OCTOBER 30, 1980

MEDICAL GRAND ROUNDS

TESTICULAR GERM CELL TUMORS

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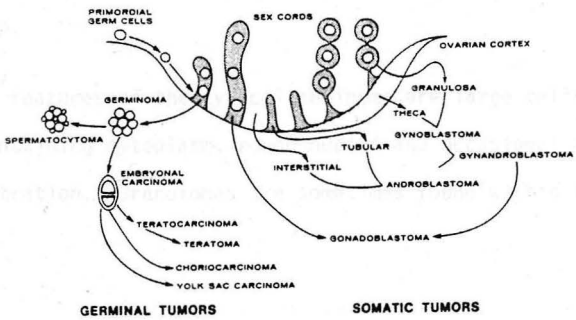
INTRODUCTION

Although accounting for only 1% of all tumors, testicular tumors are the most common neoplasm in men between ages of 25 and 35. Each of the available forms of treatment: surgery, radiation therapy and multi-agent chemotherapy is curative in some clinical settings. The overall cure rate for these tumors in all clinical settings is now near 90%. The ability of the clinician to offer such highly effective treatment is the result of developments in recent years leading to: 1. Clarification of histologic classification and clinical staging, 2. Sensitive assays for the tumor markers beta HCG and alpha fetoprotein, and 3. Increased effectiveness of chemotherapy with the use of combinations including Vinblastine, Bleomycin and Cis-Diaminedichloroplatinum. This review will discuss these developments and their integration into the management of patients with testicular tumors.

HISTOPATHOLOGY

The most widely used classification system is that of Mostofi and Price based on the work of Friedman and Moore. This system relates tumors arising in the testis to embryologic tissues.



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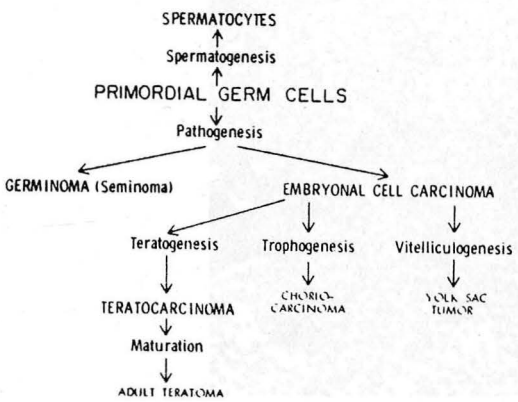

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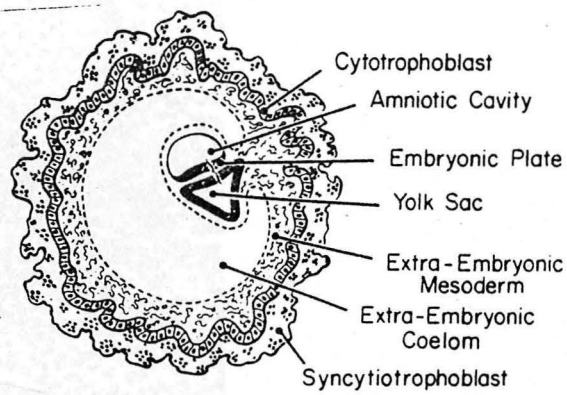

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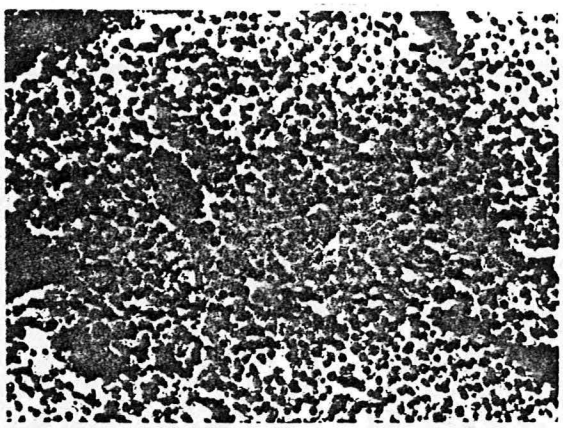
The somatic cell tumors such as the rare Sertoli cell tumor or lymphomas which may occasionally arise in the testis will not be discussed in this review. The classification used by the British Testicular Tumor Panel is based on a different concept of histogenesis that has categories which do not coincide precisely with those of the Friedmore-Moore classification.

The major categories of the germ cell tumors are seminoma, embryonal carcinoma, teratocarcinoma, choriocarcinoma, and tumors of more than one histologic type.

The seminomas account for approximately 1/3 of the total number of these tumors. Seminomas are subclassified into three groups: typical seminoma, spermatocytic seminoma and anaplastic seminoma. About 90% of the cases are in the first group.

The histologic features of the typical seminoma are large cells, clear glycogen containing cytoplasm, round nuclei and occasional areas of lymphocytic infiltration. Granulomas are sometimes found within these tumors.



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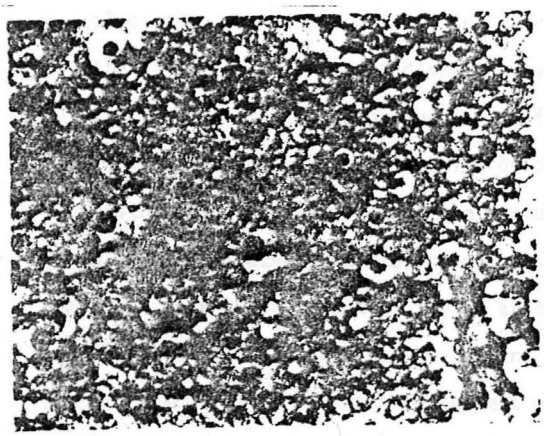
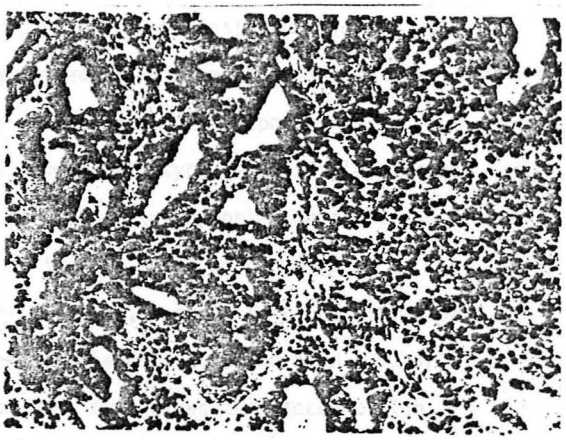
The anaplastic seminomas are characterized by a higher mitotic rate but their clinical course is probably not significantly different from typical seminoma when considering tumors of equivalent stage. The spermatocytic seminoma is a tumor that occurs in older age groups and has very little potential for metastatic growth.

The seminomas have somewhat less potential for hematogenous metastases and have greater sensitivity to radiation therapy than the non-seminomatous tumors. These tumors do not produce alpha fetoprotein. About 5% of seminomas contain syncytiotrophoblastic giant cells which may produce HCG. The significance of this finding will be discussed later.

