PROGRESS IN THE MANAGEMENT OF TESTICULAR GERM CELL TUMORS

A MODEL OF CLINICAL INVESTIGATION

INTERNAL MEDICINE GRAND ROUNDS

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INTRODUCTION

Cancer is the second leading cause of death in adults in this country. The approach to this problem is multifaceted including basic research into the biology of cancer, early detection, prevention and improved therapy. In certain tumors, significant improvements in treatment have been the key to reduction in mortality rates. Therapeutic advances require clinical trials to demonstrate their effectiveness in comparison to existing modalities as well as to develope refinements that will result in less toxicity and a better quality of life. Only a small proportion of eligible cancer patients are entered into investigational protocols. This presents a particularly serious obstacle in cancers of relatively low frequency. A concerted effort is necessary for clinical investigators to develope imaginatively designed protocols, cooperate in multi-institutional studies and be committed to recruit a high proportion of eligible patients into the trials. No better model of high quality pure clinical investigation in oncology exists than that which has resulted in the reduction in deaths due to germ cell malignancies in males. There are less than 6000 new cases in the U.S. each year, yet, in 1970 this disease was the leading cause of cancer deaths in young adult males. Today it is not on the list. It is estimated that there will be 5900 new cases in 1990 and 350 cancer related deaths (Silverberg et al,1990). This success can be predominantly attributed to an international effort of a few medical centers and cooperative oncology groups. Some notable examples include the University of Indiana, the Memorial Sloan Kettering Cancer Center, the Royal Marsden Hospital, the M.D. Anderson Cancer Institute, the National Cancer Institute, the Norwegian Radium Hospital, the Dana Farber Cancer Institute, Istituto Nazionale Tumori, the Southeastern Cancer Study Group, the Southwest Oncology Group, the Eastern Cooperative Oncology Group, the European Organization for Research on Treatment of Cancer, the British Medical Research Council, the Australasian Germ Cell Trial Group, and the Testicular Cancer Intergroup.

This presentation is intended to illustrate the evolution of the advances that have been accomplished by these clinical investigators and to remind us that important headway can be made at the bedside as well as at the bench. For clarity of illustrating these points, a simplified terminology of pathological classification and staging systems has been used. These can be found in the appendix. For more detailed discussion of these systems, the reader is referred to Devita et al,1989.

THE PROBLEM

In the early 1970's, germ cell tumors of the testis were the leading cause of cancer deaths in young males ages 25-34. Perusal of table 1 demonstrates that in patients with pure seminoma, the major barrier to a favorable outcome was the presence of distant metastases. However, in patients with NSGCT, only those with disease confined to the testis could be expected to have a better than 50% chance of cure (Rubin, 1978). The differences between these two primary histologic types were basically explained by the greater radiosensitivity of seminoma. Therefore a greater number of seminoma patients with retroperitoneal lymph node metastases could be cured with radiation therapy.

Table 1

LONG TERM SURVIVAL PROBABILITY BY STAGE AND HISTOLOGY (1970)

STAGE	SEMINOMA % SURVIVAL	NON-SEMINOMA % SURVIVAL
IA	98	77
IIA	76	42
IIB,C	74	12
III	7	3

Chemotherapy for all cell types was ineffective. Complete remission rates (CR) were reported to be in the 10-20% range and less than half of those patients had a permanent eradication of their disease.

THE BREAKTHROUGH

In 1974, phase I clinical trials demonstrated significant single agent activity for one of the coordination compounds of platinum, Cis-diamminedichloroplatinum, in metastatic germ cell neoplasms (Higby et al,1974). Shortly thereafter, two groups reported remarkable response rates and survival outcomes in patients with germ cell tumors treated with combination chemotherapeutic regimens containing cis-platinum, many of whom had previously received other chemotherapeutic agents (Einhorn and Donohue,1977 and Cvitkovic et al,1976). The regimen described by investigators at the University of Indiana, cis-platinum, vinblastine and bleomycin (PVB), in part because of its simplicity, has subsequently become the gold standard against which further advances in this disease have been measured. The results of this phase II trial are shown in table 2. Thirty-three of 47 (70%) of the patients achieved a complete remission. A further 5 (11%) had such significant partial responses that resection of residual disease could be accomplished rendering a total of 81% free of recognizable disease (NED). Sixty-four percent of the original group survived 5 years or longer without

recurrence. This represents a curative outcome in these persons.

Table 2

PVB CHEMOTHERAPY 1977
UNIVERSITY OF INDIANA

RESULTS	% OF PATIENTS
Complete Response	70
NED After Surgery	11
5 Year Survival	64

These results prompted eight other single institutions or cooperative groups to carry out confirmatory phase II trials of PVB in patients with disseminated disease who had not previously received chemotherapy. The results of these studies in 550 patients indicated worldwide uniformity in the outcome of PVB therapy (Table 3). Nearly 70% of patients with metastatic NSGCT were cured (Einhorn,1981a, Levi et al,1988). The effects were so superior to prior experience that further trials to enhance overall benefit would not require no-treatment control arms.

Table 3

PVB THERAPY IN 550 PATIENTS
WITH METASTATIC NSGCT

Results	% of Patients
Complete Response	65
NED After Surgery	10
Long Term Survival	68

THE REFINEMENTS

It was clear from these studies of PVB therapy that a number of questions could be raised regarding the role and manipulation of chemotherapy in the treatment of testicular germ cell tumors. Experiences noted above demonstrated that relatively short followup time was necessary to indicate the cure rate in these patients. The germ cell tumors are rapidly growing malignancies and 75% of recurrences will occur within the first 2 years following chemotherapy and that a two year survival NED is nearly tantamount to an eventual curative outcome. There was life threatening, and sometimes fatal, toxicity of the original PVB regimen. Could the regimen be modified to reduce unwanted side effects without impairing the long term outcome? Obviously all patients were not cured by this treatment. Could poor risk patients be identified that might require other approaches to their management? Could even more effective regimens be developed? Could the failures be salvaged? What was

the role of chemotherapy in the management of earlier stages of disease? What is the role of post-chemotherapy surgical resection of residual disease and what patients should be selected for this procedure?

