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Report on the International Workshop on Staging and Treatment of Testicular Cancer*

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THE SURVIVAL of patients with testicular cancer has dramatically improved in recent years. However many problems related to the staging and the treatment of this tumor are as yet unresolved. In order to seek new approaches, more than 30 experts in the various fields of pathology, urology, radiology, biology and medical oncology were invited from Europe and the U.S.A. to this international workshop in Lugano.

The meeting was introduced by three lecturers: Mostofi (Washington) presented a complete review of the data concerning the natural history of the disease, Golbey (New York) stressed the importance of tumor markers in the management of testicular cancer, while Rozencweig (Bruxelles) reviewed thoroughly the most important ongoing clinical trials in Europe and U.S.A.

Afterwards the participants met within four committees: pathology (chairman: Mostofi, Washington), radiotherapy (chairman: Peckham, London), staging and surgery (chairman: Pizzocaro, Milan), chemotherapy (chairman: Monfardini, Milan).

Finally an extensive general discussion (moderator: Brunner, Bern) allowed the achievement of a general agreement as regards the present management of patients with testicular cancer and the design of some proposed new clinical trials.

The results of the committee staging and surgery will be published extensively elsewhere.¶ Therefore this paper mainly summarizes the general achievements of the workshop and concentrates particularly on chemotherapy.

PATHOLOGY

Some general recommendations were forwarded by the pathologists. For the time being the WHO-classification should be regarded as the more detailed and therefore recommended. Biopsy for diagnosis of testicular tumors should be avoided, whereas fine needle biopsy is currently under investigation. However experience with fine needle biopsy in relationship to local recurrences, disturbances of lymphatics and increased risk of metastases is still extremely limited. Whenever possible special investigations like cell-kinetics, tissue cultures, immunoperoxidase should be performed.** At the meeting preliminary data concerning cell-kinetic and *in vitro* chemosensitivity of testicular tumors were presented by Pilotti and San Filippo (Milan). While no definite conclusions can be drawn from the preliminary comparative analysis between *in vitro* and *in vivo* responses, labeling indexes were found to be by embryonal carcinomas by far the highest among human neoplasias (range 13–70 %). Seminomas show generally lower values (range 3–27%) with highest values observed for the anaplastic type.

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¶G. Pizzocaro, J. C. Durand, W. Fuchs, C. E. Merrin, R. Musumeci, O. Schmucki, W. Vahlensick, W. F. Whitmore, V. L. Zvara: Staging and Surgery in Testicular Cancer, *Eur. Urol.* (in press).

**Detailed informations concerning standardization of procedures for handling testicular tumors can be requested to F. Cavalli with the mention "Report Pathology Committee, Workshop, Lugano."

STAGING AND SURGERY

This report is focused mainly on the following two topics: (a) a proposal for a clinically useful classification, (b) a re-evaluation of clinical staging procedures as compared to retroperitoneal lymph node dissection (RPLND).

There was a general agreement that both the TNM-system and the Boden and Gibb's classification are no longer appropriate for clinical purposes. However it was stressed that in most published series essential informations related to prognostic significance of pathologic parameters are lacking: e.g., extracapsular growth in N_+; size, number and exact location of N_+, invasion of retroperitoneal veins. A new working classification was proposed, which is presented in Table 1.

Data on clinical staging were extensively reviewed. Bipedal lymphangiography (LAG) is more accurate in diagnosing iliac than para-aortic lymph nodes metastases: this fact was once more underlined by the careful analysis presented by Vahlensick (Bonn) (Table 2). However para-aortic nodes are more crucial in the staging of testicular cancer, since normal lymphatic drainage from the testicle is to para-aortic nodes on the left, from the level of L 1 to L 2, and to para-caval nodes on the right, from L 1 to L 3. Those nodes can be better visualized by funicular LAG: an accuracy of 90% in seminomas and 86% in non-seminomatous testicular cancer was achieved by using simultaneously bipedal and funicular LAG (Musumeci, Milan). At Memorial–Sloan–Kettering, New York, they were recently able to improve the accuracy in detecting retroperitoneal nodes metastases from 59 to 86% in non seminomatous testicular tumors by adding tumor markers studies to bipedal LAG (Whitmore, New York).

