thus, the omission of radiotherapy for stage I seminoma is presently controversial and we believe that adjuvant radiotherapy should follow orchiectomy in clinical stage I seminoma patients.

Stage II : The classical treatment of seminoma metastatic to infradiaphragmatic lymph nodes was therapeutic retroperitoneal radiotherapy with or without prophylactic mediastinal irradiation. Radiotherapy can still be the choice of treatment for low volume disease of stage IIA, but its pre-eminent position in treatment is questioned for stage IIB and cancelled for stage IIC bulky disease. The discovery that metastatic seminoma is at least as sensitive to cis-platin based chemotherapies as nonseminoma currently justifies primary chemotherapy for at least in the latter two stages or for all stage II seminomas (13, 15).

Stage III and IV: Advanced seminomas have no alternative for treatment other than systemic chemotherapy. Adjuvant radiotherapy could well be used with or following chemotherapy and is shown to be successful in converting partial remissions to complete and rendered post-chemotherapy surgery unnecessary (16). Radiotherapy sandwiched between one full course of chemotherapy and two additional cycles are said to be effective to resolve all masses of bulky disease and resection of still persistent lesions almost always showed necrosis and fibrosis histologically. These two findings are on the behalf of omission of post-chemotherapy surgery in advanced seminoma but the subject is still enigmatic (17, 18).

THE MANAGEMENT OF NON-SEMINOMA

Stage I: The conventional management of clinical stage I nonseminomatous testicular tumours (NSTT) was to perform a retroperitoneal lymph node dissection (RPLND) and continue therapy or follow-up according to the histology of the resected specimen. The rather benign behaviour of seminomas do not hold for NSTT and these tumours are less radiosensitive. The high metastatic potential and early extralymphatic metastases warrant a more aggressive treatment schedule and remedy for extratesticular NSTT almost invariably is chemotherapy. Since low volume disease responds to chemotherapy very well then why not should we watchfully wait for clinical stage I disease and begin treatment as evidence of metastases first begin to appear? Indeed, this became popularized as "surveillance" policy in stage I disease since 1979 (19, 20). Up to now, reports about surveillance indicated 17-40 % of relapse and loo % survival rates in these patients. We had 21 patients in surveillance program. In a follow-up period of 2 to 27 months (median 9) we observed a relapse rate of 24 % in 2 to 17 months (median 4) after orchiectomy (21). The patients can be candidates for surveillance if the tumour markers are normal, thoraco-abdominal CT scans are negative for metastasis, if there is no tumour at the cut end of the spermatic cord after orchiectomy and if the patients have informed consent to a "watch and wait" protocol. These patients are followed monthly during the first, bimonthly during the second year and every three months thereafter with serum tumour markers, chest X-ray and abdominal ultrasonography (USG). In case of suspect in the two latter examinations the CT of the region is repeated. Relapse during surveillance necessitates chemotherapy. The results of chemotherapy are perfect in these patients as observed in our 4 (24 %) patients out of 21 who are in further follow-up for up to 43 months after chemotherapy (21).

The transection of sympathetic chain during a formal RPLND causes infertility because of retrograde ejaculation. Only a 40 % fertility rate could be obtained after RPLND with modified unilateral dissections perhaps compromising the effectivity of cancer surgery (22). The fertility rate after chemotherapy including post-chemotherapy surgery is about 50 to 60 % and no credit is given to the disease (23). So, surveillance and chemotherapy if needed is preferred to RPLND when fertility is considered in these young people who have clinical stage I testis cancer.

Stage II-IV: Performing aggressive surgeries for active disseminated disease is in no way justifiable today as once had been done for stage II nonseminomatous disease. Better survival rates for disease outside the testis are reported with primary chemotherapy instead of RPLND followed by adjuvant chemotherapy or irradiation. Surgery for these stages are reserved for debulking of persistent masses after chemotherpy when the disease is biochemically inactive i.e. when the tumour markers are normal.

Conventional amounts of chemotherapy are usually enough to resolve all evidence of low volume disease. However, the outcome is not similar for bulky disease and chemotherapy resistant residual masses are almost always encountered. Further courses of chemotherapy are generally ineffective in decreasing the size of these lesions but they are effective in reducing the rate of residual cancer in post-chemotherapy resected specimens which than appear as either mature teratoma or necrosis and fibrosis. The histologic evaluation of post-chemotherapy resected masses showed 3-35 % residual cancer, 27-52 % necrosis and fibrosis, and 38-45 % differentiated tumour (mature teratoma). Post-chemotherapy surgery is a part of our current treatment policy and we had 12 cases who underwent debulking surgery after sufficient courses of chemotherapy. The histology of the resected specimens showed 17 % residual cancer (2 of 12 patients), 23 % necrosis and fibrosis and 50 % mature teratoma. The patients who had residual cancer in their resected specimens were given adjuvant chemotherapy and fared well (18, 24-27).

