TESTICULAR NEOPLASMS

THE RELATION BETWEEN THE PATHOLOGIC HISTOLOGY, CLINICAL COURSE, AND REACTION TO IRRADIATION IN TESTICULAR NEOPLASMS

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The advent of irradiation treatment of testicular neoplasms has greatly altered the prognosis of this disease. Whereas in former times the diagnosis of teratoma testis with metastases meant a uniformly lethal termination, it is becoming increasingly evident that with adequate irradiation certain types of highly malignant testicular neoplasms may be completely controlled even though demonstrable retroperitoneal metastases were present. It has been known for some time that various testicular tumors and their mestastases react quite differently to irradiation. In certain instances the primary tumors and their metastases disappear precipitately and do not recur within a period of years. In other cases the primary tumors react with varying promptness, usually do not recur, whereas the metastases react well, may completely disappear so far as palpation can detect, but recur after a varying interval. Still another group is quite radioresistant. Incidental observations from time to time have convinced us that a considerable degree of correlation exists between the pathologic histology, clinical course and radiosensitivity in this group of tumors and the present paper summarizes the results of a study of the available material in the endeavor to confirm or disprove the supposed correlation.

Up to approximately the end of 1928, 150 cases of testicular neoplasms had been observed in this hospital. In by far the majority of instances the primary tumor had been removed in some other institution where a diagnosis was made and from whence the patient was referred to the Memorial for irradiation treatment. In certain instances the primary tumor was never removed, the diagnosis resting on the conformation of the tumor, the presence of palpable metastases, and the reaction of one or both to irradiation. In forty-two of the 150 cases the testis was removed either before or after irradiation at this or at another hospital and the pathological examination made. The present report deals only with these forty-two cases verified in our own laboratory.

Some fifteen years ago the first patients with testicular tumors were irradiated at this hospital. It was a fortunate circumstance that the first few cases had tumors of the very radiosensitive, embryonal, anaplastic, carcinoma type, and the spectacular disappearance of the metastatic masses was sufficiently dramatic to force one to realize the importance of this revolu-

tionary change in the treatment of testicular teratoma. From that time on these tumors have been consistently handled by irradiation. Certain general principles rapidly became obvious. Surgery assumed an importance considerably below that of irradiation and its apparent value has so dwindled that it is a matter of discussion at the present time whether any surgical procedure at all should be carried out in these cases. We will consider this point later. Some tumors rapidly disappeared under irradiation, others were but slightly affected. Some metastases vanished only to reappear, indicating the necessity of increasing the irradiation in this group. In earlier years no method other than trial and error could be utilized. In time it became apparent that the reaction of the tumor mass to irradiation indicated to some degree the type of tumor. The anaplastic embryonal carcinomas diminished rapidly and often wholly disappeared, whereas tumors containing more differentiated structures tending toward the adult type frequently failed to react. The fact became gradually apparent that the highly malignant anaplastic carcinoma was actually less to be feared than its less malignant-appearing associates. When it became desirable to correlate tumor structure with clinical behavior, on the basis of experience both in this and in other tumor fields as to the histological diagnosis of probable radiosensitivity, the following working table was constructed. To test the validity of the suppositions made in the table we have examined the records of the forty-two cases above noted. As might be expected, not all the older charts contain conclusive statements as to the rate of regression under irradiation. There are enough cases in the two main tumor groups, anaplastic embryonal carcinoma, embryonal adenocarcinoma, to check the tabulation. The other groups have occurred too rarely to be of value in drawing conclusions.

In constructing this working table all of the slides on the various cases were reviewed. Unfortunately in the majority of instances the gross material is no longer available. Furthermore the destructive effects of radiation often reduce the testicular tumor to a necrotic, caseous mass, in which it may be very difficult to secure a region which gives much indication of the histology of the original tumor. Indeed in this hospital previously to the accumulation of sufficient experience in the microscopic appearance of radiated testicular tumors, the diagnosis of gumma has been made pathologically in cases behaving clinically like the very radiosensitive teratomas. The table is not intended as a classification of testicular tumors. It is a summary of the malignant types of proliferation found in the slides available from the forty-two cases studied. Of the forty-two cases at least thirty-eight would appear to belong in the embryonal group. Of the remainder, the three cases classified as carcinoma, adult type, tubule origin, considerable doubt must exist in the absence of complete study of the gross material especially as regards the location of the tumor in the testis. In no one of these three cases is the data sufficient to exclude a teratoid origin. Moreover in another case not included in the present material—a case which histologically very strongly suggested an origin of the tumor from tubule cells—the patient was a child of eight years,

an age certainly unusual for the development of cancer. Quite recently Desjardins, Squire and Morton [1] have once more concluded that the common embryonal carcinoma with lymphoid stroma is derived from adult spermatogonial cells, thus sharing the opinion of Chevassu [2] and others, of late Dew.[3] They base their conclusions on the common property of radiosensitivity of these tumors and of spermatogonial cells in the normal organ, at best a doubtful criterion especially since the authors make no effort to dispose of the evidence advanced by Wilms [4] and Ewing [5] for the teratoid origin of these types. In this connection it is of interest to note that the age distribution of "mixed, or teratoid tumors" and of "embryonal carcinoma" is quite similar