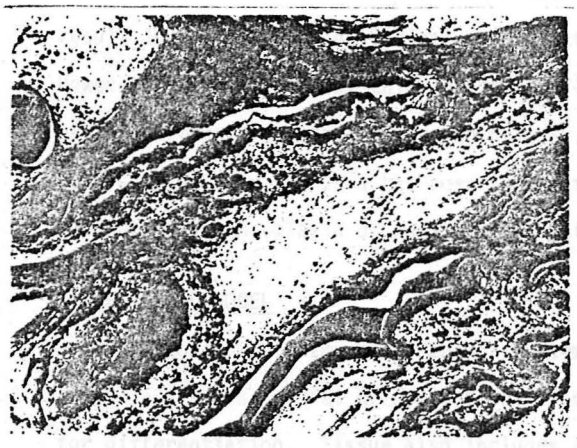
The major distinction for clinical management is between seminoma and non-seminomatous germ cell tumors. The classification of the non-seminomatous tumors is more extensive and often more difficult because of the admixture of more than one histologic type in a single tumor. The embryonal cell tumors have a pleomorphic appearance being composed of small cells with densely staining nuclei arranged loosely in irregular glandular and tubular structures with a fibrovascular stroma.



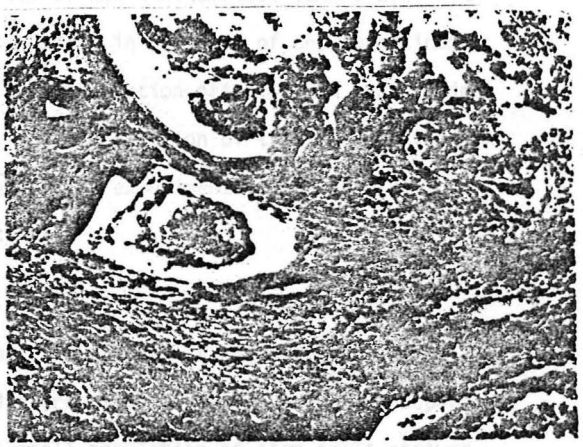
Embryonal Carcinoma (45)



Embryonal Carcinoma (45)



Teratoma (42)



Terato Carcinoma (42)

The defining characteristic of the teratomas is the presence of cells derived from endoderm, mesoderm and ectoderm. The histologic appearance and variability is well known. Teratomas arising in the testis are not distinct

histologically from those arising in the retroperitoneum, mediastinum, pineal or other sites. These tumors display varying degrees of differentiation and may be classified as malignant on the basis of an undifferentiated component.

Choriocarcinoma is not commonly found as a pure cell type in testicular tumors. Its histologic characteristic is the mixture of small cytotrophoblastic cells and large multi-nucleated syncytiotrophoblasts. It is more often encountered as a component in a tumor predominantly of another cell type, such as teratocarcinoma or embryonal carcinoma. The presence of any identifiable choriocarcinoma in a tumor specimen requires an approach to patient management that takes into account high potential for hematogenous metastases.

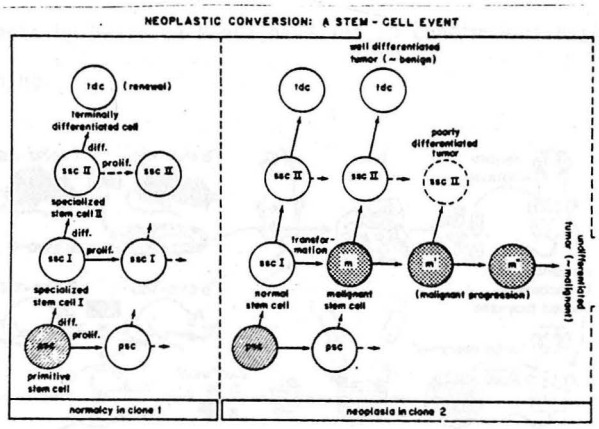
The classification into various categories of non-seminomatous tumors does not result in differences in clinical management, except in the case of choriocarcinoma. However, the existence of this diversity of differentiation often within one specimen or in different metastases from one primary, and the relation of this differentiation to events in embryogenesis has been the stimulus for experimental work leading to concepts about neoplasia of more general interest.

EXPERIMENTAL MODEL

The concept of stem cell renewal systems is important in understanding tumor growth. Tissues consist of populations of differentiated cells with limited capability for differentiation. Tissue also includes a small population of stem cells endowed with the ability to divide or to differentiate. Growth and division of stem cells replenishes the stem cell population and provides cells that make up the mature differentiated component of the tissue. Many details of this process have been identified for hematopoietic cell lines in bone marrow.

G. B. Pierce has suggested that these stem cells are the most likely targets of neoplastic transformation. A stem cell which has been transformed into a tumor stem cell may display varying degrees of differentiation.

Therefore, rather than thinking of the tumor as somatic tissue which has "de-differentiated", Pierce suggests considering the tumor, " a caricature of normal cell renewal systems". (Reference 42 and 43)

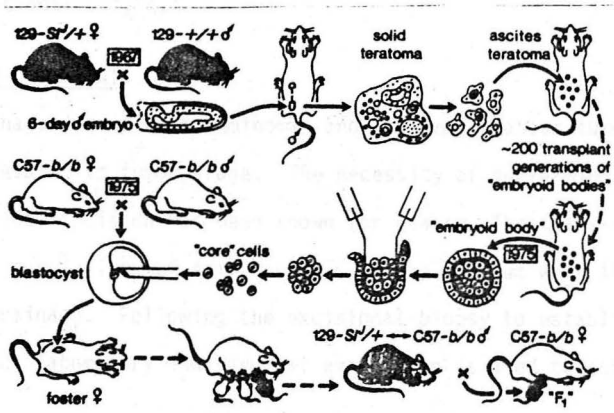


REF 41

Although stem cells have been difficult to identify histologically in normal tissues, this concept has been demonstrated by Pierce in the mouse malignant teratoma. (Reference 41) This malignant tumor can be grown in ascites form. Single cell transfer experiments showed that a cell from the undifferentiated component of the tumor could reproduce the entire histology of the tumor with as many as 15 different somatic tissues. However, cells from the well differentiated portions of the tumor were incapable of giving rise to tissues of other somatic types. This experiment demonstrates the multipotentiality of stem cells in this tumor.

This experiment led to the prediction that a benign tumor would result if the stem cell was lost or destroyed. This phenomenon seems to be illustrated by several cases reported by Javadpour and others from the National Cancer Institute. (Reference 33) In one of these cases, a patient presented with a large abdominal mass causing intestinal obstruction. This was shown to be embryonal carcinoma at biopsy. Following six months of chemotherapy, a large mass remained. Repeat CT scan showed multiple cysts. At exploration, this was demonstrated to be cystic teratoma.

Experiments by Beatrice Mintz have led to conclusions perhaps even further reaching.



REF 41

This slide summarizes about 12 years of experimental work. In it is shown the production of a malignant teratoma in mice of the same type used in the Pierce experiments. The 6 day embryo is implanted under the renal capsule of the host mouse. The embryo tissue under these conditions gives rise to a solid teratoma. This is a malignant tumor which may be carried in ascites form.

Cells from this tumor are injected into a blastocyst derived from mating of normal mice. This fused blastocyst is then implanted in a foster mother and develops into healthy offspring. Backcross analysis shows some of the normal functional tissues in these offspring are entirely derived genetically from the tumor cells. These remarkable experiments have led to the hypothesis that in addition to oncogenesis by mutational events and oncogenesis by viral transformation, there may be a category of tumors arising by a non-mutational event in which growth in an "inappropriate environment" leads to a stable but potentially reversible alteration in gene expression, but not in genetic material. There is no evidence whether or not human teratocarcinomas represent tumors of non-mutational origin.

STAGING AND TREATMENT

The management in both seminomas and non-seminomatous tumors of the testis is related to tumor stage. The necessity of performing an orchiectomy via an inguinal incision has been known for years. The trans-scrotal approach creates the possibility of tumor seeding of the scrotum with its separate lymphatic drainage. Following the excisional biopsy to establish diagnosis, radiographic, laboratory and surgical evaluation is used to establish tumor stage.