There is no way of understanding the histology of post-chemotherapy residual masses with conventiona imaging techniques if they are not resected. It is clear that histology is very important if there is residual cancer in these lesions. It has also been shown teratomas following chemotherapy may show malignant transformation in advance. These two factors emphasize the need for post-chemotherapy surgery for NSTT (28).

Our current approach to the treatment of testicular tumours are summarized in figure 1.

CHEMOTHERAPY COMBINATIONS

The two most commonly used chemotherapy regimes for testis cancer are PVB (platinum, vinblastine and bleomycin) and BEP (bleomycin, etoposide and platinum) protocols. The PVB combination was first introduced by Einhorn and Donohue in 1977 and since then it has been widely used. The complete response rate to PVB regimen was about 60 % in the original series of these two authors (29). Inr. 1983 the most myelosuppressive agent of PVB combination was replaced with etoposide (VP 16-213) by Peckham. At present the BEP protocol is one of the best combinations for testis cancer chemotherapy (table II) (30). The complete response rates with BEP protocol vary between 80 to 90 percent.

Several different combinations were introduced for testis cancer chemotherapy. They all had cis-platinum in common with the exception of some protocols with ifosfamide. The seven drug alternating regime POMB/ACE was introduced by Newlands et al., and successful results were obtained for especially bulky advanced disease. Being careful about toxic side effects POMB/ACE chemotherapy may be preferred for poor prognostic tumors (31). We had 11 patients with bulky tumours and/or very high serum tumour markers who were treated with POMB/ACE protocol and the initial response to treatment was dramatic in all patients. There were 4 mortalities in this group but all cases were at least partially responsive to therapy (32).

All types of chemotherapy necessitate a careful monitorization and follow-up of patients in regard to their renal function, bone marrow reserve and pulmonary capacity. Complications of chemotherapy and preventive measures are summarized in table III (33).

The survival, better to say cure rates in testis cancer are about 90 % for seminoma and 80 % for nonseminoma including all stages. With these figures testis cancer seems to be one of the most curable malignancies. The correct timing and sequence of medical and surgical measures are at utmost importance and emphasize the necessity of a uro-oncologic discipline in the management of these patients instead of separate oncologic and urologic approaches.

Table I.
The Royal Marsden Hospital Staging system for testis cancer.

I: Disease confined to testis
IM: Rising serum tumour markers after orchiectomy with no evidence of metastatic lesions
II: Infradiaphragmatic lymphatic involvement
A:<2 cm.
B: 2-5 cm
C:>5 cm
III: Supradiphragmatic lymphatic involvement
IV: Extralymphatic disease
L_1: Lung metastasis <3 in number
L_2: Lung metastasis >3 in number <2 cm
L_3: Lung metastasis >3 in number and at least 1 lesion >2 cm.

Table II. The BEP chemotherapy protocol.