As indicated above, the number of patients with malignant testicular germ cell tumors is relatively small. Therefore, the ability to answer the preceding questions would require the firm belief in and commitment to clinical trials such that a sizable proportion of patients with these tumors be entered into studies. It is tempting to proceed with treatments that are so successful and proven that important refinements become difficult or impossible to document. Such was not the case in this situation.

HOW MUCH IS ENOUGH?

In the original PVB experience, the most life threatening toxicity was myelosuppression. Thirty-eight percent of the patients required hospitalization for neutropenic fever, 15% had documented gram negative sepsis and 2% died of this complication. It was judged that the vinblastine was the primary contributor to this complication. Therefore, a randomized phase III trial was carried out to evaluate a lower vinblastine dose in terms of toxicity and therapeutic outcome (Einhorn and Williams,1980). Subsequently, a larger study from the European cooperative group confirmed the findings (Stoter et al,1986). Results of the EORTC study are depicted in (table 4).

Table 4

RESULTS OF RANDOMIZED TRIAL OF PVB WITH HIGH AND LOW DOSE VINBLASTINE*

PARAMETER	% HIGH DOSE	% LOW DOSE	p VALUE
Complete Response	68	71	N.S.
Severe Neutropenia	29	14	0.007
Neutropenic Fever	34	18	0.036
Mucosal Toxicity	53	36	0.015
3 Year Survival	78	82	N.S.

* Stratified by tumor burden

Two of the patients in the full dose arm died of neutropenic sepsis. There was a significant reduction in myelotoxic complications without compromising the beneficial effects. This study also demonstrated a reduction in mucositis in the lower dose arm.

The original PVB regimen included 2 years of monthly vinblastine as maintenance therapy. The Southeastern Cancer Study Group (SECSG) performed a randomized trial comparing maintenance therapy versus none in patients achieving a CR with PVB. Table 5

shows that there was no significant difference in number of relapses or NED status in either arm, thus supporting the elimination of two years of unnecessary therapy for these patients (Einhorn et al,1981b). These results were subsequently confirmed (Levi et al,1988)

Table 5

MAINTENANCE THERAPY WITH VINBLASTINE AFTER ACHIEVING NED STATUS

ARM	RELAPSED (%)	PRESENTLY NED (%)
Maintenance	9	97
No Maintenance	7	95

ARE THERE BETTER REGIMENS?

Following confirmation of the clear beneficial effects of PVB, investigators began the search for regimens that might have an even superior impact upon survival, or, at least, might have equivalent activity while producing less toxicity. An epipodophylotoxin derivative, VP-16 (etoposide), was demonstrated in phase I trials to have single agent activity in refractory germ cell tumors second only to cis-platinum (Fitzharris et al,1981). A number of phase II trials demonstrated CR rates alone or after reductive surgery of 40-45% with approximately 20-25% long term survivals in patients refractory to or relapsed from PVB therapy utilizing regimens of cis-platinum + VP-16 (Pizzocaro et al,1985, Hainsworth et al,1985, Lederman et al,1983). In addition, a phase II trial in previously untreated patients with metastatic germ cell tumors utilizing VP-16 in lieu of vinblastine in the PVB regimen (PVpB or BEP) reported 37 long term complete remissions in 43 patients (86%) (Peckham et al,1983). These observations led the SECSG to carry out a randomized trial of PVB vs. BEP in previously untreated patients with disseminated germ cell tumors (Williams et al,1987a). This study was designed to compare the therapeutic effects and relative toxicity of these two regimens in patients who were not surgical candidates with NSGCT or radiation therapy candidates with seminoma. None had received prior chemotherapy. Patients were stratified according to extent of disease as defined by prognostic categories (see section on prognostic categories). Table 6 demonstrates response data. CR rates and percentage of patients NED after reductive surgery were not significantly different for either regimen in the group as a whole. However, in those patients with advanced disease by prognostic groupings, response was significantly superior for the BEP protocol. Overall survival for all patients showed a non-significant trend in favor of BEP. However, the superior response rate for BEP in patients with advanced disease translated to superior survival as well (Fig.1)

Myelotoxicity was severe and equivalent with both regimens with 59% of all patients having a granulocyte nadir below 500 per cmm. However, serious neuromuscular toxicity was significantly less with BEP (table 7).

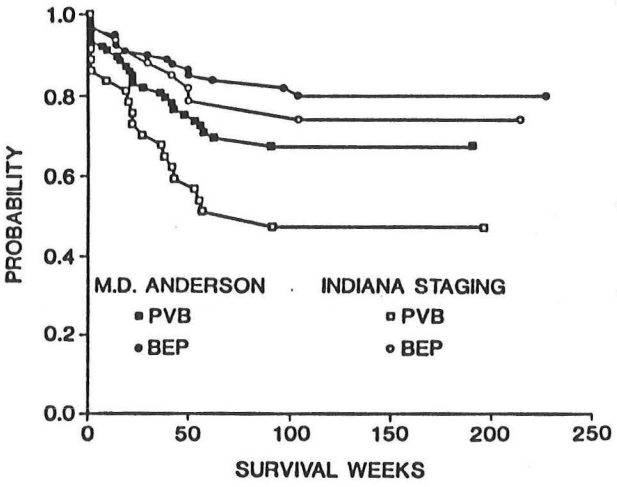
Table 6

RANDOMIZED TRIAL OF PVB VERSUS BEP IN DISSEMINATED GERM CELL TUMORS*

PARAMETER	% PVB	BEP	p Value
Complete Response	61	60	N.S.
NED After Surgery	12	23	N.S.
Recurrences	7	5	N.S.
NED Good Prognosis	96	95	N.S.
NED Poor Prognosis	61	77	<0.05
2 Year Survival	78	84	0.11

*Stratified by tumor burden

Figure 1



Survival of Patients with Advanced Disease According to Both Classification Systems for Extent of Disease.

P = 0.048 for BEP versus PVB according to the M.D. Anderson system; P = 0.017 for BEP versus PVB according to the Indiana University system.

Table 7

Neuromuscular Toxic Effects.