Classifications of tumor stage are designed to correlate with prognosis and natural history on the one hand and therapeutic choices on the other. Classifications used in literature reports are not uniform. Some systems use only clinical information whereas some include surgical and pathologic findings. An appropriate classification scheme is shown below.

Stage I: Local spread
- P1 – Confined to testis
- P2 – Involves testicular adnexa
- P3 – Involves scrotal wall

Stage II: Confined to retroperitoneal lymphatics
- N1 – Microscopic
- N2 – Gross involvement without capsular invasion
- N3 – Gross involvement with capsular invasion
- N4 – Massive involvement of retroperitoneal structures

Stage III: Beyond retroperitoneum
- M1 – Solitary metastasis
- M2 – Multiple metastases

(P = Primary, N = Node, M = Distant metastasis)

REF 31

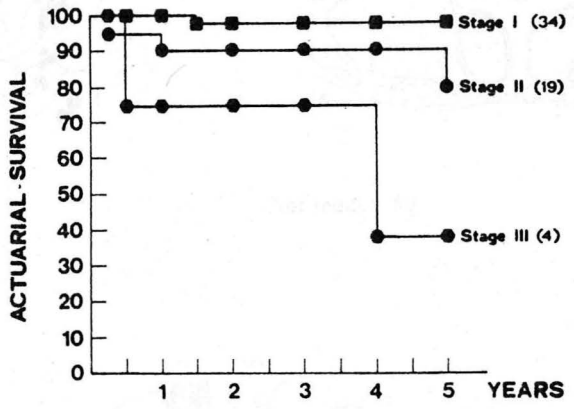
This staging system is based on the known pattern of metastatic spread. Mediastinal and supraclavicular node metastases are rare in the absence of abdominal involvement. The most common site of hematogenous metastases is the lung. Other sites of hematogenous metastases such as bone, liver and brain are seldom detected except in patients with pulmonary metastases or massive abdominal tumors.

Hence, the useful studies for clinical staging are bipedal lymphangiograms and chest tomograms. Additional studies such as IVP, liver scan, inferior vena cavagram and CT scan of the abdomen may also be helpful in defining the extent of intra-abdominal involvement.

Further evaluation and treatment depends on tumor histology. Patients with seminoma require only clinical studies for staging. About 90% of patients with seminoma will be found to have Stage I or Stage II disease. Because of the sensitivity of these tumors to radiation therapy, lymphadenectomy is not necessary. Stage I patients are usually treated with fields to include the ipsilateral pelvis and the retroperitoneum. If retroperitoneal node

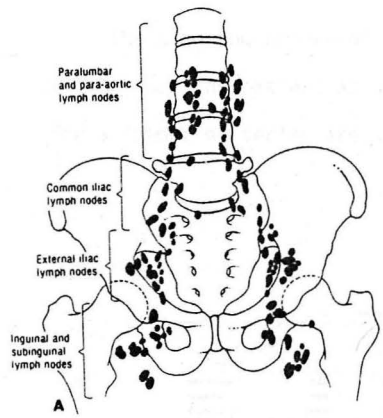
involvement has been demonstrated by lymphangiogram, CT scan or other studies, the treatment is extended to include the mediastinum and supraclavicular fields.

Results from a number of clinical trials show 91% of patients with no recurrence in two to five years. (Reference 6) In seminomas as well as all germ cell tumors recurrence is unusual after two years with clinically undetected tumor.



REF 52

Patients with non-semanomatous testicular tumors who were clinically Stage I or Stage II should undergo retroperitoneal lymphadenectomy. Lymphadenectomy is an extensive procedure having relatively low morbidity in these generally young, and otherwise healthy patients. The procedure is modified depending on the site of the primary, but most remove all major retroperitoneal lymph node chains. (Reference 35)



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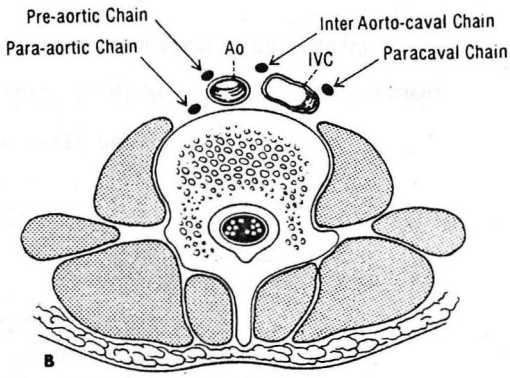

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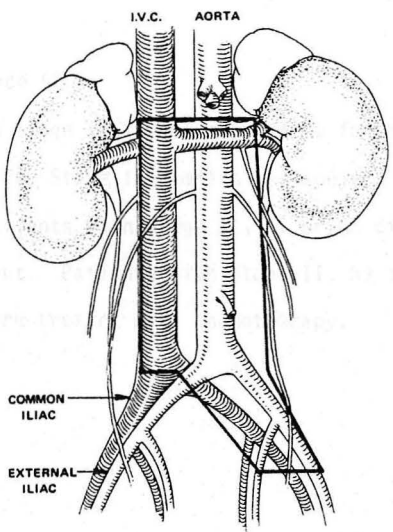


Reference 62

The low incidence of abdominal recurrence in patients undergoing lymphadenectomy indicates the success of currently employed surgical techniques for this operation.

The size and number of nodes involved is demonstrated by surgery establishes the patient as Stage I or Stage II N1-N4. Results of treatment for a number of series are shown in the table below:

Adult Germ Cell Testis Tumors (Excluding Pure Seminoma)*

Series		Embryonal Carcinoma Stage		Teratocarcinoma Stage		Totals Stage	
Author	Year	I	II	I	II	I	II
Whitmore	1968	15/16	5/8	28/33	4/8	43/49	9/16
Castro	1969	—	—	—	—	27/32	1/5
Boctor et al.	1969	1/4	3/4	7/9	2/3	8/13	5/7
Skinner et al.	1971	—	—	—	—	—	4/4
Walsh et al.	1971	10/10	2/3	14/15	1/1	24/25	3/4
Bradfield et al.	1973†	2/4	0/2	8/9	1/1	10/13	1/3
Staubitz et al.	1973	21/25	11/14	10/11	1/3	31/36	12/17
Johnson et al.	1976	14/18	—	51/54	—	65/72	—
Totals		63/77 (82%)	21/31 (68%)	118/131 (90%)	9/16 (56%)	208/240 (87%)	35/56 (63%)
		84/108 (78%)		127/147 (86%)		243/296 (82%)	

*Five-year survival after orchiectomy and retroperitoneal lymph node dissection (surgically staged).
†Three-year survivals.

Reference 62

Patients with Stage I disease require no further treatment. The optimum treatment for Stage II remains the subject of study.(Reference 13) It appears that patients with Stage II, N1 or N2 disease probably require no further treatment. Patients with Stage II, N3 or N4 and patients with Stage III tumors are treated with chemotherapy.

TUMOR MARKERS

The developed of sensitive radioimmunoassays for the tumor markers Beta HCG and alpha fetoprotein has led to some refinement of clinical and surgical staging. In the future, it may provide the basis for simplification of staging evaluation. (References 7 and 47)

Alpha fetoprotein a glycoprotein of 64,000 molecular weight is a major protein in fetal serum occurring in a concentration of 3 mg. per ml. The serum level in adults is less than 30 ng. per ml. Using the older agargel diffusion technique with a limit of detection of 2,000 ng. per ml., elevation of alpha fetoprotein was detected in patients with hepatoma and with regenerating liver after massive hepatic necrosis. With radioimmunoassays having a level of detection of 2 ng. per ml. the incidence of elevation of alpha fetoprotein in testicular tumors has become apparent.