Cavography, i.v. pyelography and sonography are considered complementary to LAG in the diagnosis of retroperitoneal lymph nodes involvement. They might be very useful in evaluating the resectability of the retroperitoneal metastases.

Computerized axial tomography (CT-scan) is very promising in increasing the accuracy of clinical staging. Fuchs (Bern) reported his experience in 124 cases: 68 patients had also LAG. The accuracy in detecting retroperitoneal metastases was 90% with CT-scan vs

Table 1. Proposal for staging

Stage I:	no evidence of metastatic spread
I A:	tumour confined to the testis and its appendages (category T1, T2 and T3 of the TNM classification);
I B:	tumour infiltrating the spermatic cord (category T4a), or a tumour arising in an undescended testis;
I C:	tumour infiltrating the scrotum (T4b) or arising after inguinal or scrotal surgery, or managed by transcrotal biopsy or orchiectomy;
I X:	the extension of the primary tumour cannot be assessed.
Stage II:	metastases to infradiaphragmatic nodes only
II A:	all metastatic nodes are $\leqslant 2$ cm;
II B:	at least one metastatic node is between 2 and 5 cm;
II C:	retroperitoneal metastasis larger than 5 cm;
II D:	palpable adominal mass or fixed inguinal nodes (N_3).
P.S.	Specify number and location of metastatic nodes in operated patients, specify extracapsular growth and invasion of veins.
Stage III:	mediastinal and supraclavicular node involvement; distant metastases
III A:	mediastinal and/or supraclavicular node involvement without any distant metastasis (N_4);
III B:	distant metastases only to the lung; 'minimal pulmonary disease': less than 5 nodules in each lung field no one >2 cm. 'advanced pulmonary disease': more than 5 nodules in each lung field or a nodule >2 cm or a pleural effusion.
P.S.	Specify the extent of concomitant lymph node disease.
III C:	any ematogenous spread outside the lung;
III 0:	persistent positive biologic markers after definite therapy and without any other evidence of disease.

Stage I and stages II A and B are considered "early stages"; stages II C and D as well as stage III represent 'advanced disease'.

Table 2. Conversion rate of lymphangiographic to pathologic findings of para-aortic and iliac nodes (Testicular Tumour Registry, Bonn)

Anatomical site of nodes	No. cases	Lymphography/pathology +/+	+/−	−/+	−/−	Accuracy (%)
Right para-aortic	204	48	26	22	108	76.5
Left para-aortic	209	50	28	19	112	77.5
Right iliac	188	2	20	5	161	86.7
Left iliac	191	7	18	4	162	88.5

70% with LAG; however, the false positive findings were only 10% by LAG vs 20% by CT-scan. LAG may fail to demonstrate large retroperitoneal nodes completely replaced by tumor, while CT-scan is able to visualize nodes larger than 1.5 cm, but it is unable to assess whether relatively small nodes are metastatic or not. Fuchs concluded that CT-scan should be done first and LAG only afterwards in patients on whom CT-scan was unable to detect definitely pathologic retroperitoneal nodes. Vahlensick (Bonn) reported 52 patients studied both by LAG and CT-scan and thereafter submitted to RPLND (Table 3). LAG

Table 3. Conversion rate of LAG and CT-scan to pathology in 52 testicular non seminoma (Testicular Tumor Registry, Bonn)

LAG and CT-scan		No. Cases	Pathologic findings positive	negative
LAG + and	CT-scan +	18	18	—
LAG + and	CT-scan −	9	6	3
LAG − and	CT-scan +	13	10	3
LAG − and	CT-scan −	12	5	7
Total		52	39	13

was able to detect 6/39 (15.4%) retroperitoneal metastases missed by CT-scan and this detected 10/39 missed by LAG (25.6%). The accuracy in detecting retroperitoneal lymph node metastases by these combined diagnostic tools was 87.2% (34/39 cases).