TABLE I

Reaction to Irradiation	Tumor type	Number of Cases
Radiosensitive	Embryonal carcinoma (diffuse tumors with very slight or no alveolar tendencies; embryonal carcinoma with lymphoid stroma)	24
	Lymphosarcoma	1
Moderately Radiosensitive	Embryonal adenocarcinoma and embryonal adenoma malignum (tumors with distinct gland-like cavities lined by cylindrical cells or with such gland-like cavities intermingled with areas of diffuse overgrowth)	10
	Embryonal myosarcoma (spindle-cell sarcomatous development in embryonal stroma, suggestive of muscle origin)	3
	Carcinoma, adult type, tubule origin (three cases of doubtful interpretation)	3
Radioresistant	Squamous carcinoma (developing in epidermal teratomatous structures)	1

(Chart I of the Desjardins, Squire and Morton). Quite recently Leroux and Hufnagel [6] have described another "seminoma" in which they demonstrated cartilage which latter they, influenced by Chevassu's interpretation of the seminoma, regard as a reactive metaplasia.

We may perhaps best deal with the material comprising this study under the following subdivisions: 1, the reaction of the primary tumor to radiation; 2, the behavior of the metastases; 3, the known length of time during which the primary tumor existed previous to the beginning of treatment; 4, the prognosis so far ascertained for different histologic types; 5, an analysis of certain failures.

When we attempt to analyze the available data on the reaction to irradiation in the anaplastic group of tumors we immediately meet with difficulties since of twenty-four histologically verified tumors of this variety, nineteen had been removed at some other institution previous to any irradiation treatment. The remaining five tumors diminished very rapidly in size follow-

ing irradiation and within a period of two to three weeks were reduced to one-third or less of their previous dimensions. In embryonal adenocarcinoma or embryonal adenoma malignum, tumors consisting of a teratoid glandular malignant proliferation with more or less well-defined glandular structures, of twelve verified cases, six entered the clinic after orchidectomy had been performed at another hospital. Of the remaining cases, three failed appreciably to diminish in size after treatment, one decreased but little, another decreased slightly, then after a stationary period of eight months, it increased in size; the sixth showed marked diminution, being reduced (in one week) to half its former dimensions. The lymphosarcoma reacted promptly and markedly to irradiation but subsequently terminated fatally in the usual manner of these tumors. The tumors classified as myosarcoma, squamous carcinoma in adult teratoma, and adult carcinoma were but slightly influenced by irradiation treatment. We may therefore conclude that the embryonal anaplastic carcinomas react like highly radiosensitive tumors, the embryonal adenocarcinomas with well-formed glandular structures are considerably less sensitive, and the other tumors in our collection are quite radioresistant. One might therefore be inclined to conclude that from the reaction of the primary testicular tumor some definite indication as to its type might be determined. This is true to a certain extent. Nevertheless certain other factors must necessarily enter into the matter, for in an adult cystic teratoma with embryonal elements capable of metastasizing, the irradiation may completely destroy the more active cellular portions and yet leave the adult structures relatively unaltered. One would therefore be misled into believing that the treatment was without effect, whereas as a matter of fact it had accomplished its purpose. In one other cellular tumor with many features justifying the diagnosis of choriocarcinoma testis the irradiation almost entirely destroyed the local tumor yet the testicular mass remained for several weeks unaltered. This lack of diminution in size was the result of thrombosis and infarction of the tumor vessels, practically converting the tumor mass into a hematoma, which of course did not diminish under irradiation.

The behavior of metastases toward irradiation is a complicated matter which, with our present material, is not clearly analyzable. Without autopsy or biopsy tissue from the retroperitoneal masses it is not possible to ascertain the exact structure of the metastases. Of course biopsy is wholly contraindicated. In complex teratomas one does not know which element or elements have metastasized. In embryonal adenocarcinomata one does not know whether the well-defined glandular form persists in the metastases or whether the latter are more anaplastic and hence more radiosensitive. Of the group of embryonal anaplastic carcinomas we have data in fifteen cases on the behavior of metastases. In one case only did the metastatic tumor fail to regress appreciably under treatment. In the remaining cases the metastatic masses showed marked or complete regression in from three weeks to ten months. Thus some disappeared in a spectacular fashion while others diminished much more slowly. In the more differentiated glandular teratoid adenocarcinomas

or malignant adenomas data is available in six instances. Four tumors reacted markedly to irradiation suggesting that they were perhaps more cellular and anaplastic than the primary tumors. In the two remaining cases the tumor metastases failed to regress.