Toxic Effect	Treatment Group PVB (N = 114)	BEP (N = 110)	P Value (95% CI)*
	% of patients		
Paresthesias			
None	62	77	0.02 (4–28)
Mild	27	19	
Severe (interfering with activity)	11	4	
Raynaud's phenomenon			
None	95	94	
Mild	4	6	NS
Severe (requiring treatment or change in activity)	2	1	
Abdominal cramps			
None	80	95	0.0008 (8–25)
Mild	12	3	
Severe (requiring hospitalization or analgesics)	8	2	
Myalgias			
None	81	99	0.00002 (12–27)
Mild	5	1	
Severe (requiring analgesics)	14	0	

*CI denotes confidence intervals of reduction, and NS not significant.

4.7 % of the 258 patients died of drug related causes. This included deaths due to neutropenic sepsis and bleomycin induced pulmonary toxicity. It was concluded that BEP was an equal or superior regimen in terms of outcome and less toxic to the neuromuscular system.

WHO DOES POORLY?

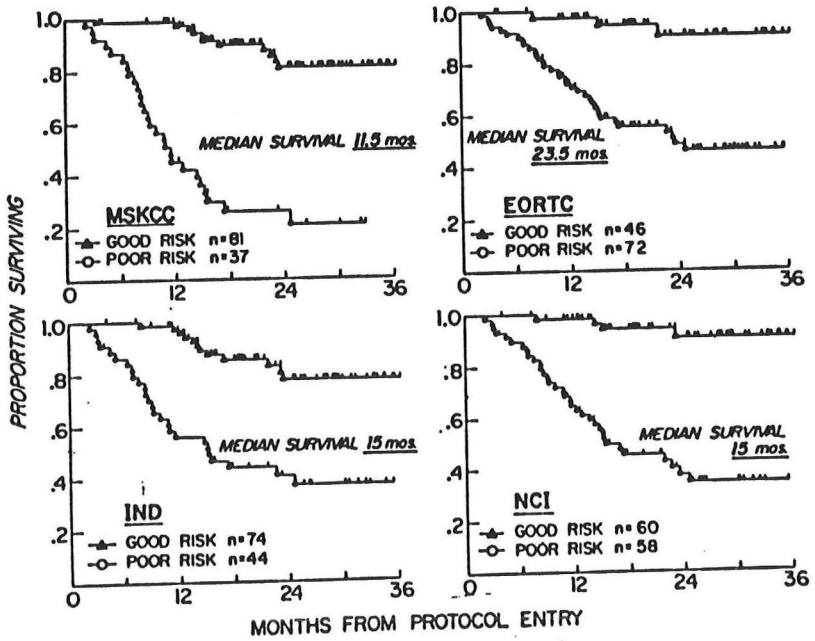
Although the majority of patients had a favorable outcome with the platinum based chemotherapy regimens, it was clear that a subset of patients either failed to become NED or relapsed and were refractory to salvage therapy. Likewise, it was clear that the toxicity of these treatment programs was not inconsiderable, and that perhaps some patients might do just as well utilizing less toxic protocols while reducing the adverse effects. With these goals in mind, a number of retrospective evaluations were carried out to determine whether pre-treatment prognostic factors could be identified which would permit the separation of patients into favorable and high risk categories in terms of response and survival (Bosl et al,1983, MRC,1985, Birch et al,1986 Stoter et al,1987a, Ozols et al,1988). A number of factors were found to be predictive of outcome (table 8).

Table 8

PROGNOSTIC FACTORS IN NSGCT

Size of RPLN Metastases	Size and Number of Lung Metastases
Size of Mediastinal Metastases	Liver Metastases
CNS Metastases	Bone Metastases
Total Number of Metastases	Obstructive Uropathy
Extragonadal Primary Tumor	Pure Choriocarcinoma
Serum Level of bHCG	Serum Level of AFP

Figure 2



Survival distributions by poor-risk criteria. Each graph includes the same 118 patients allocated to either good- or poor-risk groups by the various eligibility criteria. The log rank χ^2 comparing good- and poor-risk groups is 59.66 for MSKCC, 36.34 for NCI, 26.15 for IND, and 19.48 for EORTC.

These factors were evaluated by multivariate analyses and a number of staging systems were derived for patients with metastatic NSGCT. These were capable of predicting CR rates of 90% or better versus patients whose likelihood of CR was 50% or worse. In addition, there was a clear predictive value for survival outcome as well (fig 2). A comparative evaluation of some of these systems has been published (Bajorin et al,1988). These observations permitted the design of clinical trials directed more specifically at good and poor risk individuals.

WATCH AND WAIT OR CHEMOTHERAPY?

The development of highly effective chemotherapy for metastatic NSGCT permitted the consideration of another strategy in the treatment of some patients with this disease. Standard therapy for patients following initial inguinal orchiectomy who have no clinical evidence of distant or retroperitoneal metastases (stage IA) is retroperitoneal lymph node dissection (RPLND). Likewise, patients who have clinical evidence of non-bulky retroperitoneal metastases but no distant metastases (stage IIB) also traditionally underwent RPLND if the tumor was considered resectable (Vogelzang et al,1983). Of the latter group of patients as well as those found to have microscopic metastases (stage IIA), relapse rates were about 50%. Adjuvant chemotherapy prior to the cisplatin era was of little benefit in preventing these relapses. Since PVB or related regimens can cure over 90% of patients with low volume disease, then two potential approaches to patients following RPLND with apparently completely resected disease would be the traditional observation with treatment of recurrences if they develope or to give brief post-RPLND chemotherapy. Phase II trials suggested that the latter option was potentially viable (Pizzocaro and Monfardini,1984, Vugrin et al,1983). An International multi-institutional phase III trial was designed which included members from 9 cooperative groups and two individual institutions (the Testicular Cancer Intergroup Study) (Williams et al,1987b). Following apparently successful RPLND, patients were randomized to either observation or 2 cycles of cisplatin based combination chemotherapy. Followup exceeded 2 years with a median of 4 years. There were 195 evaluable patients. Results are summarized in table 9. Only 1 patient who received the adjuvant chemotherapy relapsed and died of testicular cancer. Although the expected approximately 50% of the observation group relapsed, only three subsequently died of testicular cancer and two of these were non-compliant with the salvage therapy. There were no predictive factors for relapse. Results with adjuvant therapy have been confirmed (Hartlapp et al,1988). Thus these two options are equivalent relative to survival and provide a greater than 95% chance of cure in stage II operable disease. No toxic deaths occurred with adjuvant or salvage chemotherapy. Non-compliance with the planned monthly followup was frequent. Salvage chemotherapy requires more courses and therefore more toxicity. On the other hand, approximately 50% of patients will receive "unnecessary chemotherapy" in the adjuvant approach. This presents an interesting enigma but a clear and equal choice of options that can be individualized (Lange and Fraley, 1988).