Histochemical staining has shown that alpha fetoprotein is produced in the yolk sac of the normal embryo. In testicular tumors, alpha fetoprotein is most often detected in non-seminomatous tumors containing yolk sac elements. (Reference 42) Immunohistology has also demonstrated alpha fetoprotein in intracellular deposits in embryonal carcinoma cells. This finding explains the fact that AFP is sometimes detected in tumors lacking yolk sac elements. (Reference 37) Elevated AFP is found in 65% of patients with non-seminomatous tumors. It is not found in seminoma or in choriocarcinoma.

Human chorionic gonadotrophin is a 40,000 molecular weight glycoprotein secreted by the synctiotrophoblasts of the placenta. (Reference 40) The protein has two polypeptide chains. The alpha chain closely resembles the alpha chain of TSH and LH. The beta chain also has extensive homology with the LH beta chain, but has a sequence of 28 aminoacids not present on the LH beta chain. Vaitukaitis in 1972 developed a radioimmunoassay using this specific aminoacid sequence as the antigen, thus overcoming the previous difficulty of cross-reactivity with LH.

Elevation of beta chain HCG is found in 60% of cases of non-seminomatous germ cell tumors, 100% of choriocarcinomas and 5 to 10% of seminomas.

An elevated level, to be significant, must be persistent on at least two determinations. If elevated, measurement should be repeated after any treatment procedure. The recommended interval for measurement of a marker after treatment, for example, after orchiectomy, is five times the half time for clearance of the marker from the serum. The clearance times are given in the chart.

Units and Subunits	Half-Life	Cross-React	Source	Normal (ng/ml)
AFP	5 days	None	Fetal liver Testis tumor	<40
HCG	24 hr	FSH, TSH, LH	Placenta Testis tumor	<1
α-HCG	20 min	FSH, TSH, LH	Placenta Testis tumor	<2
β-HCG	60 min	None	Placenta Testis tumor	<1

Reference 34

One or both of these tumor markers is elevated in about 90% of cases of non-seminomatous tumors. The relation of the tumor marker to histology is given in the chart.

Tumor Type	AFP	hCG
Pure seminoma	–	–
Seminoma + syncytiotrophoblastic giant cells	–	+
Embryonal carcinoma	+	+
Endodermal sinus tumor	+	–
Choriocarcinoma	–	+
Teratoma	–	–

Reference 7

The technique of immunochemical staining using other tumor markers such as testosterone or carcinoembryonic antigen might make a contribution in the differential diagnosis of non-germinal cell tumors of the testis as well. An example is the use of staining for testosterone as done by Clive Taylor to distinguish anaplastic Sertoli cell tumor from histiocytic lymphoma in the testis. (Reference 59)

Other conditions causing elevation of either of these markers are listed in the chart below. From the practical standpoint of interpreting marker studies in a patient with testicular tumor, there are essentially no false positives.

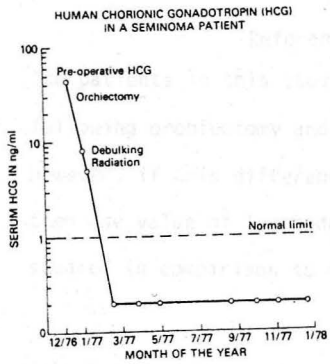
DIAGNOSIS	NO. OF PATIENTS AND PERCENTAGE WITH ELEVATED AFP*	NO. OF PATIENTS AND PERCENTAGE WITH ELEVATED β-HCG†
Hepatocellular carcinoma	130 (72%)	82 (17%)
Testicular cancer	101 (75%)	98 (51%)
Pancreatic carcinoma	44 (23%)	42 (33%)
Gastric carcinoma	91 (18%)	73 (22%)
Colonic carcinoma	193 (5%)	112 (12%)
Breast carcinoma	44 (0%)	–
Nonhepatic benign disease	300 (.3%)	–
Normal controls over 1 year of age	200 (0%)	443 (1%)

*Data from Waldmann and McIntire.[114]
†Data from Vaitukaitis *et al.*[116]

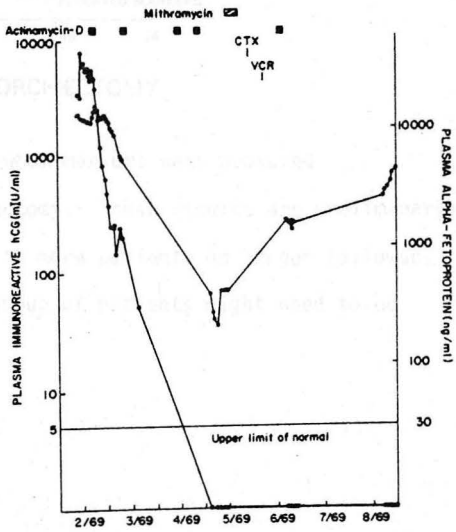
Reference 29

The clinical use of tumor marker studies was explored by Javadpour and Scardino. (References 29 and 56) 111 patients with germ cell tumors were studied. In 91%, either one or both marker could be detected by radioimmunoassay. No patient who was cured demonstrated persistent marker elevation. All patients with elevation of markers following any form of treatment invariably demonstrated recurrence or progressive tumor growth.

An example of marker levels reflecting response to treatment is shown in the diagram. Discordance of HCG and AFP may be observed in relapsing cases.



Reference 30

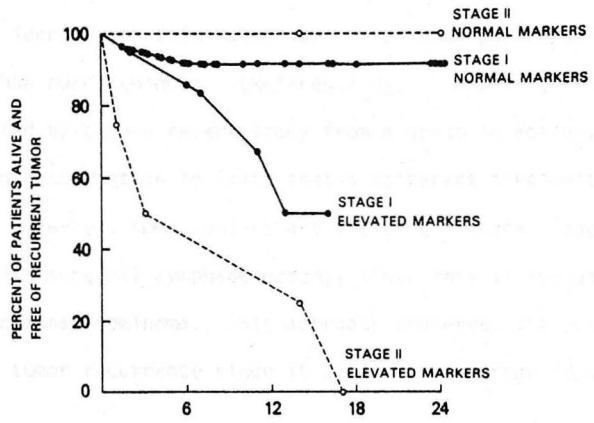


Reference 4

Elevations of one or both markers were detected in 16 of 24 patients followed by Scardino, who were clinically free of tumor. All of these patients ultimately suffered recurrence.

Therefore, markers are a sensitive and specific technique for early detection of advanced or recurrent tumor, but will miss about 10% of tumors that are negative for markers when diagnosed and about 1/3 of tumors that are negative at the time of recurrence.

There is preliminary evidence from Scardino that elevation of tumor markers prior to lymphadenectomy indicates a poor prognosis regardless of pathologic stage.



Reference 56

The patients in this study are patients in whom markers were measured following orchiectomy and before lymphadenectomy. These results are preliminary. However, if this difference is confirmed with more patients on longer followup, then the value of lymphadenectomy in this group of patients might need to be studied in comparison to chemotherapy.

Alpha fetoprotein has been found in only 4% of patients with seminomas. As expected from the immunohistologic study, these cases invariably turn out to have non-seminomatous metastases. (Reference 30) Thus, it appears that persistent elevation of alpha fetoprotein is incompatible with the diagnosis of seminoma.

