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TREATMENT OF MALIGNANT TESTICULAR TUMOURS

A report on 355 patients

by

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Malignant testicular tumours are rare. According to GILBERT & HAMILTON (1942) they comprise 1 to 2 % of all malignant growths in men, and 9.5 % of all malignant tumours of the male genito-urinary tract. The Swedish Cancer Registry in 1959 reported 93 cases, constituting 1 % of all male cancer cases in Sweden, or 5.4 % of cancer of the male genito-urinary tract. About 1 % of all deaths from malignancy in the male are caused by these tumours (DALGAARD 1956).

Coloured patients, in whom malignant testicular tumours are very rare, are not reprensented in this series. The ratio between coloured and white patients, according to the literature, is about 1 : 6 (GRUMET & MCMAHON 1958); in age groups over 50 it changes, however, to approximately 1 : 1 (SCHREK 1944).

The majority of the tumours in our series occurred in early adult life. This is in agreement with other reports (NASH & LEDDY 1943, MÜLLER 1962). The age distribution in cases of seminoma and carcinoma at the time of primary treatment are shown in Fig. 1. The average age for seminoma was 40 years

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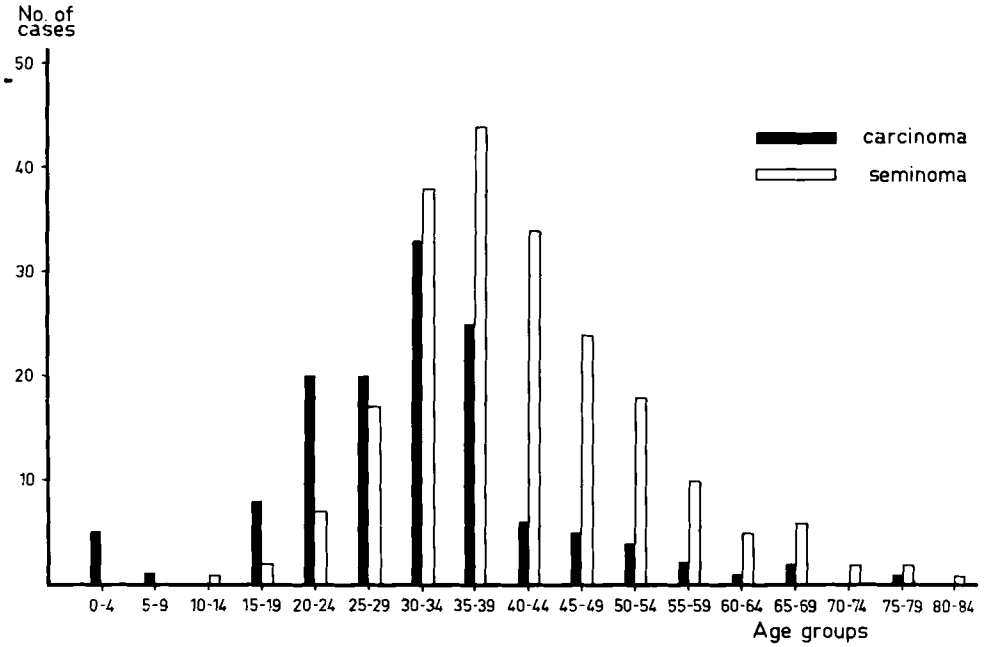

Fig. 1. Age distribution in a material of 344 patients with testicular seminoma and carcinoma.

(range 14 to 80) and for carcinoma it was 31 years (range 0.5 to 77). No seminomas occurred before puberty, but in several cases carcinoma arose during the first 4 to 5 years of life. There is no evidence for heredity of malignant testicular tumours, but several cases have been reported in brothers (GORDON-TAYLOR & WYNDHAM 1947, CAVICCHI 1956, NOTTER 1956, MÜLLER 1962).

Histopathology and classification. The malignant testicular tumours are a heterogeneous group of highly malignant tumours whose genesis and histopathologic classification have long been debated. Following pioneer studies by CHEVASSU (1906), EWING (1911), TEILUM (1944, 1951), FRIEDMAN & MOORE (1946) and DIXON & MOORE (1952), a distinction is made between two types of tumours: (1) germinative tumours, which develop from the omnipotent germinal cell, and (2) non-germinal tumours, which develop from the testis mesenchyma.

The first group comprises about 96 % of male testicular tumours. Moore's classification divides the germinal group into the following types: (1) seminoma, (2) embryonal carcinoma, (3) teratoma, (4) teratocarcinoma, and (5) choriocarcinoma.

The histologic pattern of these tumours may be uniform but frequently presents several components, especially a combination of seminoma and

carcinoma. According to FRIEDMAN & MOORE (1946), 6 % of the primary embryonal carcinomas and 15 % of the teratocarcinomas contain foci of choriocarcinoma, and according to DIXON & MOORE (1952) these may also be observed in 25 to 30 % of the metastases of teratocarcinoma.

The possibility of variable differentiation from the omnipotent germinal cell has also been demonstrated in experiments in animals (PIERCE et coll. 1959). Transplanted teratocarcinoma in the ascitic fluid developed cysts with three different cell types but after several passages only a low-differentiated cell type with ability to adapt to the changed growth conditions remained.

Clinical symptomatology permits no distinct differentiation of the testicular tumour. Gynecomasty, for instance, may be observed with embryonal carcinoma, teratocarcinoma and choriocarcinoma (FRIEDMAN & MOORE 1946, PIERCE et coll. 1959).

Nor is the production of hormones bound to any particular histologic tumour type. Choriogonadotrophin may be demonstrated with choriocarcinoma and embryonal carcinoma, as has also been verified in experiments in animals. If the choriogonadotrophin-producing embryonal carcinoma is implanted on cortisone-treated hamsters, the carcinoma continues to grow as an embryonal carcinoma but still produces choriogonadotrophin (PIERCE et coll.).