Table 9

RANDOMIZED TRIAL OF OBSERVATION VERSUS ADJUVANT CHEMOTHERAPY IN STAGE II NSGCT FOLLOWING RPLND*

	% OBSERVATION	ADJUVANT CT
Recurrence	49	6**
Death from All Causes	5	3
Death from Testicular Cancer	3	1

*Stratified by tumor extent
**5 of 6 relapses refused adjuvant chemotherapy

WATCH AND WAIT OR OPERATE?

The demonstrated ability to successfully treat recurrent or metastatic NSGCT provided the opportunity to evaluate an alternative to another standard approach in the treatment of certain patients. Following orchiectomy, if patients had no clinical evidence of retroperitoneal or distant spread **(clinical stage I)**, traditionally they were managed by radiation therapy to the retroperitoneum, RPLND or both. With radiation therapy alone, long term survival approximated 80%. In those undergoing RPLND, pathologic stage I patients had a cure rate of about 93% and pathologic stage II patients, about 45%. Following the advent of cis-platinum, RPLND became the treatment of choice for clinical stage I. Radiation therapy was accompanied by significant long term complications and chemotherapy tolerance and results were worse with prior radiotherapy. In the cis-platinum era, this approach has resulted in a curative outcome of 99% for pathologic stage I patients and approximately 94 % for pathologic stage II patients with the ability to salvage relapses with chemotherapy (Fung and Garnick,1988). The primary disadvantage of this approach was that the majority of patients undergoing RPLND became sterile due to retrograde ejaculation, as well as the morbidity of any abdominal surgical procedure. It is known that clinical staging results in an approximately 25-30% failure to demonstrate retroperitoneal metastases (Fung et al,1988). Nevertheless, with the ability to salvage such a large proportion of patients with chemotherapy, phase II trials were designed to test the alternate strategy of "watch and wait" or **surveillance** rather than RPLND in clinical stage I NSGCT. These required meticulous initial staging and equally painstaking followup to detect recurrences at the earliest possible stage. A number of procedures are involved in the initial staging and subsequent followup (table 10). Also lung tomogram, abdominal ultrasound, IVP and selected radionuclide scans have been used in some studies.

Table 10

MINIMUM REQUIREMENTS FOR SURVEILLANCE IN CLINICAL STAGE I NSGCT

STAGING (Post-Orchiectomy):

Normal Chest CT Scan
Normal Abdominal and Pelvic CT Scan
Normal Pedal Lymphangiogram
Normal Serum bHCG, AFP and LDH Levels
(Absence of Unfavorable Histopathologic Features)

FOLLOWUP (At least 1st year):

Monthly Physical Examination
Monthly Serum Marker Levels
Monthly Chest X-Ray
Monthly Abdominal X-Ray (While LAG Dye Remains)
Chest and Abdominal CT Scans Every 2-3 Months
Patient Compliance

Initial results were encouraging indicating only about 20% relapses and a high salvage rate (Fung and Garnick,1988, Sogani et al,1984).

Table 11

OUTCOME OF SURVEILLANCE TRIALS IN 471 PATIENTS WITH CLINICAL STAGE I NSGCT

TRIAL	RELAPSED	1ST YEAR	RENDERED NED	PRESENTLY NED
Pizzocaro, 1986	31	83	94	98
Hoskin, 1986	28	86	97	99
Gelderman, 1987	22	100	91	98
Sogani, 1988	25	-	88	97
Dunphy, 1988	30	89	-	-
Thompson, 1988	33	83	83	94
Combined	28	88	92	98

All values are expressed as percent

Nonetheless, the results needed to be at least equal to those using RPLND as standard first treatment.Particularly since nerve sparing RPLND techniques were developed that could be used in patients whose abdomen appeared normal at the time of surgery. This modified surgery retained normal ejaculatory function in 80-90% of the subjects (Lange et al,1983, Richie and Garnick,1985). Several such studies have become more mature (29-42 months median followup) and are summarized in table 11. (Sogani et al,1988, Dunphy et al,1988,

Thompson et al,1988, Hoskin et al,1986, Pizzocaro et al,1986, Gelderman et al,1987). Of note, relapse rates are higher than 20 %. The highest relapse rate was in the only series that did not employ staging lymphangiogram. The lowest relapse rate was in the series that used the most staging procedures. Over 10% of relapses occur after 1 year and a few have been seen up to 4 years. Nevertheless, the overall long term achievement of disease free status of 98% is comparable to the traditional results. The pattern of relapses is different than after RPLND where most of the recurrences are distant, predominantly in the lung and infrequently in the retroperitoneum. Relapse patterns with surveillance are shown in table 12.

Table 12

PATTERN OF RELAPSE WITH SURVEILLANCE IN CLINICAL STAGE I NSGCT

SITES OF RELAPSE*				
LUNG ONLY	RPLN ONLY	BOTH	MARKERS ONLY	OTHER
27	43	12	16	2

*Percent of 132 patients who relapsed

Over half of the patients relapse retroperitoneally, alone or with other sites. These are more difficult to detect and usually are of greater tumor burden than found with initial RPLND.

In order to better define the group who do not relapse and therefore receive the primary benefit of surveillance, these series evaluated prognostic factors that might predict for varying likelihoods of recurrence. The only consistent variable was the presence or absence of vascular and/or lymphatic invasion in the orchiectomy tumor specimen (table 13). There is a highly significant difference in these two relapse rates. A review of 259 patients from 10 surveillance studies in England also demonstrated histopathologic factors, by multivariate analysis, that permitted the development of a simple model that had high predictive value for relapse (Freedman et al,1987). Figure 3 shows the probability of remaining disease free using the algorithm.