Beta HCG is elevated in about 10% of patients with seminoma. Occasionally, further study of the pathologic specimen reveals a focus of choriocarcinoma. However, in most cases, the beta HCG can be localized to occasional syncytiotrophoblast giant cells present in the tumor. (References 30 and 42) The natural history of this variant of seminoma is not yet clarified. The initial report by Friedman in 1970 identifying this sub-group of seminoma patients indicated a worse prognosis than pure seminoma. (Reference 25) However, this finding has not been supported by a more recent study from a group in Boston. (Reference 39) There is insufficient information to state that a different treatment is required for these patients. However, some centers are treating clinical Stage I and Stage II patients with surgical lymphadenectomy, since this is adequate treatment for conventional seminoma. This approach preserves the possibility of chemotherapy for tumor recurrence since it avoids bone marrow injury from radiation.

The following conclusions are supported by the work on tumor marker studies. 1. persistently elevated markers after orchiectomy invariably indicates Stage II or Stage III tumor. 2. persistent elevation of markers after lymphadenectomy indicates Stage III tumor even if no tumor was found in the resected lymph nodes. 3. persistent elevation of alpha fetoprotein is incompatible with the diagnosis of pure seminoma.

CHEMOTHERAPY IN STAGE III NON-SEMINOMATOUS TUMORS

Results with multi-drug chemotherapy have improved significantly in recent years.

A number of drugs have activity when used as single agents.

Activity of Single Agents in Advanced Testicular Cancer

Treatment	No. of Patients	No. of Complete Responses	Response Rate (%)	
			Complete	Overall
Phenylalanine mustard[2]	42*	19†	45	90
Cyclophosphamide[3-6]	14	4	29	79
Ifosfamide[7]	18	2	11	83
Actinomycin D[8-11]	61	11	18	33
	22	5‡	23	36
Mithramycin[12]	133	12[3]	9	37
Adriamycin[13-16]	29	0	0	17
Bleomycin[17-23]	54	6	11	43
Vinblastine[8,24-26]	41	5	12	37
	21	4[1]	19	52
Cis-diamminedichloroplatinum[27-34]	86	16	19	60

* Seminomas only — see text.
† = Number of complete responses for at least 2 yr.
‡ Series reported separately to detail CRs that persisted > 2 yr.

Reference 28

A number of combinations based on Actinomycin-D led to only slight improvement in response rate and few complete remissions.

The combination of Vinblastine, Bleomycin and Cis-platinum introduced by Einhorn and Donohue has been a major advance. (References 15 and 16) Attempts to add Adriamycin, Actinomycin-D or Cytoxan resulting in reduction of the doses of the three initial drugs have not improved results.(Reference 17)

PVB Regimen of Einhorn and Donohue[50]

(P)	DDP	20 mg/m^2 as 15 min IV infusion on days 1-5, q 3 wks for 3 courses
(V)	Vinblastine	0.2 mg/kg IV days 1 & 2, q 3 wks for 5 courses; then, 0.3 mg/kg IV q 4 wks for 2 years (decreased 25% in cases of prior radiotherapy)
(B)	Bleomycin	30 units IV weekly on days 2, 9, and 16 of each DDP course, and with DDP 6 hrs after vinblastine; then, weekly for 12 weeks (stopped at total dose of 360 units)

Reference 28

Reports based on the Einhorn three-drug regimen have demonstrated complete response rates of 50 to 80%.

Recent results with this protocol have suggested that four or five induction courses without maintenance therapy results in a lower incidence of relapse. (References 5, 23, 46)

Patients achieving complete remission have about a 10% relapse rate in two years.

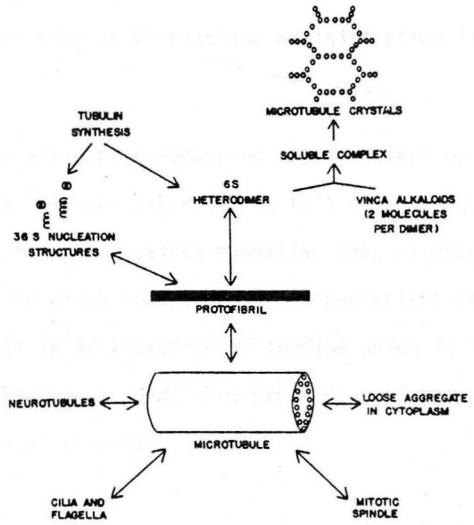
TREATMENT RESULTS IN METASTATIC TESTICULAR TUMORS

	PTS. in C.R.	RELAPSES
Bosl, et.al, 1980	23/28 (82%)	1
Einhorn, et.al, 1979	63/79 (80%)	7
Garnick, et. al, 1979	23/25 (92%)	0
Samson, et. al, 1979	64/126 (51%)	7

References 5, 17, 27, 55

The toxicology and pharmacology of these drugs is of interest, although they have relatively limited effectiveness in more commonly occurring tumors.

Vinblastine (Velban) is a Vinca alkaloid structurally very similar to Vincristine. The diverse effect of this drug may be mediated by effects on microtubule formation.

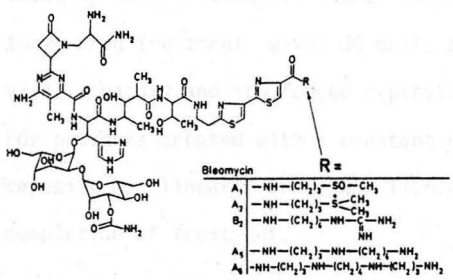


Reference 10

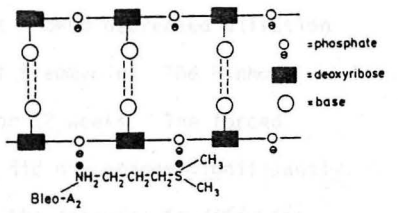
Microtubules are needed for axonal transport in neurons as well as for the formation of mitotic spindles. They are assembled from fibrils which in turn are in equilibrium with their tubulin components. Binding sites have been identified on tubulin for Vinblastine, which are distinct from a colchicine binding site. The formation of Vinblastine-tubulin complexes prevents assembly of monomers of tubulin to fibrils and thus shifts the equilibrium to favor disaggregation of fibrils. The more labile microtubule structures in the cells, such as mitotic spindles, may then disaggregate.

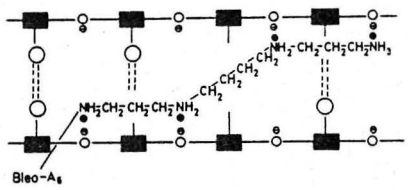
Although these findings are likely to explain some of the toxic effects, they may not be the reason for the anti-tumor effect. It has been shown that cells in S-phase of division, the time of DNA synthesis are more sensitive to Vinblastine than cells in M-phase, the stage when mitotic spindles are formed, implying a separate effect on DNA synthesis. Inhibition of DNA synthesis has been demonstrated, but the mechanism for this has not been determined. The dose limiting toxicity in Vinblastine administration is bone marrow suppression.

Bleomycin is an antibiotic recovered from a Streptomyces fermentation broth. Its activity has been described as that of a pseudo-enzyme. (Reference 43) It has endonuclease activity against mammalian DNA, although the K_m is lower than that of any other known endonuclease. Non-covalent binding of Bleomycin to DNA appears to result in deliberation of thymine which is followed by hydrolysis of the exposed ribophosphate bond. The production of strand scission correlates experimentally with cytotoxicity.

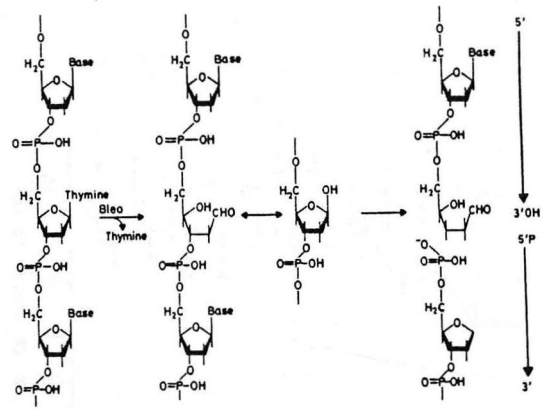


Chemical structure of bleomycin. The terminal amine moieties of bleomycin-A_1, -A_2, -B_2, A_5 and -A_6 are given (6).