Malignant testicular tumours do, however, show internal differences. They vary, for instance, in their sensitivity to ionizing radiation, a circumstance that has so far defied explanation. It is conceivable that BARR's technique (1949), with examination of the sex chromatin of the cells, has opened up new perspectives. It was found that teratoid tumours in the male contain feminine sex chromatin while seminomas contain only masculine, which may suggest that the teratoid tumours are developed by autofertilization of haploid germ cells whereas seminomas arise from diploid germ cells. If these suppositions are correct, an essential genetic difference between seminoma and carcinoma is indicated. Such a difference has, however, not been found among the different types in the carcinoma group.

Since it is impossible to distinguish clearly between the different carcinoma types, either clinically or histologically, we prefer, like authors such as HÖST & STOKKE (1959) and MÜLLER (1962), a simplified classification of the germinal tumours, distinguishing only between: (1) seminoma (pure), (2) germinative carcinoma (including embryonal carcinoma, teratocarcinoma and all mixed forms with seminoma and also choriocarcinoma-structures), (3) adult teratoma, and (4) choriocarcinoma (pure).

Adult teratoma and pure choriocarcinoma are assigned to special groups in view of their histologic features and the prognosis.

Present material. The present series comprises 355 patients with malignant testicular tumours, treated during the period 1921—1960. The average number treated annually was 20 in recent years. The patients were admitted to, or

Table 1

Histologic classification of 355 malignant testicular tumours treated at Radiumhemmet from 1921—1960 as compared with other series

Histologic type	Present series (355 cases)		Dixon and Moore (900 cases)	Höst and Stokke (256 cases)
	No	%	%	%
Germinal tumours				
Seminoma	212	59.7	37.0	61.0
Embryonal carcinoma	132	37.2	19.8	23.0
Pure teratoma	8	2.2	9.0	15.2
Teratocarcinoma	—	—	31.6	—
Pure chorioepithelioma	—	—	1.0	0.4
Non germinal tumours				
Androblastoma	2	0.6	1.2	—
Interstitial cell-tumour	1	0.3	0.4	0.4

consulted the hospital directly and came from different parts of the country; about half of them had already been operated upon in other hospitals at the time of admittance for irradiation.

The material may therefore be regarded selective in two respects: (1) the most advanced cases may be missing and (2) some of those with small tumours and without metastases were perhaps not sent for irradiation because they were considered to have been cured by operation alone.

Out of the total number of patients, 294 were treated before 1958 and 61 between 1958 and 1960; the 2-, 5-, and 10-year survival rates have been assessed according to the length of observation time. All cases were histologically examined (or re-examined) by Professor L. Santesson. The distribution of cases according to the various types of tumour is shown in Table 1. A comparison is made with other materials. The series includes 3 non-germinal tumours, 2 tubular androblastomas and one interstitial cell tumour. Tumours of the testicular tunics, rete testis, epididymis and spermatic cord are not included in this series.

Side affected. There seems to be a slight predominance (53 %) in involvement of the right testis in all types of tumour (Table 2). This has also been reported by e. g. Fergusson (1962), Müller (1962) but the cause is unknown. Similar reports have been made for Sertoli cell tumours in dogs (Müller 1962) and for dysgerminoma (Santesson 1947). Santesson found 51 % right-sided and 17 % bilateral tumours among 206 cases of dysgerminoma. It has been suggested that this could be due to the right ovary developing more slowly and less completely than the left, and that a delayed differentiation of omnipotent tissue might be responsible for the greater tumour frequency on the right side. It is not known whether there is a similar mechanism in testicular development.

Table 2

Distribution of 352 testicular tumours according to the side affected

	Right	Left	Bilateral	Total
Seminoma	113	97	2	212
Carcinoma	68	63	1	132
Teratoma	6	2	—	8
Total	188	161	3	352

Bilateral tumours. Only 3 simultaneous bilateral tumours, 2 seminomas and one embryonal carcinoma, have been observed in this series; the histologic type was the same on both sides. The tumour in one testicle was in the carcinoma case in all probability a metastasis from the opposite side, and probably in one of the seminoma cases as well. The tumours were discovered and operated upon at 10 and 5 months, respectively, after the first orchiectomy. In both these cases there were further metastases at the primary treatment and both patients died at 15 and 13 months, respectively, after the first orchiectomy. Also in the third patient, a metastasizing unilateral tumour was probably present, but the possibility of a primary bilateral tumour could not be definitely excluded. The tumour in one testis measured 5 × 3 × 3 cm. No metastases could be demonstrated clinically or roentgenologically, nor was there any tumour in the other testicle. The second tumour was discovered purely by chance at biopsy from the testis in conjunction with hormone analysis a few days after the first orchiectomy. In spite of bilateral orchiectomy, the patient three weeks later developed metastases in the mediastinum, supraclavicular fossa, and in the lungs and skull, and died 8 months after operation.

Multiple malignant tumours. Seven of the patients with seminoma, 2 % of this series, developed a second malignant tumour of another type. Two died with carcinoma ventriculi, at 2 and 14 years, respectively, after the primary treatment, two developed thyroid cancer and are living 9 and 18 months after orchiectomy, one patient died from a glioma, another from a rectal carcinoma and a third from pulmonary carcinoma more than 10 years after the primary treatment. All these tumours have been verified histologically by biopsies or post-mortem examinations.

Hormone excretion. An increased excretion of hypophyseal gonadotrophin (HMG) may be observed in a large number of patients with malignant testicular tumours before and after semi-castration. This is considered to be caused by a reduced production of androgens owing to tumour growth in the testicle (HAMBURGER 1958), a reduction of functioning testicular tissue after semi-castration, or radiation damage in the remaining testicle. HMG is most often increased with testicular cancer (MOORE 1951) as well as in about 75 % of

seminomas (HAMBURGER et coll. 1936). Active hormone formation in the tumour, in the form of choriogonadotrophin (HCG), always occurs in pure choriocarcinoma but has also been demonstrated in 25 % of embryonal cancers (HAMBURGER 1958) and in 8 to 13 % of seminomas (NIELSON 1952, DIXON & MOORE 1953). HAMBURGER (1941) observed increased follicle-stimulating (HMG) and luteinizing (HCG) gonadotrophin in 2 out of 377 cancer patients. If HCG exists even before treatment the titre level is of prognostic importance. Rising HCG values after operation also suggest active metastases and indicate poor prognosis (TWOMBLY et coll. 1942). Increased estrogen values and Leidig cell hyperplasia, as a result of choriogonadotrophin production, are also unfavourable findings (DIXON & MOORE 1952, UMIKER 1954, TWOMBLY et coll. 1947). The excretion of hormone in the urine has in the present material been studied in 43 seminoma and 6 cancer patients. The excretion of 17-ketosteroids and 17-corticosteroids, estrogens and total gonadotrophin have been examined. In patients in whom the HMG was increased, separation was also made for HCG. A moderate increase in the HMG (around and above 30 mg/l) was observed in 6 out of 43 seminomas; the gravidity tests, on the other hand, were negative and HCG could not be demonstrated. Two of these patients died 6 and 2 years after operation from later metastases, while the other four are free from symptoms 3 years after operation.