Controversy remains regarding the relative value of immediate RPLND versus surveillance in clinical stage I NSGCT. A summary of the pros and cons is shown in table 14. It is clear however, that if this approach is to be used, staging must be extensive, followup frequent and meticulous, and probably ought to be reserved for patients whose histopathologic findings suggest a low probability of recurrence. (Also see addendum page 22)

Table 13

RELATIONSHIP OF VASCULAR AND/OR LYMPHATIC INVASION TO PROBABILITY OF RELAPSE IN 367 PATIENTS WITH CLINICAL STAGE I NSGCT TREATED BY SURVEILLANCE

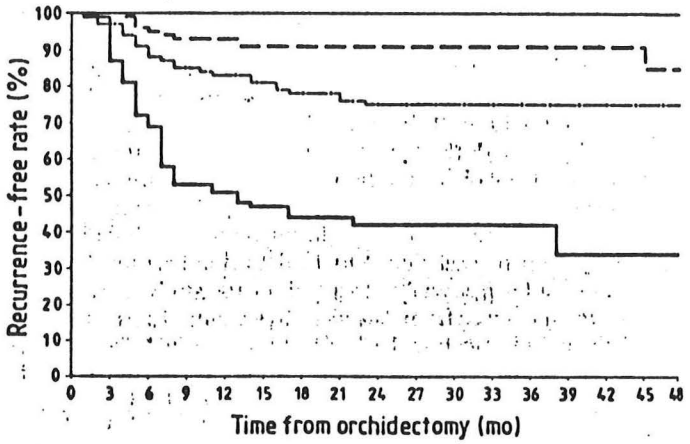
RELAPSED (%)		
Present	Absent	p Value
54	20	< 0.0001

Table 14

PROS AND CONS OF SURVEILLANCE IN CLINICAL STAGE I NSGCT

FOR	AGAINST
70% of patients will be saved an unnecessary operation	Relapses are commonly in RPLN
10-20% of pathologic stage I will relapse	Relapses may be of more advanced stage
Potential for loss of ejaculation with RPLND	Nerve sparing surgery now available
Long term NED results compare with outcome after RPLND	Patients are often non-compliant with followup
	Requires meticulous and costly staging and followup
	Requires precise pathologic study of testis for poor prognostic criteria
	Nearly 100% of patients treated with RPLND remain NED or are salvaged with CT

Figure 3



— Recurrence-free curves for 4 INDEX-S groups:
Group 1 (8 patients); — — — Group 2 (81 patients);
— Group 3 (89 patients); Group 4 (55 patients).

HOW MUCH IS ENOUGH? II

The initial PVB protocol employed four cycles of therapy at three week intervals. Subsequently, the prolonged maintenance therapy with vinblastine was demonstrated to be unnecessary. An ensuing controlled trial showed that an alternate regimen, BEP was at least as effective and significantly less toxic than PVB for the treatment of disseminated germ cell tumors. During the course of these studies as well as those from other investigators, it was demonstrated that a variety of pre-treatment factors could predict for the likelihood of a curative outcome. Both regimens were capable of achieving long term survival in well over 90% of patients with favorable prognostic characteristics. At this juncture, the SECSG initiated a

Table 15

COMPARISON OF THREE OR FOUR COURSES OF BEP IN FAVORABLE PROGNOSIS NSGCT

	%	
	3 COURSES	4 COURSES
Complete Response	75	77
NED After Surgery	23	20
Total NED	98	97
Relapsed	6	5
Long Term NED	93	97

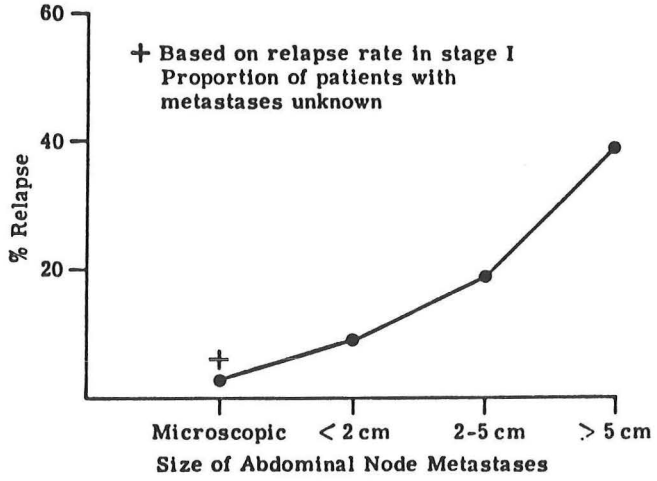
randomized comparative trial to determine whether reducing the number of cycles of treatment from 4 to 3 would

permit equivalent results in patients with favorable presentations. If so, the ultimate benefit would be reductions in toxicity and costs of treatment. The results are summarized in table 15 (Einhorn et al,1989).

WHAT ABOUT SEMINOMA?

Because of the radiosensitivity of seminoma, patients with clinical stage I or II pure seminoma have been traditionally treated with radiotherapy alone following orchiectomy (infradiaphragmatic with or without supradiaphragmatic fields). This results in a long term survival of at least 95% for stage I disease. Because of this approach, it is not clear how many of these patients have microscopic (IIa) metastases (Fung and Garnick,1988). The results of radiotherapy for patients with clinically recognizable retroperitoneal involvement (IIb,c) are in the range of a 75-85% cure rate (Mason and Kearsley,1988, Ball et al, 1982, Lederman et al,1989). Evaluation of the results of radiotherapy (RT) in these patients indicated that the probability of subsequent failure was related to the volume or bulk of the retroperitoneal masses (fig.4) (Ball et al,1982).

Figure 4



Relapse rate and size of infradiaphragmatic metastases in patients receiving radiotherapy for Stage I and II disease.

Several other investigators confirmed these observations (reviewed in Mason and Kearsley,1988, Lederman,1989). A summary of the relationship to survival is shown in table 16. Definition of "bulky" varies in different studies from >5cm., >10cm. to palpable mass, which probably explains the variation seen from one series to another.

Table 16

SURVIVAL IN STAGE II SEMINOMA TREATED WITH RADIOTHERAPY RELATED TO TUMOR VOLUME*

Long Term Survival (%)	
Small Volume	Large Volume
89 (80-100)	63 (33-75)

*Results in 405 patients from 9 collected series

Following the introduction of platinum-based chemotherapy, it was demonstrated that seminoma was generally as sensitive as NSGCT (reviewed in Loehrer et al,1987, Fossa et al,1987, Motzer et al,1988). A summary from several series is shown in table 17.