In conclusion, participants felt that by combining optimally CT-scan, funicular and pedal LAG and tumor markers, it may today be possible to detect nearly 90% of retroperitoneal metastases in non-seminomatous germ cell tumors. At this point the question arises, whether RPLND with its well known morbidity concerning ejaculatory disturbances is still justified in patients with clinical stage I. This point will be further discussed in the chapter dedicated to future trials. At the workshop it was agreed upon that RPLND can be restricted to ipsilateral nodes in patients with no evidence of disease at surgical exploration, because isolated controlateral metastases are quite exceptional.

RADIOTHERAPY

In recent years there was a somewhat different approach between some European countries and the U.S.A. as regards radiotherapy, specially in non-seminomatous testicular cancer. Nowadays, however, there is a tendency to a new uniformity in indications as a result of a better multimodality approach. In fact radiotherapy in early stages might impair the feasibility of a late intensive chemotherapy (Peckham, London).

Seminomas

Because of the high degree of radiosensitivity of these tumors, radiotherapy remains the treatment of choice. Combination chemotherapy with *cis*-platin (P), vinblastin (V) and bleomycin (B) was reported to be almost as active in seminomas as in non-seminomatous tumours in advanced disease (Einhorn, Indiana).

About 10–20% pure seminomas are reported to be anaplastic or to have positive serum HCG. These patients seem to bear a poor prognosis. As a rule, for the time being they should still be treated according to the stage of their disease, but more attention should be paid on their follow-up. In patients with clinical stage I 2500–3000 rad in 3 weeks to bilateral para-aortic and ipsilateral iliac nodes are sufficient to give a 90–100% cure rate. The inguinal nodes should be irradiated

only in category T_4 patients or in patients who had previously inguino-scrotal surgery.

In patients with clinical stage II the overall cure rate with radiotherapy alone approaches 80%. However it is often difficult to manage patients with bulky retroperitoneal disease (N_3). It is suggested, that these patients receive 2–3 courses of PVB-chemotherapy before radiotherapy in order to reduce the size of irradiated fields. Thereafter 3500–4000 rad should be given in 4 weeks to the retroperitoneal nodes and, later on, 2500–3000 rad to the mediastinum and neck. If the serum HCG remains positive after the completion of irradiation, further chemotherapy should be given. Furthermore, if a CR is not achieved by radiotherapy, retroperitoneal lymphadenectomy should be considered.

In patients with clinical stage III the approach remains similar as long as the disease affects only the lymphatics. In the presence of ematogenous spread, chemotherapy becomes the primary treatment: after 3–4 courses of PVB a consolidation with radiotherapy to the areas of major or residual disease may then be appropriate.

Non-seminomatous tumors

These tumors require larger doses of radiotherapy (4000–5000 rad in 5–6 weeks). In selected patients with clinical stage I (negative markers after orchidectomy, negative CT-scan and LAG) a 'wait and see' policy may be advocated. In stage II patients, radiotherapy alone allows an 80% long term survival in patients with retroperitoneal nodes not larger than 2 cm (Peckham, London; Van der Werf-Messing, Rotterdam). In these cases irradiation of the mediastinum and the supraclavicular regions seems unnecessary (Banfi, Milan). If the retroperitoneal nodes are larger than 2 cm, radiotherapy should probably be avoided, as it allows only a 35–40% 5 yr survival. Furthermore in most cases where lymphadenectomy was performed after radiotherapy, many of those nodes were still found to bear tumors cells (Hünig, Basel).

CHEMOTHERAPY

This section deals essentially with non-seminomatous tumors. At the workshop Einhorn (Indiana) and Golbey (New York) updated their results for PVB and VAB III–IV: with those combinations 60–70% of patients with advanced tumors achieved CR with a potential cure rate ranging from 45–60%. These data document the major advance achieved with the DDP-containing combinations in the treatment of testicular tumors. Similar results were presented by various European authors, who reported on several DDP-containing regimens (Table 4). At present it seems quite difficult to obtain better remission-rates with the design of new combinations. However the rate of drug-related deaths with current regimens varies from 3 to 5%. Most deaths occur because of septicemia in neutropenic patients. Initial results presented by Einhorn would indicate that a PVB-regimen with a lower dosage of vinblastine (0.3/kg instead of 0.4/kg) achieves a comparable CR-rate with less toxicity. Pinedo (Amsterdam) presented the recently activated study of the EORTC, in which patients are randomly allocated to the two different VLB-dosages within the PVB-regimen. At present two questions seem to be of outstanding importance in the field of chemotherapy: the first relates to salvage treatments, the second to maintenance chemotherapy.