Five of the six cancer patients had no histologically demonstrable choriocarcinoma structures. All six had increased HMG values of between 30 and 300 mg/l, and four had an HCG excretion between 72 and 12 000 I. E./l. None of these patients had gynecomasty. All died with metastases within 19 months after operation. Three patients had distant metastases already at the primary treatment, one had metastases in the epigastrium; in one there was no clinically demonstrable metastasis.

One carcinoma patient had histologically demonstrable choriocarcinoma structures, raised HMG and HCG values and bilateral gynecomasty. This patient died with metastases 12 months after operation.

Thus, in our material increased total gonadotrophin (HMG) was found to be of no prognostic importance. Choriogonadotrophin (HCG) excretion, on the other hand, indicated a very poor prognosis.

Gynecomasty. Unilateral gynecomasty was present in 13 patients and bilateral in 6. Of these 19 patients, 15 had carcinoma with metastases, 3 of which with choriocarcinoma structures. One bilateral gynecomasty from an interstitial cell tumour disappeared shortly after orchiectomy.

The cause of gynecomasty is unknown. It is assumed to result from an overweight of estrogens and increased production of hypophyseal gonadotrophin and in rare instances from choriogonadotrophin produced in the tumour or its metastases. Gynecomasty may be present before treatment, but sometimes occurs 2 to 6 months after orchiectomy. It is of no prognostic importance.

Table 3

Association of testicular tumour with imperfect descent — analysed according to side and type of tumor

		Cancer		Seminoma		Type of retention		
		Right	Left	Right	Left	Inguinal	Abdominal	Combined
Unilateral retention	27							
Ipsilateral tumour	24	2	3	11	8	23	1	—
Contralat.tumour	3	1	2	—	—	3	—	—
Bilateral retention	13	4	—	5	4	8	3	2
Total	40	12		28		34	4	2

Etiologic factors. The etiologic role of *trauma* in the development of malignant testicular tumours is difficult to evaluate and the incidence of trauma varies considerably in different materials. There was an established history of trauma in 15 % of the patients. It is difficult, however, to know whether the injury involved a 'normal' testis or an incipient, clinically latent tumour.

Imperfect descent leads to atrophy and functional insufficiency as early as after the fifth year of life; to prevent this, orchipexy at an early age is therefore recommended (ROBINSON & ENGLE 1954, STRAY 1952). Early operation however probably affords no effective tumour prophylaxis; at any rate observations after 'late' operation at the age of 14 revealed no effect. RAINES & HURDLE (1955) described a seminoma in a 51-year-old patient with prepubertal imperfect and later spontaneous descent. KAPLAN & ROSWITT (1950) reported a case which, 27 years after bilateral orchipexy at the age of 14, developed a seminoma of the right, and 4 years later a teratocarcinoma of the left, testicle. GRAF (1940), GORDON-TAYLOR & WYNDHAM (1947), RUSCHE (1952) and GROVE (1954) have described further cases.

The risk of tumours in retained testicles seems to be connected with atrophy and not with ectopy. Both are probably caused by embryonic malformation or hormonal disturbance.

A tumour is formed in roughly 0.8 % of all testicles with imperfect descent (WINTERSTEIN 1953, KURTZAHN 1943), but only in 0.0013 % of testicles with normal descent. If a tumour develops in a case of unilateral imperfect descent, the cryptorchid testicle is involved in 97.5 %. In bilateral cryptorchism, tumours occur in both testicles in 24 %. The connection between imperfect descent and tumour genesis may be questioned, however, as we do not know the real frequency of imperfect descent at birth, the statistics varying between 0.5 % and 5 % (GROVE 1954). False conclusions may also be drawn as a result of confusion between retention and pseudo-retention (BROWNE 1949).

The incidence of imperfect descent in relation to testicular malignancy varies slightly in the literature, i. e. 10 % (REA 1939), 13 % (GORDON-TAYLOR 1938), 14.3 % (DEAN 1956). It was 11 %, or occurred in 40 out of 355 cases, in the present series (Table 3). Pseudo-retention was present in 4 cases. In

27 cases there was unilateral and in 13 bilateral retention. Twenty-eight cases developed a seminoma and 12 a carcinoma. The tumour arose in the contralateral 'normal' testicle in 3 of the cancer cases. In spite of bilateral retention, only unilateral tumours developed: 4 carcinomas and 5 seminomas in the right and 4 seminomas in the left testicle. The ratio between inguinal, abdominal and combined retention was 17 : 2 : 1.

Orchipexy had been performed in 7 cases, two of these in childhood; in the latter cases the tumours developed first at the ages of 30 and 48, respectively. In 3 other cases orchipexy had been performed at 11, 16 and 24 years of age; these tumours arose after 34, 19 and 35 years, respectively. Two orchipexies had been performed at the ages of 33 and 48, the tumours being discovered 9 and 5 months later, respectively.

The clinical prognosis depends on the histologic features of the tumour, not on the type of imperfect descent. There was inguinal retention in all the twelve cancer patients. Nine died after 9 months (average), range 2 to 29 months. Four of them had clinical metastases at the primary treatment. Three patients were alive more than 3 years after operation. Of 28 patients with seminoma, 22 had inguinal retention, 4 abdominal and 2 combined retention. Five patients died after 23 months (average), 3 of these having metastases before treatment. Twenty-two patients are alive, 12 more than 10 years after treatment in spite of the fact that three of these had metastases at the primary treatment.