Table 17

OUTCOME OF TREATMENT OF METASTATIC SEMINOMA WITH PLATINUM-BASED CHEMOTHERAPY

% of Patients	
Rendered NED	Long Term Survival
87 (68-100)	81 (62-100)

291 patients from 10 series

The variation seen from one series to another in terms of response was explored by the SECSG Loehrer et al,1987). They found that both extent of disease (using the staging system developed for NSGCT) and the history and degree of prior RT were independent predictors of outcome by multivariate analysis. Extensive prior irradiation (abdominal and supradiaphragmatic) in advanced stage patients was a particularly poor subgroup. These relationships are illustrated in table 18. Toxicity was also enhanced in patients with prior irradiation. These observations have led to the suggested approach of utilizing chemotherapy as primary treatment of patients with bulky stage II (stage IIc) disease. This proposal is being tested in a randomized trial. Clearly, chemotherapy is the treatment of choice in disseminated (stage III) seminoma.

Table 18

PROGNOSTIC FACTORS FOR RESPONSE TO CHEMOTHERAPY OF METASTATIC SEMINOMA

	% Rendered NED
Overall	68
Minimal/Moderate Stage	84
Advanced Stage	52
No Prior RT	78
Prior RT	61
Prior Extensive RT	42
Advanced - No or Limited RT	62
Advanced - Extensive RT	25

WHAT DOES RESIDUAL DISEASE IMPLY?

Early on in chemotherapy clinical trials it was recognized that some patients had significant tumor regression but that residual masses in the lung and or retroperitoneum could be identified (Einhorn et al,1979). Surgical exploration with an attempt at resection of these lesions became a standard part of the management of the disease. Complete resection of residual masses permitted an additional group of patients to be rendered "disease free". Subsequently, in depth review of the findings and resultant course of these surgically managed patients was carried out by a number of investigators. These studies permitted the further refinement of the indications for, and consequences of, resection of residual disease. It is presently recognized that the significance of residual masses in NSGCT and seminoma is disparate and their management differs.

NSGCT: 20-25% of patients will have residual masses after chemotherapy (Nichols et al,1987). If the patient remains seropositive for AFP or βHCG, residual malignancy is invariably found and attempts at resection are usually unsuccessful and provide no benefit (Einhorn et al,1981a, Vugrin et al,1981, Brenner et al,1982). These patients are now treated with additional chemotherapy without surgical exploration. The findings and eventual outcome in patients who are seronegative at the time of evaluation for surgery are illustrated in table 19. The finding of fibrosis, inflammation or granulomas has the same significance as if the patient had obtained a complete remission with chemotherapy alone. The discovery of teratoma is accompanied by a significant chance of subsequent recurrence with either more teratoma or frank malignancy, sometimes very late, and indicates the need for prolonged careful followup. (Loehrer et al,1986). The observation of residual malignancy predicts a more ominous course, but a reasonable proportion can be salvaged with further chemotherapy, particularly when all of the recognizable disease can be resected (Bosl et al,1986, Nichols et al,1987). Some investigators have suggested that the histology of the testicular tumor, degree of

response and size of the residual mass can serve as predictors of the findings at exploration and could permit the avoidance of surgery for a subset of these "partial responders" (Donohue et al,1987, Dexeus et al,1989).

Table 19

FINDINGS AND OUTCOME OF POST-CHEMOTHERAPY CYTOREDUCTIVE SURGERY IN SERONEGATIVE PATIENTS WITH NONSEMINOMATOUS GERM CELL TUMOR

Pathology	Frequency	Percent of Patients Recurrence	Long Term*
Fibrosis, necrosis	37	5	98
Teratoma	38	39	84
Malignancy	25	54 **	56
Completely resected		37	66
Partially resected		78	44

* Percent of patients NED with that pathology
** Following post-surgery chemotherapy

Seminoma: The significance of residual masses after chemotherapy for seminoma appears to be different (table 20).

Table 20

EVALUATION OF RESIDUAL MASS FOLLOWING CHEMOTHERAPY FOR SEMINOMA

	Number of Patients (%) Combined Series		Motzer et al		Other Series	
No. Patients	164		41		123	
Residual Masses	102	(62)	23	(56)	79	(64)
Resected	41		19		22	
Viable Tumor	6	(15)	5	(26)	1	(5)
Observed*	59		4		55	
Relapsed**	9	(15)	1	(25)	8	(15)

* Approximately 1/3 received post-chemotherapy radiotherapy
** Relapsed in site of residual masses

One-half to two-thirds of patients will have residual abnormalities identifiable by radiologic studies. Results from six published series indicate that fewer will have viable malignancy when

surgically explored than with NSGCT (Jain et al,1984, Friedman et al,1985, Peckham et al,1985, Srougi et al,1985, Motzer et al,1987, Schultz et al,1989), particularly when one series is excluded (Motzer et al,1987). In that series, the higher incidence of viable tumor was seen only in patients with residual masses $\geq$3 cm. This frequency or relationship was not confirmed in any of the other series. Dense fibrosis is often found and surgical removal is difficult or impossible. Post-operative deaths have occurred (Friedman et al,1985). The relapse rate in sites of residual disease is low and most patients can be salvaged with additional therapy. Post-chemotherapy irradiation does not appear to reduce the relapse rate (Peckham et al,1985). Most investigators now recommend only close followup after complete or partial responses to chemotherapy for seminoma.

HOW MUCH IS ENOUGH ? III

A significant problem with the initial platinum based combination chemotherapy programs was the frequency and degree of acute toxicity. These included myelosuppression and sepsis, thrombocytopenia, mucositis, and neuromuscular problems. Pulmonary toxicity related to bleomycin was also a frequent problem, at times fatal and also potentially associated with mortality in patients subsequently undergoing reductive surgery (Williams et al, 1987a, Goldinger and Scheweizer,1979). When it was recognized that patients could be separated into good and poor prognosis subgroups, trials were initiated to determine whether less toxic modifications of these regimens could be employed without loss of effectiveness. Reductions in vinblastine dose, replacement of vinblastine with etoposide and reduction of total cycles have been discussed above. Additional randomized trials have been completed or are ongoing in patients with good prognosis presentations (table 21).