Concerning the latter question, the only available randomized trial is that of the Swiss Group (Sonntag, Bern), comparing maintenance chemotherapy with VLB, MTX and CCNU to radiotherapy on initially involved sites. The results of this study after 2.5 yr of follow-up are not yet conclusive. The participants of the workshop felt that the value of maintenance chemotherapy should be ascertained with a randomized study. Before randomization, however, patients should be stratified according to prognostic factors such as histology, tumor markers and previous extent of disease. A first attempt in this direction is presented by the current EORTC trial (Pinedo, Amsterdam) in which patients are randomized between no treatment and maintenance chemotherapy with VLB and DDP.

As far as long term toxicity is concerned Golbey (New York) stressed once more the already reported increased risk of cardiopulmonary complications due to oxygen toxicity during anaesthesia for patients having received a maximal cumulative dose of BLM. The problem of the maximum tolerated dose of DDP is still open: however for the time being no relevant cumulative nephro- or ototoxicity have been noted by Monfardini (Milan) after 500 mg/m^2, by Cortes-Funes (Madrid) after 1200 mg/m^2 and by Pinedo (Amsterdam) after 1900/2000 mg/m^2 cumulative dose.

According to the present status of knowledge, optimal combination chemotherapy should permanently control the disease in about half of the cases. Therefore in the other half of the patients (PR after the first combination or in relapse after CR) salvage treatments are needed. In patients achieving only PR, salvage surgery should be carefuly evaluated before considering further chemotherapy.

The development of salvage combination chemotherapies depends heavily on new drugs. Since phase II studies are nowadays performed in very heavily pretreated patients, they are confronted with new methodological problems, which are only partially resolved (Rozencweig, Bruxelles). Recently among several new drugs, VP-16/213 and iphosphamide have been reported to be active in testicular cancer. Table 5 shows a summary of the preliminary available informations on VP-16, which seems to have a quite remarkable single agent activity. The differences in the reported results depend on patient selection and criteria of evaluation. As far as iphosphamide is concerned Schmoll (Hannover) reported 2 CR and 13 CR in 18 patients treated in monochemotherapy. However details on pretreatment were not available. VP-16 has been used in combination with ADM and DDP±BLM by Einhorn in 28 patients, whose disease could not be controlled by previous PVB. Ten patients achieved CR and 15 PR.

On the basis of these experiences participants felt that salvage combination after PVB should probably include new agents such as VP-16 and/or iphosphamide together with adriamycin and/or actinomycin-D. Since DDP is probably the most active single agent in the treatment of this disease, its use in a salvage chemotherapy should be considered, furthermore that there are suggestions of a possible synergism of DDP with some of the new drugs. First experiences with the combinations DDP/iphosphamide/VP-16 and DDP/ADM/

Table 4. Complete remission rate with CDDP including combinations in testicular germ tumors

Author	Treatment*	No. patients	CR rate (%)
Pinedo *et al.*	CDDP–VLB–BLM	40	60
Sonntag *et al.*	VLB–BLM + ADM–CDDP	62	60
Scheulen *et al.*	VLB–BLM + ADM–CDDP	71	53
Cortes-Funes *et al.*	CDDP–VLB–BLM	46†	58
Newland *et al.*	VCR–MTX–BLM–DDP→VP–16–ADM–CTX→VLB–HU–CHL	27	70
Monfardini *et al.*	CDDP–VLB–BLM	25	24
Klepp *et al.*	CDDP–VLB–BLM	50	48

*CDDP = *cis*-platinum; VLB = vinblastine; BLM = bleomycin; ADM = adriamycin; VCR = vincristine; MTX = methotrexate; HU = hydroxyurea; CHL = chlorambucil.