Clinical signs and Diagnosis

The first symptom is usually a slowly increasing, initially not tender, hard swelling in the testicle, which is unfortunately often being misinterpreted by the patient for far too long. He generally does not consult a doctor until after several months by which time metastases may already have formed; in many cases though metastases may be clinically latent. The tumour is sometimes discovered at operation for a scrotal hernia, hydrocele or varicocele. The diagnosis is complicated by inguinal and above all abdominal retention, when the tumour or metastasis may reach a considerable size before giving rise to signs. The tumour may be painful and be mistaken for epididymitis or orchitis. If treatment with sulphonamides or antibiotics fails to produce rapid improvement in such cases, the diagnosis should be clarified by biopsy. It is of the utmost importance for an early diagnosis to be made that the presence of a testicular tumour be suspected. It is not uncommon for the first clinical signs to be caused by retroperitoneal lymph node metastases. These can often be palpated in the epigastrium but they are for the most part small. Backache in the lumbar and sacral region, pain in the lower extremities, gastro-intestinal disturbances and intermittent pain, vascular compression in the pelvis with resulting oedema in one or both legs, or compression of the ureters with renal stasis may constitute signs of retroperitoneal lymph node metastases. Urography,

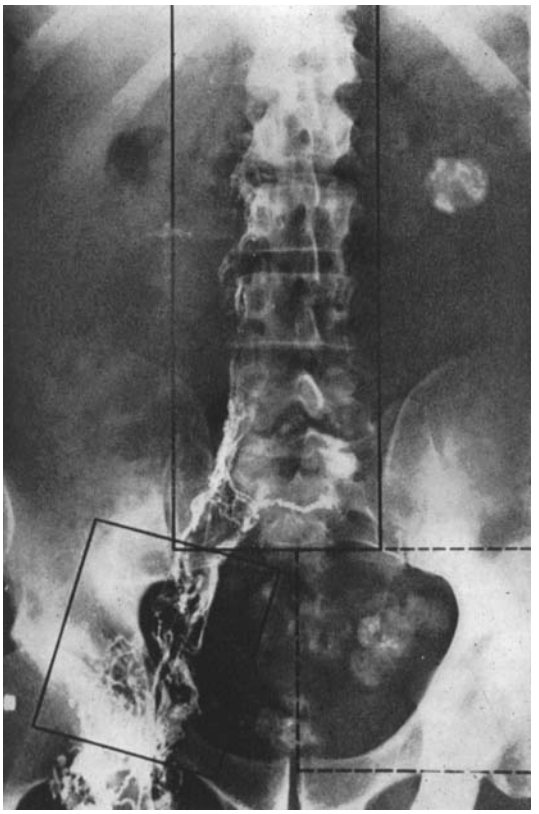

Fig. 2. Lymphogram of iliac and periaortic lymph vessels and position of epigastric and iliac portals for irradiation of retroperitoneal lymph nodes in a patient with right-sided testicular tumour. Left side of pelvis: iliac portal commonly used in this series. Right side of pelvis: more favourable placement for the pelvic portal in relation to the anatomy of the iliac lymph vessels.

cavography and lymphography can be useful in the diagnosis of these metastases (Fig. 2). In a number of patients, distant metastases give the first clinical evidence of a testicular tumour, e. g. supraclavicular lymph node metastases, pulmonary or mediastinal metastases or, more seldom, skeleton, liver, brain or skin metastases.

Other tumours, such as malignant lymphoma, carcinoma or sarcoma may form metastases in the testicles and suggest a primary testicular growth. The nature of the tumour, however, will be apparent from the histologic examination. Gynecomasty may be a sign of a testicular tumour and should lead to careful palpation of the testicles and examination of the hormone excretion.

Aspiration needle biopsy is contraindicated as a diagnostic procedure when a malignant testicular tumour is suspected. The testicular tunics are perforated by the puncture, with resultant dissemination of the tumour. STEPHEN (1962) recommended hemiscrotectomy after aspiration biopsy, having seen some cases of foudroyant tumour spread. He also pointed to the risk of delaying the diagnosis of a malignant tumour by uncritical antibiotic treatment of pseudo-

inflammatory tumour forms and recommended early explorative operation in doubtful cases, a recommendation that the present authors unreservedly support.

Treatment

Nearly all patients in the present series were treated with orchiectomy and resection of the spermatic cord, as high as possible in the inguinal channel, followed by irradiation. Two patients were not operated upon, and two were operated upon but not irradiated because of a poor general condition and generalized metastases. About half the number of patients in our series had been operated upon at other hospitals before admittance to Radiumhemmet for irradiation. The interval between operation and irradiation was about 20 days (average) for seminoma and carcinoma but in 1957 it was increased to 38 days for those carcinoma patients in whom retroperitoneal lymphadenectomy had been performed.

Roentgen examination of the lungs, intravenous pyelograms and, in recent years, cavography and lymphography of the abdomen were performed in all cases immediately after the primary operation and as soon as the histologic examination confirmed malignancy.

Prophylactic irradiation of the mediastinum, lungs, or the supraclavicular fossae had not been given. Nor had the radiosensitivity of the tumour been tested by preoperative irradiation, as suggested by FRIEDMAN (1962). For practical reasons, we distinguish between 3 different clinical stages (BODEN & GIBBS 1951):

Stage I: tumours limited to the testis and spermatic cord with no malignant cells identified at the resection of the cord.

Stage II: cases with local lymph node metastases, which include iliac, periaortal and perirenal metastases up to diaphragm level; cases with malignant cells at the resection of the cord and tumour infiltration in the scrotum.

Stage III: cases with metastases beyond these locations, i. e. distant metastases.

This division is of practical importance in treatment and prognosis.

Seminoma. Stage I tumours will be cured by orchiectomy alone and do not need irradiation. There are, however, good reasons for supposing that many of the cases classified as stage I have in fact clinically latent metastases in the retroperitoneal lymph nodes. These cases belong in reality to stage II, for which irradiation is needed. It is practically not possible to distinguish definitely between these two groups and it is generally accepted that because seminomas are very radiosensitive they should all receive postoperative irradiation.