Table 21

PHASE III CLINICAL TRIALS IN GOOD PROGNOSIS PATIENTS WITH DISSEMINATED GERM CELL TUMORS

Investigators	Study
SECSG	BEP 3 vs 4 Cycles
MSK and Others	VAB-6 vs PE
EORTC	BEP vs PE
ECOG	BEP vs PE
Australasian	PVB vs PV
MSK and Others	E plus Platinum or Carboplatinum

One trial carried out by four institutions has been published. This compared VAB-6 (which includes bleomycin) to the two drug regimen of platinum and etoposide (Table 22).

Table 22

COMPARISON OF VAB-6 AND PLATINUM-ETOPOSIDE IN GOOD RISK PATIENTS WITH METASTATIC GERM CELL TUMORS

	%	
	VAB-6	PE
Complete Remission	65	74
NED After Surgery	31	19
Total NED	96	93
Relapse	11	12
Surviving*	94	88

* Median followup 2 years

Outcome was not different and reduction in vomiting, mucositis, thrombocytopenia, neutropenia and pulmonary toxicity were appreciated with the two drug regimen (Bosl et al,1988a). Preliminary results of trials comparing PV±B (Levi et al,1986) and EP±B (Stoter et al,1987b) indicate similar findings.

WHAT ABOUT FAILURES AND POOR RISK PATIENTS ?

It was soon apparent, after initial trials with cis-platinum based chemotherapy, that some patients did not achieve NED status with treatment, including reductive surgery. Others did so but relapsed and often could not be "salvaged" with standard regimens.

Table 23.

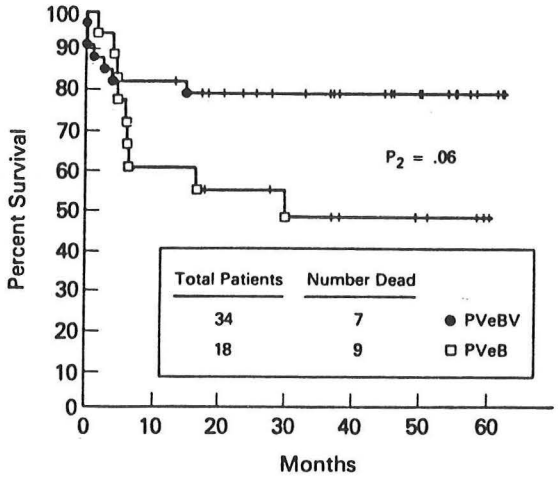
CLINICAL TRIALS OF SALVAGE THERAPY OR INITIAL THERAPY IN POOR RISK PATIENTS

INVESTIGATORS	PHASE	PATIENTS	STUDY	AUTHORS
SECSG	III	UNTREATED	PVB VS BEP	WILLIAMS ET AL, 1987A
MSK	II	POOR RISK	VAB-6 ALT BEP	BOSL ET AL, 1988B
MSK	II	POOR RISK	EBC	BOSL ET AL, 1988B
NCI	III	POOR RISK	PVB VS BEPV	OZOLS ET AL, 1988
INDIANA	II	SALVAGE	VIP OR EIP	LOEHRER ET AL, 1988
AUSTRALASIAN	II	SALVAGE	EAM	LEVI ET AL, 1990
INDIANA	I	SALVAGE	EC + ABMT	NICHOLS ET AL, 1988
ECOG	III	POOR RISK	EIP VS BEP	ONGOING
SWOG, SECSG	III	POOR RISK	BEP (HI VS LO P)	ONGOING
ECOG	II	SALVAGE	EC + ABMT	ONGOING

A: ACTINOMYCIN; B: BLEOMYCIN; C: CARBOPLATIN; E: ETOPOSIDE I: IFOSFAMIDE; M: METHOTREXATE
P: CIS-PLATINUM; V: VINBLASTINE; ABMT: AUTOLOGOUS BONE MARROW TRANSPLANT

As noted, pre-treatment prognostic factors were demonstrated to be helpful in predicting which patients had a significant probability of having these unfavorable outcomes. Approaches to dealing with these failures often overlapped. When better regimens were devised, they were applied to these patients. Likewise, when successful regimens were developed that salvaged relapses, they were then prospectively studied as "first line" therapy in poor prognosis patients. Some of the most pertinent studies, both completed and ongoing are summarized in table 23. One phase III trial in previously untreated poor risk patients demonstrated a possibly better outcome for the experimental regimen (Ozols et al,1988b) (Fig. 5). This compared standard PVB to a regimen in which etoposide was added and the platinum dose was doubled. However, myelotoxicity was significantly worse as was hearing loss. This has led to a phase III prospective trial by SWOG and SECSG to study high dose platinum in BEP in poor risk patients.

Figure 5



Survival of high-risk germ-cell cancer patients treated with PVeBV or PVeB.

Two recently described salvage regimens are of interest. One employed a new alkylating agent, ifosfamide, in combination with platinum and either vinblastine or etoposide, depending upon whether the patients had failed PVB or BEP (Loehrer et al,1988). These patients had previously been heavily treated with cis-platinum, but nevertheless there was a reasonable long term salvage rate (table 24). This prompted a phase III comparative trial by ECOG comparing BEP to EIP in poor risk patients. A second salvage regimen in PVB failures using a three drug regimen is of note because platinum was not included (Levi et al,1990). A remarkable long term salvage rate was found (Table 24). This cannot be directly compared to the ifosfamide program since none of the patients had previously received etoposide.

Table 24.

SALVAGE REGIMENS IN PATIENTS WHO HAVE FAILED STANDARD CHEMOTHERAPY FOR GERM CELL TUMORS

	%	
	VIP/EIP*	EAM*
Complete Response	22	14
NED After Surgery	14	15
Total NED	36	29
Relapsed	55	0
Long Term NED	16	29

VIP/EIP 58 patients; EAM 51 patients
* See legend table 23

Finally, a phase I trial employing etoposide and high dose carboplatinum (a cis-platinum analog with minimal renal toxicity but more myelotoxicity) followed by autologous bone marrow infusion has been reported. Six of 15 patients (40%) who had failed standard chemotherapy achieved NED status (Nichols et al,1988). This regimen has been adopted for a phase II salvage therapy trial by ECOG.