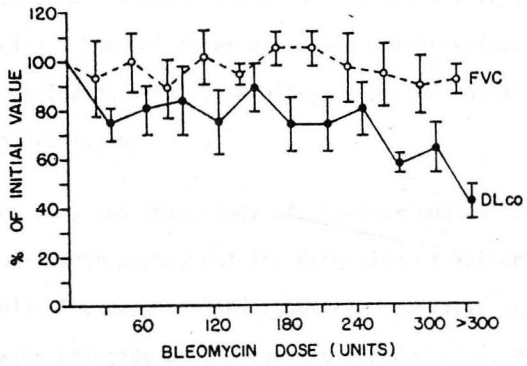
Reference 43

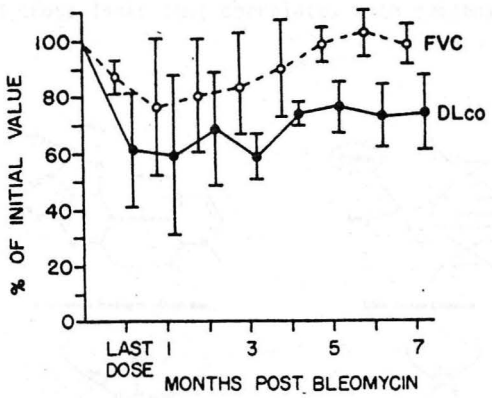


Reference 43

The effect of the drug on various tissues appears to correlate with differences in drug accumulation and with different levels of an enzyme that inactivate the drug.

The major toxicity of Bleomycin is pulmonary fibrosis. Fatal pulmonary fibrosis occurs in 1 to 2% of patients treated, but measurable abnormalities in lung function occur in almost all patients. A group of patients with testicular tumors studied by Comis showed decreased diffusion capacity when treated with more than 60 units of Bleomycin. The Einhorn three-drug treatment gives 30 units per week for 12 weeks. The forced vital capacity and the forced expiratory volume did not change significantly. For patients treated with a constant dose rate, the decrease in diffusion capacity was linear. There was little recovery up to 7 months following the completion of treatment.

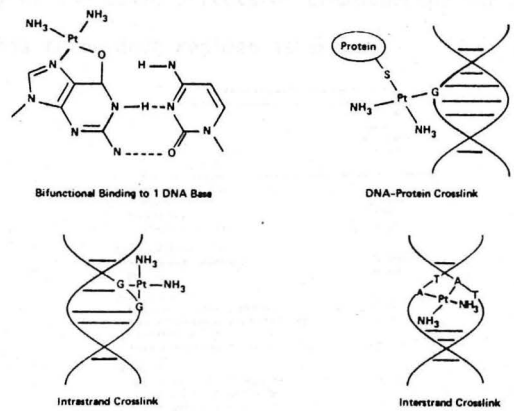

120
100
80
60
40
20
0
% OF INITIAL VALUE
FVC
DLco
60
120
180
240
300
>300
BLEOMYCIN DOSE (UNITS)


100
80
60
40
20
0
% OF INITIAL VALUE
FVC
DLco
LAST DOSE
1
3
5
7
MONTHS POST BLEOMYCIN

Reference 8

This lung injury, even if asymptomatic, may be a significant long term hazard of treatment. It is already apparent that it presents an increased risk for general anesthesia. These patients have a sensitivity to the development of oxygen toxicity. Several cases of fatal adult respiratory distress syndrome immediately following surgery have been reported in patients previously treated with Bleomycin.

The chemistry and toxicology of Cis-Diaminedichloroplatinum is unlike any other anti-tumor agent, but its mechanism of action is not unique. (Reference 51) The compound undergoes electrophilic attack at the O-6 position of guanine with chloride as the leaving group. J. J. Roberts has demonstrated that cross-strand linkage can occur, probably guanine to guanine. Other bi-functional reactions, such as intrastrand and DNA to protein linkage can also be formed. Zwelling, Filipski, and Kohn have shown that it is the formation of interstrand cross links that correlates with cytotoxicity. (Reference 63)



Reference 63

Tissue distribution studies in dogs showed the highest levels achieved in kidney and ovary. (Reference 38) The finding of testicular and prostatic atrophy in animals injected for toxicology testing with Cis-platinum led to testing for anti-tumor activity against tumors of these tissues.

The dose limiting toxicity with the use of Cis-platinum is renal injury. Hydration with IV fluids and administration of Mannitol during Platinum infusion has considerably lowered the incidence of significant renal impairment. A recent study by B. J. Kennedy and associates using the Einhorn three-drug protocol had only one patient of 28 treated with a persistent elevation of creatinine above 2 mg. per deciliter as a result of treatment. (Reference 5) The use of aminoglycoside antibiotics however, does seem to carry an increased risk in these patients and is to be avoided if possible. (Reference 11)

High frequency hearing loss occurs with Cis-platinum treatment, but is not commonly symptomatic.

A summary of the toxic effects of chemotherapy for metastatic testicular tumors with this three-drug regimen is shown:

Toxicity (total No. of patients = 25)

Type	No. of patients with toxic effect (%)
Systemic	
Alopecia	25 (100)
Weight loss	24 (96)
cis-Platinum reactions	5 (20)
Gastrointestinal	
Nausea and vomiting	25 (100)
Mucositis	20 (80)
Bone marrow	
Leukopenia (wbcs < 3000/mm³)	15 (60)
Thrombocytopenia (platelets 75,000-100,000/mm³)	3 (12)
Anemia (hemoglobin decrease > 4 g)	9 (23)
Renal	
Azotemia (BUN > 25 mg/100 ml, creatinine > 1.5 mg/100 ml)	4 (16)
Hypomagnesemia (magnesium < 1.4 mEq/liter)	14 (56)
Hepatic	4 (16)
Combined renal, hepatic, and pulmonary	2* (8)

*Fatal reactions in both patients

Reference 2

The likelihood of success in treatment with chemotherapy of metastatic testicular tumor is related to the size and extent of disease.

Comparison of CR rates in 3 series by anatomic extent

	Samuels et al (12) (No. of CRs/ No. of patients treated)	Einhorn et al (13) (No. of CRs/ No. of patients treated)	Present study (No. of CRs/ No. of patients treated)
Positive markers only		3/3 (100%)	2/3 (67%)
Supraclavicular nodes	4/7 (57%)		3/3 (100%)
Minimal pulmonary disease	9/11 (81%)	9/10 (90%)	9/11 (82%)
Advanced pulmonary disease	12/21 (57%)	6/9 (67%)	5/19 (26%)
Minimal abdominal ± minimal pulmonary disease		8/9 (88%)	1/1 (100%)
Advanced abdominal or visceral disease	3/17 (17%)	9/16 (56%)	1/8 (12%)

Reference 12

Minimal pulmonary disease is defined as no lesion larger than 2 cm. in diameter.

The favorable results for patients in the categories minimal pulmonary disease or marker elevation only are the main data suggesting that Stage I and Stage II, N1 and N2, patients need not be given adjuvant chemotherapy. If these patients are followed carefully, those who relapse will be in the "minimal disease" categories and have a high likelihood of complete remission with chemotherapy. This expectation is supported by the studies of Einhorn and Donohue. (Reference 18)

Data from Einhorn, Donohue (Reference 18)

Stage I

57 patients followed > 1 year, 36 > 2 years

4 relapses, all patients now N.E.D.