Due to the lymphatic flow from the testis along the spermatic cord to the iliac-periaortal and perirenal lymph nodes (HORROWITZ & ZEISSL 1897,

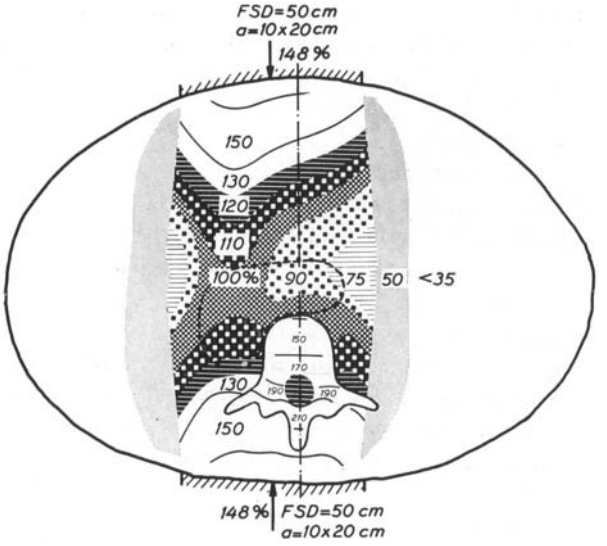

Fig. 3. Dose distribution resulting from two opposing roentgen beams (HVL 2.0 mm Cu) at level of L2. High absorption in the vertebra and medulla, and high dose level near the surface of the body compared with inhomogeneous dose distribution in the area of the metastases (marked with broken line).

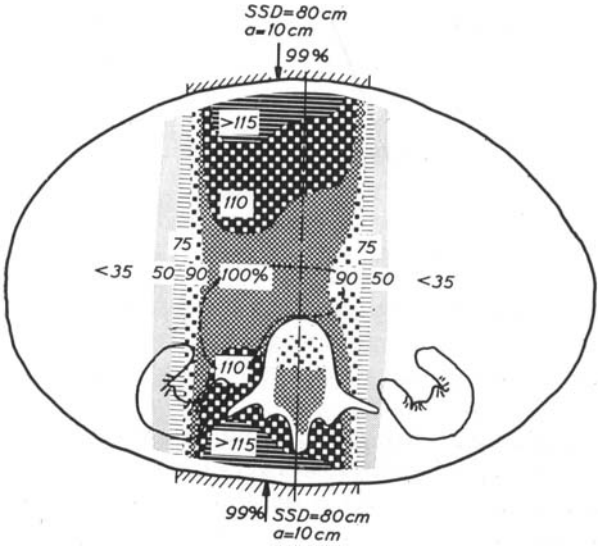

Fig. 4. Dose distribution resulting from two opposing ^{60}Co beams at the same level as in fig. 3. More homogeneous dose distribution in the area of the metastases and the surrounding tissues compared with fig. 3.

CUNEO 1901, JAMIESON & DOBSON 1910) irradiation has to cover a large tissue volume. Because of the numerous collaterals between the right and left sides it has to include all the lymph vessels on both sides of the vena cava and aorta from the bifurcation of the latter up to the level of the diaphragm (Fig. 2). There are no such collaterals in the pelvic region, and irradiation is required only on the homolateral side. The groin must be irradiated only if the scrotum has been invaded by the tumour.

It would appear to the authors that the tumour dose required need not be higher than 1 000 to 1 500 rad during 14 to 16 days and may be applied without radiation hazards to the surrounding tissues, in particular the sensitive kidneys. All cases of seminoma had been irradiated up to 1957 with conventional roentgen rays with radiation qualities corresponding to HVL 1 to 2 mm Cu. A standard technique was used, with one anterior and one posterior portal for the epigastrium, and with one anterior and in some cases one posterior portal for the iliac region (see Fig. 2). Since 1957 a few cases have been irradiated with ^{60}Co as well. The dose distribution obtained with the two qualities of radiation is shown for a horizontal cross-section at the level of L2 in Figs 3 and 4. Corrections have been made for the higher absorption in the lumbar vertebrae compared with that of the soft tissues in both instances (SPIERS 1946, H. E. JOHNS, N B S Handbook 78, 1959). The density of the lumbar vertebrae has been taken as 1.4 cm/cm^3 in calculating the absorbed dose.

So as to facilitate comparison between the two dose distributions, these have been reduced to normal in relation to a calculated average dose in the tumour area (SUNDBOM & ÅSARD 1964) using the formula:

$$\text{tumour dose} = \frac{\int_{\text{tumour area}} D\,dA}{\int_{\text{tumour area}} dA}$$

D = dose in the area 'dA'.

It is difficult to determine the amount of energy absorbed in the tumour tissue because the dose in the region of the tumour varies considerably, especially when conventional roentgen rays are used, due to the inhomogeneity of the tissue. An idea of the energy absorbed by the irradiated volume may be derived from Figs 3 and 4.

Irradiation is given through a cranial and caudal portal for physical and anatomical reasons (Fig. 2). Irradiation of very large areas may not be practical when the output is low or the SSD is limited. Moreover the anatomy of the lymph nodes differs in these two areas. The lymph nodes from the diaphragm down to the sacral promontory are situated in a cylindrical tissue volume, approximately in the center of the body just in front of and beside the anterior half of the vertebral bodies. The lymph vessels in the pelvic region run from the

Fig. 5. Lateral horizontal lymphogram of the iliac and lower periaortic region, demonstrating the difference in depth of the lymp vessels from the surface of the body at the level of the promontory and symphysis. The arrows point to the promontory and os pubis.

sacral promontory to the groin (Fig. 5) about 6 to 8 cm nearer the anterior surface of the body, causing special physical problems for the distribution of a homogeneous tumour dose. For this reason ^{60}Co or supervoltage roentgen rays are preferable for the irradiation of the abdomen, even when only smaller doses are needed. Cytostatic therapy and irradiation, or a combination of the two, may be chosen for seminomas with distant metastases. The high sensitivity of seminomas to irradiation has in general lead to this form of therapy being used first. It should be emphasized, however, that seminomas are often more disseminated in the body than the clinical and roentgenologic examinations may indicate. Early administration of cytostatic agents in connection with, and after the operation, may therefore be of value in the treatment of advanced seminomas.