Of twenty-four patients with embryonal anaplastic carcinomata, ten are clinically well. Of these cases four had metastases. In reporting these cases we are concerned only with the histologically verified cases, thereby leaving out many clinically undoubted tumors successfully treated but without pathological material for personal study. The metastases in the four cases above mentioned were in the following locations: right abdomen, right inguinal region and right abdomen, left hypochondrium, left upper abdomen. These cases are well—that is, free from demonstrable disease, two years and seven months, three years and eight months, three years and nine months, and ten years. Two verified cases of embryonal adenocarcinoma are clinically free from disease. Of these cases one had metastases in the right upper abdomen. This patient is clinically well four years and ten months.

The following case is of interest in demonstrating the enormous quantity of irradiation required to destroy these tumors and the uselessness of small dosages of X-ray or radium.

The patient was a negro chauffeur, aged thirty-seven years. He was admitted to the hospital in May, 1925, with a history of painless swelling of the right testis over a period of five months. The testis steadily increased in size and two weeks before admission first became painful. Three months prior to entering the hospital the patient began to cough and had frequent night sweats. He had lost thirty-six pounds in weight. Examination revealed a tumor of the right testis measuring fourteen centimetres in circumference. A mass 5 x 7 centimetres was palpated in the right abdomen and X-rays of the chest showed extensive pulmonary metastases. In addition there was a hard supraclavicular node measuring 1 x 2 centimetres. No operation was done. The patient was treated with a great deal of high voltage X-ray and with radium. The testis was reduced to a firm fibrotic mass. The metastases disappeared and the patient is now clinically well and free from demonstrable disease for four and a half years from the time treatment was first instituted. The skin shows pratically no effect from the treatment. The radiation employed in this case is charted in the following table.

TABLE II

Radium treatment

Date	Milli-curies	Time	Milli-curie hours	Filter	Dis-tance	Location of treatment		Apparatus
10/ 6/26	1935	6 hrs. 10 min.	12000	2 mm. brass	10 cm.	Ant.	epig.	emanation pack
10/ 7/26	1844	4 hrs. 12 min.	8000	2 mm. brass	10 cm.	Ant.	epig.	emanation pack
8/25/27	4000	3 hrs.	12000	2 mm. br. 0.5 mm. pt.	15 cm.	L.U.Q.	post.	element pack
8/31/27	4000	3 hrs.	12000	2 mm. br. 0.5 mm. pt.	15 cm.	L.U.Q.	post.	element pack
9/ 5/27	4000	3 hrs.	12000	2 mm. br. 0.5 mm. pt.	15 cm.	L.U.Q.	ant.	element pack
9/10/27	4000	3 hrs. 15 min.	13000	2 mm. br. 0.5 mm. pt.	15 cm.	L.U.Q.	ant.	element pack
9/17/27	4000	2 hrs. 45 min.	11000	2 mm. br. 0.5 mm. pt.	15 cm.	L.U.Q.	post.	element pack
9/20/27	4000	3 hrs.	12000	2 mm. br. 0.5 mm. pt.	15 cm.	L.U.Q.	post.	element pack