Stage II

Treatment Group

A - Adjuvant Actinomycin

B - Adjuvant P.V.B. X 2

C - No Adjuvant Treatment

Stage II

Group	A	B	C
Number	31	7	24
Followed 1+ years	31	7	24
Followed 2+ years	31	3	14
Relapses	15	0	7
Presently N.E.D.	30	7	23
Dead	1	0	1*

*Unrelated causes

In these studies, 118 of 119 patients who were Stage I or Stage II, achieved no evidence of disease status, either with adjuvant chemotherapy or with chemotherapy at the time of recurrence.

In patients with advanced tumor, complete remission is sometimes attainable by surgical resection of any mass lesions detectable after chemotherapy. (References 9, 15, 27) Residual masses are not necessarily malignant tumor.

Postinduction Operation for Residual Disease

Pretreatment Histology	No. Cycles of Chemo-therapy	Site of Residual Disease	Pathologic Diagnosis
Embryonal carcinoma, yolk-sac tumor	4	Retroperi-toneum	Teratocar-cinoma
		Lung	Teratoma
Teratocarcinoma, seminoma	4	Lung	Necrosis
Teratocarcinoma	4	Lung	Necrosis
Embryonal carcinoma	5	Liver	Scar
Embryonal carcinoma, seminoma	6	Retroperi-toneum	Embryonal carcinoma*

* Dead.

Reference 5

Residual tumor may also be discovered in patients thought to be in complete remission who are subjected to retroperitoneal lymphadenectomy. (Reference 27) However, in view of the low relapse rate following chemotherapy-induced complete remission, it is not yet clear that surgery is necessary in patients with no clinically detectable residual masses. (Reference 19) Surgery for residual lesions adds about another 10% of patients presenting with metastatic disease to the complete remission group.

In summary, the approach to patients with testicular tumor depends on classification of histologic type and clinical staging employing tumor marker measurements. A combination treatment approach using surgery and chemotherapy can produce long lasting remissions for non-seminomatous tumors in more than 90% of Stage I and Stage II tumors and at least 60% of Stage III tumors.

1. Anderson, T., et al., Testicular Germ-Cell Neoplasms: Recent Advances in Diagnosis and Therapy, ANNALS OF INT. MED. 90: 373-385, 1979

2. Anderson, T., et al., Chemotherapy for Testicular Cancer: Current Status of the National Cancer Institute Combined Modality Trial, CANCER TREAT. REP. 63: 1687-1692, 1979

3. Batata, M.A., Vnal, A., The Role of Radiation Therapy in Relation to Stage and Histology of Testicular Cancer, SEMINARS IN ONCOLOGY 6 (1): 69-73, 1979

4. Baunstein, G.D., et al., Discordance of Human Chorionic Gonadotropin and Alpha-Fetoprotein in Testicular Teratocarcinomas, CANCER 31 (5): 1065-1068, 1973

5. Bosl, G.J., et al., Vinblastine, Bleomycin, and cis-Diamminedichloro-platinum in the Treatment of Advanced Testicular Carcinoma, AMER.J. MED. 68 (4): 492-496, 1980

6. Caldwell, W.L., et al., The Management of Testicular Seminomas, 1979, Cancer 45: 1768-1774, 1980

7. Catalona, W.J., Tumor Markers in Testicular Cancer, UROL. CLIN. N.A. 6 (3): 613-628, 1979

8. Comis, R.L., et al., Role of Single-Breath Carbon Monoxide-diffusing Capacity in Monitoring the Pulmonary Effects of Bleomycin in Germ Cell Tumor Patients, CANCER RES. 39: 5076-5080, 1979

9. Comisarow, R.H., Grabstald, H., Re-exploration for Retroperitoneal Lymph Node Metastases from Testis Tumors, JOURNAL OF UROLOGY 115: 569-571, 1976

10. Creasey, W.A., Vinca Alkaloids, CANCER CHEMOTHERAPY III, Edited by Brodsky, I., p. 49-58, 1978

11. Dentino, M., et al., Long-Term Effect of Cis-Diamminedichloroplatinum on Renal Function and Structure in Man, CANCER 41: 1264-1286, 1978

12. DeWys, W.D., et al., Chemotherapy for Advanced Germinal Cell Neoplasms: Preliminary Report of an Eastern Cooperative Oncology Group Study, CANCER TREAT. REP. 63: 1675-1680, 1979

13. DeWys, W.D., Basis for Adjuvant Chemotherapy for Stage II Testicular Cancer, CANCER TREAT. REP. 63: 1693-1695, 1979

14. Drewinko, B., Gottlieb, J.A., Action of cis-Dichlorodiammineplatinum (II) (NSC-119875) at the Cellular Level, CANCER CHEMOTHERAPY REPORTS,Part I 59: 665-673, 1975

15. Einhorn, L.H., Donohue, J., Cis-Diamminedichloroplatinum, Vinblastine, and Bleomycin Combination Chemotherapy in Disseminated Testicular Cancer, ANN. INT. MED. 87: 293-298, 1977

16. Einhorn, L.H., Furnas, B., Improved Chemotherapy in Disseminated Testicular Cancer, JOURNAL CLIN. HEMATOLOGY AND ONCOLOGY 7: 662-671, 1977

17. Einhorn, L.H., Combination Chemotherapy with cis-Dichlorodiammineplatinum (11) in Disseminated Testicular Cancer, CANCER TREAT. REP. 63: 1659-1662, 1979

18. Einhorn, L.H., Williams, S.D., Donohue, J.P., High cure rate of Stage I or II Testicular Cancer with or without Adjuvant Therapy, Proc., AM. SOC. CLIN. ONC. 21: C-407, 1980

19. Einhorn, L.H., The Role of Surgery in Disseminate Testicular Cancer, AMER. ASSOC. FOR CANCER RES., PROCEEDINGS 21: 635, 1980

20. Einhorn, L. H., Williams, S.D., Chemotherapy of Disseminated Seminoma, CANCER CLIN. TRIALS 3: 307-313, 1980

21. Fowler, J.E., McLeod, D.G., Stutzman, R.E., Critical Appraisal of Routine Supraclavicular Lymph Node Biopsy in Staging of Testicular Tumors, UROLOGY 14: 230-232, 1979

22. Fraley, E.E., Lange, P., P.H., Kennedy, B.J., Germ-Cell Testicular Cancer in Adults, N.E.J.M. 301: 1370-1377, 1420-1426, 1979

23. Frei, E., Canellos, G.P., Dose: A Critical Factor in Cancer Chemotherapy, AM. J. MED. 69: 585-594, 1980

24. Frick, M.P., Feinberg, S.E., Knight, L.C., Evaluation of Retroperitoneum with Computerized Tomography and Ultrasonography in Patients with Testicular Tumors, COMPUTERIZED TOMOGRAPHY 3: 181-184, 1979

25. Friedman, M., Pearlman, A.W., Seminoma with Trophocarcinoma, Cancer 26: 46, 1970

26. Friedman, N.B., Pathology of Testicular Tumors in Genitourinary Cancer, Edited by Skinner, D.G., and deKernion, J.B., 1978

27. Garnick, M.B., Sequential Combination Chemotherapy and Surgery for Disseminated Testicular Cancer: cis-Dichlorodiammineplatinum (11), Vinblastine, and Bleomycin Remission-Induction Therapy Followed by Cyclophosphamide and Adriamycin, CANCER TREAT. REP. 63: 1681-1686, 1979