Carcinoma. Semicastration and resection of the spermatic cord was the usual primary treatment even in cases of carcinoma. A retroperitoneal node dissection was performed in stage I and early stage II cases with clinically latent metastases. If no metastases could be demonstrated histologically, no irradiation was given. If metastases were present, on the other hand, irradiation was initiated 10 to 14 days after the operation.

Nowadays, only ^{60}Co in conjunction with an individually planned dose distribution is used. The technique most commonly employed at present is a combination of 3 portals, two with and one without a wedge filter. Two typical examples are illustrated in Figs 6 and 7. These dose-plans have been corrected for oblique incidence with the '2/3 h method' (Dutreix et coll. 1962). No

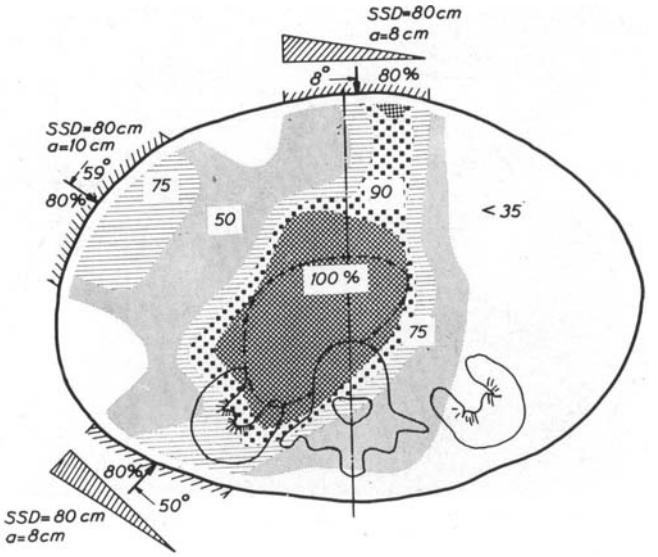

Fig. 6. Dose distribution obtained by using one open and two wedge filter beams of ^{60}Co.

corrections have been made for inhomogeneous tissue as the importance of this factor in these cases is relatively slight in ^{60}Co irradiation. These planned dose distributions have, however, been normalized in relation to a calculated average dose for the tumour area.

The tumour dose aimed at has been 4 500 to 5 000 rad in 35 to 40 days. Even though the irradiation was planned so as to minimize the dose received by the surrounding tissues, e. g. the kidneys, liver, spleen and medulla, these tissues, especially the homolateral kidney, sometimes receive considerable doses.

The treatment is usually a great strain on the patient. The blood and electrolyte condition must be carefully checked both before and during the treatment. While it is occasionally possible to combine radiation and cytostatic therapy, most patients are unable to tolerate both at once due to toxic depression of the bone marrow. The cytostatic therapy therefore cannot generally be started until radiation therapy has been concluded. Cytostatic therapy has sometimes been used in conjunction with and after operation, before radiation therapy could be started.

Cytostatic treatment. The development of cytostatic and antimitotic agents has increased the possibility of treating metastasizing testicular tumours. The authors have used the following substances:

Triethylenthiophosphamide (ThioTEPA):

0.2 to 0.3 mg/kg daily i.v. for 10 to 12 days;

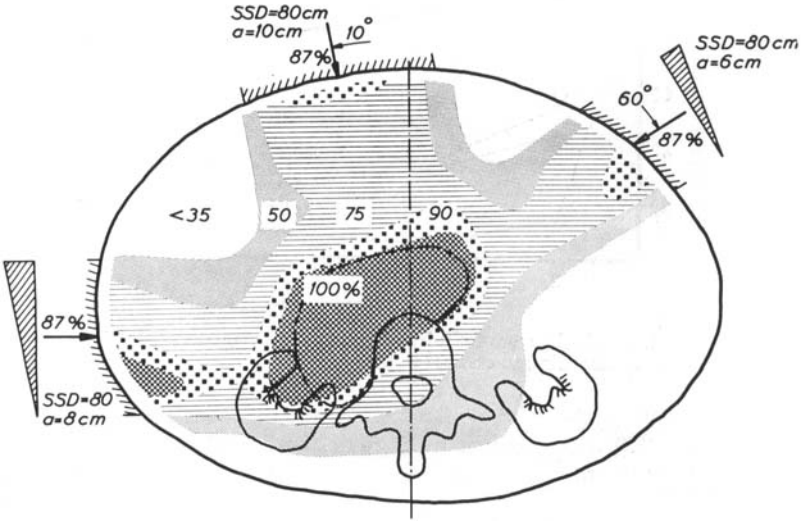

Fig. 7. Same conditions as in fig. 6 but with another direction of the beams and other field sizes.

Cyclophosphamide (Endoxan):

3 to 4 mg/kg daily i.v. for 20 to 30 days, or 6 mg/kg daily i.v. for 8 to 10 days as initial treatment and thereafter 2 × 50 mg perorally as long as the bone marrow tolerates the drug.

Methotrexate:

0.1 mg/kg daily perorally until toxicity in the form of mucositis, diarrhoea and depletion of the function of the bone marrow.

Actinomycin D: 0.5 mg daily i.v. for 5 days.

Mithramycin:

50 μg/kg daily i.v. for 5 to 8 days as initial dose, 60 μg/kg/week thereafter during 8 weeks.