X-Ray treatment

Date	Time	Milli-amps.	Filter	Sp. Gap	Focal dist.	Region treated
5/ 7/25	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium
5/ 8/25	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right lower abdomen
5/ 9/25	25 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right testis and cord
5/13/25	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right chest posterior
5/15/25	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Left chest posterior
5/18/25	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right chest anterior
5/19/25	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Left chest anterior
1/12/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right groin and testis
1/15/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right abdomen anterior
1/19/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right abdomen post.
1/20/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right chest posterior
1/25/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right chest anterior
1/27/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Left chest anterior
1/29/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Left chest posterior
4/ 2/26	25 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	L. Supraclavicular
5/24/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium, right
5/27/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Abdomen anterior
6/ 1/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium, right
6/ 1/26	60 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Abdomen, posterior
6/ 4/26	7 min. (water cooled tube)	20	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Right groin & scrotum
8/26/26	40 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Mediastinum, centre, ant.
8/28/26	14 min. (water cooled tube)	20	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	L. upper abdomen ant.
8/30/26	(water cooled tube)	20	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	L. upper abdomen post.
10/ 6/26	10 min.	20	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium posterior
10/ 8/26	7 min.	20	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium posterior
10/23/26	40 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium anterior
11/30/26	40 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Epigastrium anterior
12/30/26	40 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	L. abdomen oblique
1/ 4/27	40 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen oblique
1/15/27	40 min.	4	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	L. abdomen oblique
1/26/27	5 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen oblique
	(the last and all subsequent treatments with water cooled tube)					
2/ 4/27	5 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen, upper post.
2/11/27	5 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen, upper ant.
2/18/27	5 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen, upper post.
3/22/27	6 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen, upper ant.
3/22/27	10 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. scrotum and groin
3/26/27	6 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen, upper ant.
3/29/27	6 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. abdomen, upper post.
4/12/27	6 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	L. abdomen, upper post.
4/19/27	3 min.	30	0.5 mm. cu. 1.0 mm. al.	90	25 cm.	L. abdomen, upper ant.
4/26/27	6 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	Posterior mediastinum
5/ 3/27	10 min.	30	0.5 mm. cu. 1.0 mm. al.	90	50 cm.	R. groin and scrotum

Where irradiation has failed to control the tumors analysis has shown that the treatment has been insufficient. Indeed, during the past two years the quantity of irradiation received by these patients has been very nearly doubled. There are, of course, cases in whom the disease is so far advanced where metastases are enormous and patients are cachectic, and under such conditions sufficient treatment to control the tumors cannot be administered. These die before they can be sufficiently irradiated. One case autopsied within

the last few months may illustrate this situation. The patient, aged thirty-eight years, applied for treatment three and one-half years after removal of the primary tumor. A very large right abdominal metastasis melted away under treatment and the patient gained strength. However, he soon became worse and died only four months after admission. At autopsy the metastatic masses completely filled the abdominal cavity, infiltrated the diaphragm, extended up along the aortic and mediastinal nodes to the supraclavicular region. On the irradiated side the tumor was reduced to a spongy, hæmorrhagic, fibrinous reticulum with practically no tumor cells in evidence in sections, whereas on the side which had had no irradiation the tumor was very active. The size and distribution of the metastases in this case had not been suspected and the patient was inadequately irradiated. This tumor was of the highly radiosensitive type. The more radioresistant embryonal adencarcinomas with distinct glandular formations will undoubtedly continue to from time to time defy successful irradiation treatment. In such cases the struggle becomes a contest between the amount of irradiation necessary to control the tumor and the quantity which can be withstood by the patient.

	Cases		Cases
9–12 months	1	4–5 years	3
1–1.5 years	5	5–6 years	3
1.5–2 years	9	6–7 years	2
2–2.5 years	6	7–8 years	0
2.5–3 years	2	8–9 years	2
3–4 years	6	9–10 years	1
		10 years	1

Much discussion has arisen relative to the propriety of removing the primary tumor after its irradiation. At this hospital it is the custom to perform an orchidectomy for the following reasons: (1) To determine the type of tumor and to thereby gain some information as to the probable prognosis and the probable amount of irradiation necessary. (2) To obviate the necessity of subsequent over-irradiation of the opposite testis. (3) To prevent a local recurrence in a possible adult teratoma where the presumption is that resumption of activity of more anaplastic portions may again occur. These last two reasons for orchidectomy are at present merely theoretical.

Strangely enough it appears quite impossible to ascertain from the history of the duration of the primary tumor any definite information as to its type. If the histories given by patients are correct then it would seem that tumors classified histologically and behaving clinically like embryonal anaplastic carcinomas may have been present for from three months to seven years. This is perhaps a valid argument for interpreting these tumors as a one-sided development of a complex teratoid tumor whose cellular portions have obliterated adult differentiated portions existing over a long period. On the other hand the history of development of the embryonal adenocarcinomas or embry-

onal malignant adenomas ranges from three months to one and one-half years. In other words the most radiosensitive tumors are not necessarily the most rapidly growing.

At the time this article is written we are able to present data on 113 patients treated and followed in this hospital. Of these 113 cases, forty-one are living and clinically free from disease. The above table indicates the time duration:

Of these 113 patients, thirteen were primary operable cases with no palpable metastases. Ten, or seventy-nine per cent., are alive and clinically free from disease. Sixteen were primary inoperable cases with demonstrable metastases. Four, or twenty-five per cent., are clinically well. Three were recurrent operable cases (local recurrences). Three, or 100 per cent., are clinically well. Eighty-one were recurrent cases with inoperable local recurrences and inoperable metastases. Twenty-four, or thirty per cent., are without evidence of disease.

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