28. Jacobs, E.M., Muggia, F.M., Rozencweig, M., Chemotherapy of Testicular Cancer from Palliation to Curative Adjuvant Therapy, SEMINARS IN ONCOLOGY 6 (1) 3-13, 1979

29. Javadpour, N., Bergman, S., Recent Advances in Testicular Cancer, CURR. PROB. SURG. 15 (2), 1978

30. Javadpour, N., McIntire, K.R., Waldman, T.A., Human Chorionic Gonadotropin (HCG) and Alpha-Fetoprotein (AFP) in Sera and Tumor Cells of Patients with Testicular Seminoma, CANCER 42: 2768-2772, 1978

31. Javadpour, N., Staging Procedures and the Role of Surgery in Testicular Cancer, CANCER TREAT. REP. 63: 1637-1641, 1979

32. Javadpour, N., et al., The Role of the Radioimmunoassay of Serum Alpha-Fetoprotein and Human Chorionic Gonadotropin in the Intensive Chemotherapy and Surgery of Metastatic Testicular Tumors, JOURNAL OF UROLOGY 119: 759-762, 1978

33. Javadpour, N., Anderson, T., Doppman, J.L., Computed Tomography in Evolution of Testicular Cancer During Intensive Chemotherapy, JOURNAL OF UROLOGY 122: 565-567, 1979

34. Javadpour, N., The Value of Biologic Markers in Diagnosis and Treatment of Testicular Cancer, SEMINARS IN ONCOLOGY 6 (1): 37-47, 1979

35. Kaswick, J.A., Bloomberg, S.D., Skinner, D.G., Radical Retroperitoneal Lymph Node Dissection: How Effective is Removal of All Retroperitoneal Nodes? JOURNAL OF UROLOGY 115: 70-72, 1976

36. Kohn, K.W., Ewig, R.A.G., DNA-Protein Crosslinking by trans-Platinum (II) Diamminedichloride in Mammalian Cells, a New Method of Analysis, BIOCHIMICA ET BIOPHYSICA ACTA 562: 32-40, 1979

37. Kurman, R.J., et al., Cellular Localization of Alpha-Fetoprotein and Human Chorionic Gonadotropin in Germ Cell Tumors of the Testis Using an Indirect Immunoperoxidase Technique, CANCER 40: 2136-2151, 1977

38. Litterst, C.L., Distribution and Disposition of Platinum Following Intravenous Administration of cis-Diamminedichloroplatinum (II) (NSC 119875) to Dogs, CANCER RES. 36: 2340-2344, 1976

39. Mauch, P., Weichselbaum, R., Botnick, L., The Significance of Positive Chorionic Gonadotropins in Apparently Pure Seminoma of the Testis, INT.J. RAD. ONC. BIOL. PHYS. 5: 887-889, 1979

40. Midgley, A.R., Pierce, G.B., Immunohistochemical Localization of Human Chorionic Gonadotropin, J. EXPT. MED. 115: 289, 1962

41. Mintz, B., Genetic Mosaicism and In Vivo Analyses of Neoplasia and Differentiation, CELL DIFFERENTIATION AND NEOPLASIA, Edited by Saunders, G.F., 1978, p. 27-53

42. Mostofi, F.K., Pathology of Germ Cell Tumors of Testis, CANCER 45 (7): 1735-1754, 1980

43. Muller, W.E.G., Zahn, R.F., Bleomycin, an Antibiotic that Removes thymine from Double-Stranded DNA, in PROGRESS IN NUCLEIC ACID RESEARCH AND MOLECULAR BIOLOGY 20: 22-57, 1977

44. Munchausen, L.L., Rahn, R.O., Biologic and Chemical Effects of cis-Dichlorodiammineplatinum (11) (NSC-119875) on DNA, CANCER CHEMOTHERAPY REPORTS Part 1 59: 643-646, 1975

45. Nochomovitz, L.E., and Rosai, J., Current Concepts on the Hitogenesis, Pathology, and Immunochemistry of Germ Cell Tumors of the Testis, PATHOLOGY ANNUAL Vol. 13, 1978, Edited by Sommers, S.C., and Rosen, P.P., p. 327-362

46. Norton, L., Simon R., Tumor Size, Sensitivity to Therapy, and Design of Treatment Schedules, CANCER TREAT. REPORTS 61: 1307-1317, 1977

47. Pearson, J.C., Spaulding, J.T., Friedman, M.A., Testicular Cancer: Role of Biological Tumor Markers, CANCER TREAT. REP. 6: 217-221, 1979

48. Pierce, G.B., Teratocarcinoma: Model for a Developmental Concept of Cancer, CURRENT TOPICS IN DEVELOPMENTAL BIOLOGY, Vol. 2, 1967, Edited by Moscona, A.A. and Monroy, A.

49. Pierce, G.B., Wallace, C., Differentiation of Malignant to Benign Cells, CANCER RES. 31: 127-134, 1971

50. Pierce, G.B., Cox, W.F., Neoplasms as Caricatures of Tissue Renewal, CELL DIFFERENTIATION AND NEOPLASIA, Edited by Saunders, G.F., 1978, p.57-66

51. Prestayko, A.W., et al., Cisplatin (cis-Diamminedichloroplatinum 11), CANCER TREATMENT REVIEWS 6: 17-39, 1979

52. Quivey, J.M., et al, Malignant Tumors of the Testis: Analysis of Treatment Results and Sites and Causes of Failure, CANCER 39: 1247-1253, 1977

53. Ramsey, E.W., Bowman, D.M., Weinerman, B., Management of Disseminated Testicular Cancer, CANADIAN J. SURGERY 22: 418-420, 1979

54. Roberts, J.J., Pascoe, J.M., Cross-Linking of Complementary Strands of DNA in Mammalian Cells by Antitumor Platinum Compounds, NATURE 235: 282-284, 1974

55. Samson, M.K., et al., Vinblastine, Bleomycin, and cis-Dichlorodiammine-platinum (11) in Disseminated Testicular Cancer: Preliminary Report of a Southwest Oncology Group Study, CANCER TREAT. REP. 63: 1663-1667, 1979

56. Scardino, P.T., et al., The Value of Serum Tumor Markers in the Staging and Prognosis of Germ Cell Tumors of the Testis, J. UROL. 118: 994-999, 1977

57. Skinner, D. G., Management of Non-Seminomatous Tumors of the Testis, GENITOURINARY CANCER Edited by Skinner, D.G., p. 470-493, 1978

58. Stone, P.J., Kelman, A.D., Sinex, F.M., Specific Binding of Anti-Tumour Drug cis-Pt $(NH_3)_2CI_2$ to DNA Rich in Guanine and Cytosine, NATURE 251: 736-737, 1974

59. Taylor, C.R., Kurman, R.J., Warner, N.E., The Potential Value of Immunohistologic Techniques in the Classification of Ovarian and Testicular Tumors , HUMAN PATHOLOGY 9 (4): 417-427, 1978

60. Watson, R.C., Lymphography of Testicular Carcinoma, SEMINARS IN ONCOLOGY 6 (I): 31-36, 1979

61. Weber, B.L., Germ Cell Tumors of the Testis, CANCER TREAT. REP. 63: 1629-1635, 1979

62. Whitmore, W.F., Surgical Treatment of Adult Germinal Testis Tumors, SEMINARS IN ONCOLOGY 6 (1): 55-68, 1979

63. Zwelling, L.A., Filipski, J., Kohn, K.W., Effect of Thiourea on Survival and DNA Cross-Link Formation in Cells Treated with Platinum (11) Complexes, L-Phenylalanine Mustard, and BIS (2-Chloroethyl) Methylamine, CANCER RESEARCH 39: 4989-4995, 1979