These medicaments have in part been used before, during and immediately after operation of testicular carcinomas, in combination with radiation and thereafter. They have been used singly as well as in combination according to the methods of Li et coll. (1958, 1960). Only in a very few cases have the tumour metastases undergone objective regression and then only temporarily. The reaction on the bone marrow has varied. Some patients were well able to stand massive treatment with several agents, but in the majority a toxic effect on the bone marrow function, above all on the thrombocytopoiesis, lymphocytopoiesis and reticulocytopoiesis soon developed. With simultaneous irradiation, this effect occurred more rapidly, and either the irradiation or the cytostatic treatment generally had to be interrupted. In no patient did a

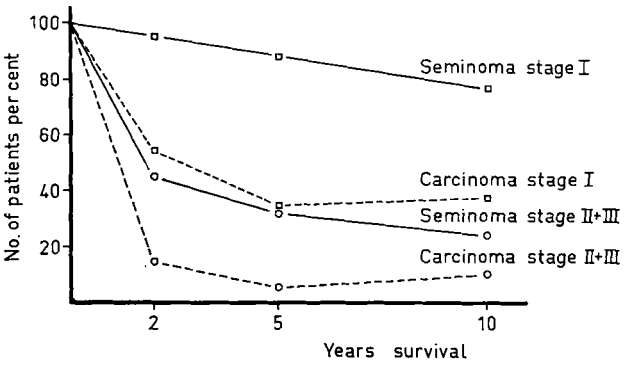

Fig. 8. Survival curves from 344 patients with seminomas and carcinomas according to clinical stages.

tumour disappear after cytostatic treatment, but tumour growth in some was clearly delayed while in others the metastases decreased or became necrotic.

No use was made of extracorporal perfusion or continuous or intermittent arterial infusion or injection of cytostatic agents in treating testicular carcinomas with metastases. The metastases are often so widespread in the body that the selective application of cytostatics seems insufficient. Intensive irradiation often decreases the blood supply to the metastases and angiography has later shown that large metastases have had a reduced vascular supply. Subsequent surgery has disclosed increased fibrosis, cystic degeneration and local necrosis, besides viable tumour cells. Poor vascular supply and reduced blood flow naturally curtail the possibility of treatment with cytostatics, as these cannot then reach the tumour cells. Cytostatic therapy before intensive irradiation may therefore be more effective.

The authors have found to date that the treatment of malignant testicular tumours with cytostatic agents has only a very limited palliative effect on the course of the disease and they can only hope for more tumour-specific and less toxic substances in the future.

Results

The 2-, 5-, and 10-year survival rates are given in Table 4, according to the histologic type of the tumour and the incidence and dissemination of metastases at the primary treatment. The 5-year survival rate for seminomas decreases from 88.6 % for cases without metastases to 38.4 % if local metastases, and to 20 % if distant metastases are evident. In the carcinoma group the corresponding rates are 35 %, 10 % and 3.3 % (Fig. 8).

The prognosis in the series for carcinoma of stage I is no worse than for seminoma of stage II: 54.8 % and 55.5 %, respectively, after 2 years, and 35.0 % and 38.4 % after 5 years (Fig. 8). In 79 %, the seminomas were

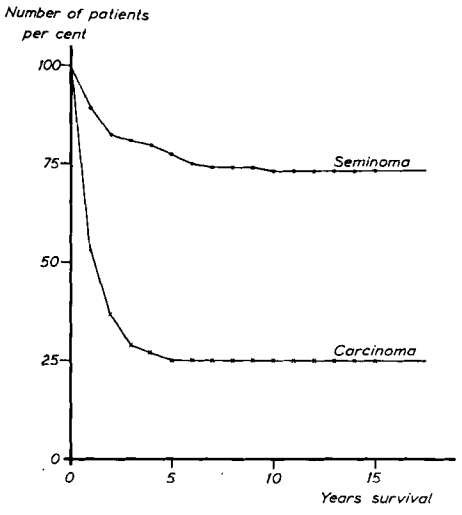

Fig. 9. Survival curves from 344 patients with seminomas and carcinomas according to the actuarial method.

without metastases at the primary treatment but only in 55.3 % of the carcinomas. These figures are however not quite comparable because the clinical diagnosis of metastases is less accurate in seminoma than the histologic diagnosis in lymphadenectomized carcinoma. In 7 of the 59 carcinomas of stage II, the metastases were first detected by lymphadenectomy so that, but for this opera-

Table 4

Survival rates for 355 patients with malignant testicular tumours according to histologic type and incidence of metastases at primary treatment (1921—1960)

Histologic type			2-year-survival		5-year-survival		10-year-survival	
	No	%	No	%	No	%	No	%
Seminomas	(212)		(178/212)	83.9	(130/173)	75.2	(87/133)	65.4
Stage I	168	79.2	158/166*	95.2	117/132	88.6	79/102	77.4
Stage II	27	12.8	15/27	55.5	10/26	38.4		
Stage III	17	8.0	5/17	29.4	3/15	20.0		
Stages II + III	44	20.8	20/44	45.4	13/41	31.7	8/31	24.2
Carcinomas	(132)		(49/132)	37.1	(24/110)	21.8	(22/81)	27.2
Stage I	73	55.3	40/73	54.8	21/60	35.0	19/52	38.2
Stage II	25	19.0	6/25	24.0	2/20	10.0		
Stage III	34	25.7	3/34	8.8	1/30	3.3	3/29	10.4
Stages II + III	59	44.7	9/59	15.2	3/50	6.0		
Adult teratoma 8 (all cases without met.)			8/8		8/8		7/7	
Nongerminal tumours 3 (all cases without met.)			3/3		1/1		0/0	
Total	355	100 %						

Stage I — no metastases, stage II — local metastases, stage III distant metastases.
* Two cases not followed up.

Table 5

Incidence in per cent of clinical metastases diagnosed by palpation and roentgen examinations, at the primary treatment and after, and the average intervals, in months, between the primary operation and diagnosis of metastases

	At primary treatment		After primary treatment			
	Seminoma 44 cases	Carcinoma 59 cases	Seminoma 54 cases		Carcinoma 79 cases	
	%	%	%	Average interval months	%	Average interval months
Lgll. aortoabdominales	64	64	41	16	24	9
iliacales	16	7	15	27	11	10
inguinales	18	7	9	14	6	3
mediastinales	16	3	30	20	13	9
supra. claviculares	11	22	17	12	19	6
colli	2	3	7	12	1	8
Pulmones	9	27	30	22	83	8
Hepar	—	7	7	22	7	8
Ossea	—	2	20	17	20	10
Local recidives	—	—	2	12	8	3

Table 6

Five-year survival rate for 334 patients with testicular tumour

Periods of observation, yrs	Tumour without metastases at primary treatment (stage I)						Tumour with metastases at primary treatment (stages II and III)					
	Seminoma			Carcinoma			Seminoma			Carcinoma		
	No obs	5-year-surv. rate		No obs	5-year-surv. rate		No obs	5-year-surv. rate		No obs	5-year-surv. rate	
		No	%		No	%		No	%		No	%
1920—1940	44	39/44	88.6	22	10/22	45.5	18	3/18	—	18	2/18	—
1941—1950	50	43/50	86.0	22	6/22	27.3	14	4/14	—	12	1/12	—
1951—1957	38	35/38	91.2	16	5/16	31.1	9	6/9	—	20	0/20	—
Total	132			60			41			50		
Average			88.6			35.0			31.7			6.0

tion, 61 % of the carcinomas would have been classified as stage I and 13.6 % as stage II.