†Including 5 cases of ovarian germ cell tumors.

Table 5. VP-16 activity in testicular carcinomas

Author	No. patients	No. responses CR	PR > 50%	PR < 50%
Newlands *et al.*	24	3	8	2
Cavalli *et al.* (EORTC)	28	—	5	7
Einhorn *et al.*	2	—	2	—
Monfardini *et al.*	3	—	1	—

VP-16 were presented by Cavalli (Bellinzona).

ADJUVANT CHEMOTHERAPY

Approximately 50% of patients with positive nodes at RPLND will eventually relapse. A rational selection of patients to be treated with adjuvant chemotherapy should be based on an accurate analysis of the relapse free interval and survival after surgery alone according to the retroperitoneal extent of the disease. Unfortunately such information is only partially available. Therefore it may be speculated that about 50% of patients may not need postoperative chemotherapy at all and that those who relapse with 'minimal disease' during a close follow-up may be rescued with optimal modern chemotherapy. Interesting data were presented by Einhorn (Indiana). In his series relapse occurred in 4/57 patients with stage I after RPLND: all 4 patients achieved CR and are presently NED. Among 31 patients treated from 1973 to 1979 with adjuvant actinomycin-D there were 14 relapses: 13 were successfuly treated with PVB and are presently NED. Four patients out of 24 treated after 1977 with surgery alone for stage II relapsed and all achieved subsequently CR. Based on this data a randomized study similar to the one recently activated by the American Testicular Cancer Intergroup Study (adjuvant chemotherapy vs observation only and the same chemotherapy upon new evidence of disease) was judged to be mandatory. This study will probably end up with minimal differences in survival, but could certainly provide essential information on the relationship between extent of retroperitoneal disease and relapse free interval. Considering that usually a relapse occurs within 6–8 months after RPLND an adjuvant chemotherapy lasting 12–24 months is probably not justified. Adjuvant chemotherapy should probably be administered for a time equivalent to the one needed in advanced disease to achieve a CR, i.e., 3–4 months.

PROPOSALS FOR NEW STUDIES

A great deal of endeavour was devoted in order to design proposals for new studies, which could then be implemented by multilateral cooperation among centers represented at the workshop.

Concerning advanced stages, it was felt that the current EORTC-protocol with some minor modification could very well fit to the conclusions of the workshop. This protocol should particularly include a more sophisticated stratification and devise innovative salvage chemotherapies.* Concerning the other stages of non-seminomatous testicular cancer, the following recommendations were made:

1. Clinical stage I. For centers, which are able to perform optimal staging procedures, it is strongly recommended to perform a randomized trial between "wait and see' and lymphadenectomy. Since optimal staging procedures can probably allow an accuracy of 90% or more and considering that almost all recurrences after RPLND alone occur as distant metastases, this study could eventually prove that a loco-regional treatment (RPLND or radiotherapy) is not needed in these patients.
2. Patients with small retroperitoneal metastases (stage IIA). These patients do very well after radiotherapy or lymphadenectomy alone. Since the relapse rate lies between 20–30%, they should probably be treated by chemotherapy only upon recurrence. Surgery might be preferable to radiotherapy, mainly because it does not impair the bone marrow reserve and allows a pathological staging of the disease. For the time being the participants could not propose any new study.
3. For patients with retroperitoneal metastases between 2 and 5 cm (stage II B), there was an unanimous proposal for a randomized study after radical RPLND comparing 4 courses of PVB and observation, with PVB in case of recurrence.
4. Patients who have retroperitoneal metastases more than 5 cm in size or invasion of funicular or retroperitoneal veins or didn't have radical dissection (macroscopic tumor left) are considered advanced disease (stage III C) and should be treated accordingly.

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*A detailed description of the purposes of the proposed studies, criteria for eligibility and exclusion, parameters for stratification, study design, criteria of evaluation and rules for follow-up can be forwarded after request to F. Cavalli with the mention "Proposed studies, Workshop, Lugano."