HOW ARE THEY NOW ?

Most of the trials discussed have had median followup times in the 2-3 year range. Two questions that have recently been addressed are the status of patients several years later in terms of relapse and survival and whether significant long-term adverse effects of the chemotherapy exist.

Long-term survival. A series of 239 consecutive patients with *disseminated* germ cell tumors treated at a single institution between 1974 and 1980, with a minimum followup of 6 years, has been reported (Roth et al,1988). 30% died of their tumor or toxicity of the treatment. 15% of CR's relapsed, 4% after 2 years. The long term NED was therefore 70%. Of the survivors, 95% returned to their pre-morbid functional status, 88% were fully employed and only 4% were unemployed for health reasons (not apparently related to their disease or treatment). The 12 year probability of survival (including patients dying of other causes) is 65%.

Long-term complications. Two recent series have carefully attempted to document long term complications of the disease or treatment (Roth et al,1988, Boyer et al,1990).

Fertility. This represents the most bothersome problem in these patients. There are three mechanisms contributing to infertility: pre-treatment azoospermia (75-80%), extended RPLND (retrograde ejaculation due to sympathetic plexus injury) and chemotherapy (injury to germinal epithelium). A greater proportion of patients treated with chemotherapy alone recover fertility than those also

treated with RPLND. One-third of the large series have fathered children, but the number trying is unknown (Roth et al,1988). In another study, 55% of those attempting to do so were successful (Rieker et al,1990).

Vascular effects. 25-50% of patients treated with platinum based regimens including bleomycin and vinblastine have *Raynaud's phenomenon.* This is generally mild and not disabling. Less than 5% of patients in these two series have had *symptomatic coronary heart disease.* Most had known risk factors but half had mediastinal radiation.

Neurologic problems. Non-disabling *distal parasthesias* were noted by 30-40%, but nerve conduction studies were abnormal in 50%. *Ototoxicity* manifest by high frequency hearing loss was found in 87%, but only one patient noted the problem.

Second malignancies. These have been rare and there is no clear evidence that there is an increased frequency.

Renal function. 40-50% of patients have a mildly decreased creatinine clearance which is stable and clinically insignificant.

These observations translate into the fact that in 1990 it is estimated that 94% of patients with germ cell tumors can be expected to be cured of their disease and return to a functional life and that an increasing number may be capable of fathering healthy children (Silverberg et al,1990) (Table 25).

Table 25

ESTIMATED LONG TERM SURVIVAL PROBABILITY BY STAGE AND HISTOLOGY (1990)

STAGE	SEMINOMA % SURVIVAL	NON-SEMINOMA % SURVIVAL
IA	99	98
IIA	98	98
IIB,C	90	90
III	80	70

ADDENDUM

MORE ON SURVEILLANCE

Since preparation of this protocol, a prospective study investigating the option of surveillance in "good risk" clinical stage I NSGCT and adjuvant chemotherapy in "poor risk" patients has been published (Pont et al, 1990). The study was small. Poor

risk was defined as pathologic evidence of blood vessel invasion in the orchiectomy specimen. Lymphangiography was not used in staging. Chemotherapy was two cycles of BEP. Median followup is 30 months. There was only one tumor related death (Table 26).

Table 26

RESULTS OF RISK-ADAPTED THERAPY OF CLINICAL STAGE I NSGCT*

	No. (%) Relapsed	NED
Good Risk (Surveillance)	1 (5)	22 (100)
Poor Risk (Chemotherapy)	2 (11)	17 (94)

* 22 good risk and 18 poor risk patients

Appendix

PATHOLOGIC CLASSIFICATION TERMINOLOGY USED IN THIS PROTOCOL

Seminoma	Pure with negative AFP βHCG may be elevated
Non-Seminoma	
Embryonal Carcinoma Teratoma Yolk Sac Tumor Choriocarcinoma	Pure tumors or admixtures of any combination (including seminoma)

(See DeVita et al, 1989)

STAGING TERMINOLOGY USED IN THIS PROTOCOL

STAGE	DEFINITION
I	Tumor confined to the testis (Ia = clinical)
II	Metastases confined to retroperitoneal lymoh nodes
a	Microscopic and $\leq$ 5 lymph nodes involved
b	Clinically demonstrable $\leq$ 5 cm or > 5 lymph nodes
c	> 5 cm
III	Metastases to other sites

CRITERIA FOR ASSIGNING RISK GROUPS IN GERM CELL TUMORS

MSKCC "poor-risk disease"

1. All patients with NSGCT of extragonadal origin.
2. Testicular NSGCT with probability of CR <0.5 calculated by: prob CR = $\exp^k/(1 + \exp/h)$, where h = 8.514 − 1.973 log (LDH + 1) − 0.530 log (HCG + 1) − 1.111 TOTMET, and TOTMET = 0, 1, or 2 depending on whether there are 0, 1, or 2 or more sites of metastases.

IND: "advanced disease"

1. Advanced pulmonary metastases.
   (A) Mediastinal mass >50% of intrathoracic diameter;
   (B) >10 pulmonary metastases/lung field;
   (C) pulmonary metastases with largest >3 cm (± non-palpable RP disease, ± cervical nodes).
2. Palpable abdominal mass plus pulmonary metastases.
3. Hepatic, osseous, or CNS metastases.

NCI: "poor-prognosis testicular cancer"

1. Advanced abdominal disease.
   (A) Palpable abdominal disease, or disease >10 cm by CTT;
   (B) obstructive uropathy;
   (C) hepatic involvement.
2. CNS involvement.
3. Advanced lung disease.
   (A) Pulmonary or mediastinal mass >5.0 cm;
   (B) >5 metastases per lung field;
   (C) pleural effusion.
4. Extragonadal primary.
5. Stage III disease with AFP >2,000 ng/mL, or HCG >10,000 mIU/mL.

EORTC: high-volume metastases

1. RP lymph node metastases >5 cm.
2. Lung metastases >2 cm.
3. B-HCG >10,000 ng/mL.
4. AFP >1,000 ng/mL.
5. Liver, osseous, or CNS metastases.

Abbreviations: exp, exponential; TOTMET, total number of sites of metastases; RP, retroperitoneal.

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