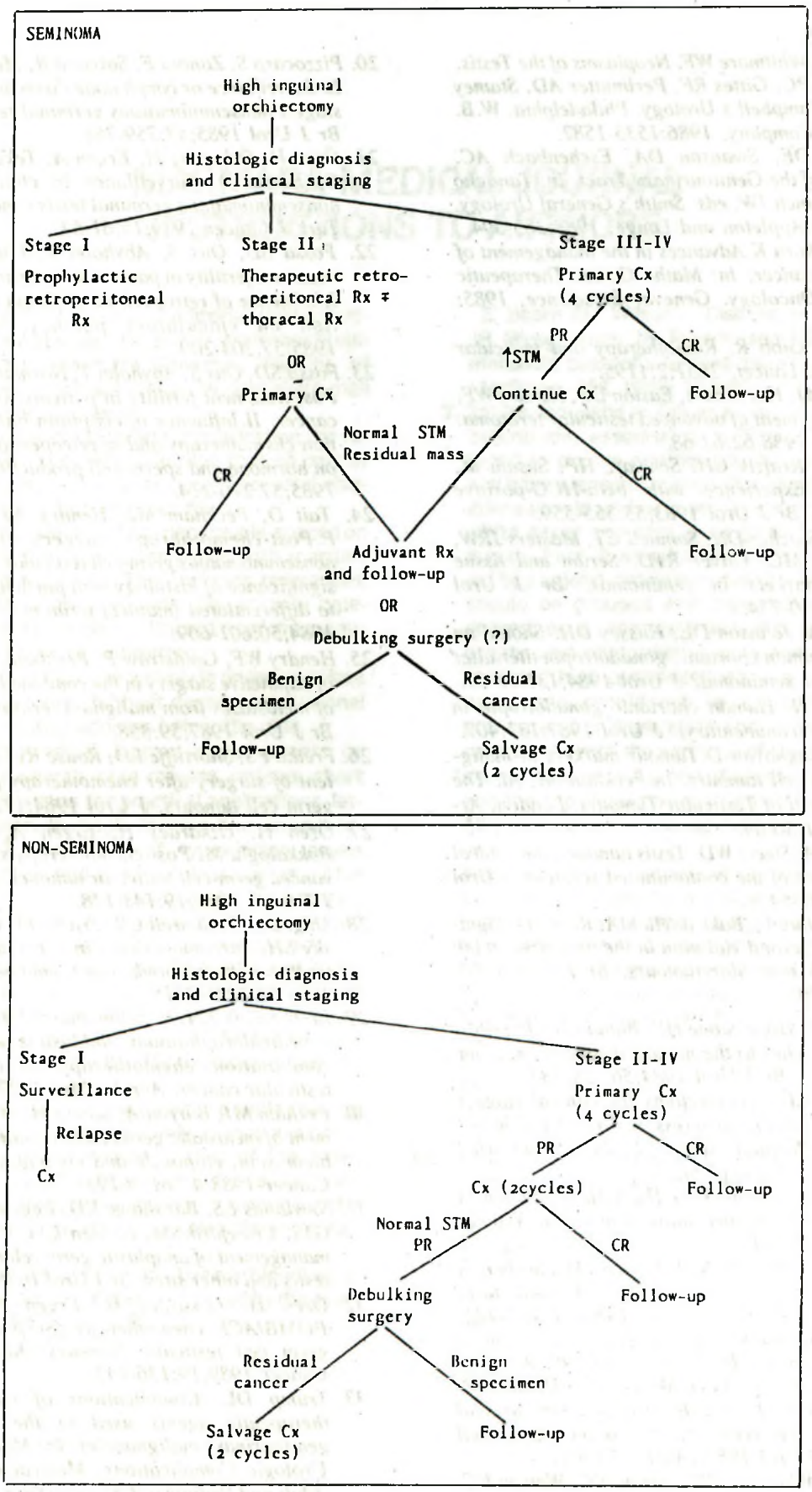
Bleomycin	30 mg	IV	Days 2,9,16
Etoposide (VP 16-213)	100-120 mg/m²	IV infusion	Days 1-3
Platinum	20 mg/m²	IV infusion	Days 1-5

Cycles are repeated every 3 weeks

Table III. The toxic side effects of testis cancer chemotherapy and preventive measures.

Agent	Prominent toxic side effects	Prevention
Cis-platinum	Nephropathy	Hydration and obtaining a good diuresis
	Hearing loss	
	Hypomagnesemia	IV magnesium supplementation
	Gonadal toxicity	
Vinblastine	Myelosuppression	Adjustment of dose and intervals
	Neuropathy	
	Gonadal toxicity	
Etoposide	Myelosuppression	Adjustment of dose and intervals
	Neuropathy	
	Diffuse myalgia	
Bleomycin	Skin pigmentation	—
	Interstitial pulmonary fibrosis	Do not exceed 200 mg/m² total dose
	Fatal pneumonia	
	Hyperpyrexia	Antihistaminics or cortisone
	Oral ulceration	—
Cyclophosphamide*	Myelosuppression	Dose adjustment or cessation of therapy
	Hemorrhagic cystitis	
	Gonadal toxicity	
Methotrexate*	Folate deficiency	Folinic acid rescue
Actinomycin-D*	Oral ulceration	—
Vincristine*	Neuropathy	Adjustment of dose

*Agents of POMB/ACE protocol



Rx=Radiotherapy Cx=Chemotherapy PR=Partial remission CR=Complete remission
STM=Serum tumour markers

Figure 1. Algorithm for the management of germ-cell testis cancer.

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