The survival figures for seminomas and carcinomas, calculated in accordance with the 'actuarial method', are apparent from Fig. 9. For seminomas the curve becomes horizontal after 9 years, for carcinomas as early as after 4, i. e. a patient with seminoma may be regarded as 'cured' 9 years after primary treatment, a patient with carcinoma 4 years after treatment.

The incidence and anatomical distribution of clinical metastases (diagnosed by palpation and roentgen examination) are seen in Table 5. It is evident that the great majority of the metastases in seminoma as well as carcinoma cases are located in the periaortic lymph nodes. In cases of seminoma the metastases

Table 7

Survival of patients with testicular carcinomas according to histologic type and incidence and dissemination of metastases at primary treatment

Histologic type	No of patients	2-year-survival	5-year-survival
Embryonal carcinoma			
Stage I	26	11	5
Stages II + III	24	1	—
Teratocarcinoma			
Stage I	—	—	—
Stages II + III	5	3	2
Mixed types (seminoma, carcinoma, teratocarcinoma)			
Without structures of chorioepithelioma			
Stage I	42	26	14
Stages II + III	24	6	1
With structures of chorioepithelioma			
Stage I	5	2	2
Stages II + III	6	—	—
Total	132	49/132 = 37.1 %	24/110 = 21.8 %

Stage I — no metastases, stages II + III local and distant metastases.

are mainly disseminated in the lymphatic system but in carcinoma there was also a high number of pulmonary metastases at the time of the primary treatment. Late metastases of seminoma and carcinoma are mainly located in the lymphatic system, lungs and bones. The average time between primary operation and the detection of late metastases is nearly twice as long with seminoma as with carcinoma, which may be a sign of the more rapid dissemination and higher malignancy of carcinomas.

There was over the years a successive improvement in the ratio of the seminomas of stages I and II, but not in that of carcinomas, as shown in Table 6. The 5-year-survival rate of testicular tumours compared for different periods of time has not significantly improved in the present material, nor has MÜLLER (1962) been able to demonstrate any improvement in the Danish material, as was possible in Norway (HÖST & STOKKE 1959) and in the cases of the Royal Marsden Hospital (SMITHERS 1962). However, only a few cases in our material were treated with ^{60}Co which, as SMITHERS pointed out, has improved the results in the English material.

In Table 7, the 2- and 5-year survival rates for the different types of carcinoma and the incidence and dissemination of metastases at the primary treatment are recorded. It is evident that most of the survivors belong to the 'mixed' group of carcinomas without structures of chorioepithelioma and without metastases at the primary treatment. This suggests that it is not necessarily the lowest differentiated component in the tumour that determines the prognosis, as postulated by DIXON & MOORE (1953). It may be that the higher

Table 8

Tumour mortality in per cent after diagnosis of primary or secondary metastases and intervals between diagnosis of metastases and death

	Months < 2	Months 2—< 6	Months 6—< 12	Years 1—< 2	Years 2—< 3	Years 3—< 5	Years > 5	Total number of patients
	%	%	%	%	%	%	%	%
Seminoma.....	6	33	18	24	10	6	4	49
Carcinoma	12	33	34	17	1	2	—	99

radiosensitivity of seminoma structures, or perhaps the slower growth of a more highly differentiated teratocarcinoma component, are of importance. The prognosis is poor if structures of choriocarcinoma are present and in all patients with metastases at the primary treatment.

In the period between 1957 and 1960, 17 out of 35 patients with carcinoma have been operated upon with homolateral lymphadenectomy. Of 7 patients with histologically verified metastases in stage II, 3 survived after operation and irradiation (26, 42 and 59 months) and four have died. None of the unoperated patients has survived. Of 16 carcinomas in stage I, 8 were operated upon. Five of these patients are alive after 42 months (average) and 3 died after 23 months (average). Of 8 patients not operated upon, 3 have survived 47 months (average) and 5 died after 6 months (average).

No conclusions as to the therapeutic value of the operation can be drawn, however, from this material, as the cases have not been operated upon at random; only those with negative cavography have been subjected to operation, the rest having been regarded as inoperable. It is therefore hardly surprising that those with larger metastases showed higher mortality. Unfortunately it is very difficult to arrange a statistically satisfactory analysis of operated and non-operated cases selected at random; this might throw light on the therapeutic value of retroperitoneal lymphadenectomy.

Cavography has proved an unreliable indication for lymphadenectomy. It proved a false criterion in 12 out of 20 negatively assessed cases, and later histologic examination revealed metastases. A subsequent examination of the roentgenograms — with the results of operation known — supported the diagnosis in five cases but in seven the metastases were completely invisible with cavography. No false positive diagnosis had been made. Small lateral, particularly left-sided, perirenal metastases do not deform or displace the vena cava and therefore do not alter the venogram. Lymphography has greater possibilities and permits a safer diagnosis of the metastases, as could be shown by a comparison between lymphographies and simultaneous cavography (Mahafi 1964). It must, however, be kept in mind that small retroperitoneal metastases cannot be detected by any roentgenologic methods and that at any rate most of the cases with demonstrable metastases are in reality inoperable.

Tumour mortality after discovery of the metastases is shown in Table 8. For 2 to 6 months, the mortality for seminoma and carcinoma is 33 %; for 6 to 12 months it is unchanged for carcinoma but declines by a half for seminoma. After 2 years, almost all the carcinoma patients have died from the metastases while the prognosis for those with seminoma is somewhat more favourable.

Renal damage by irradiation. Renal damage by irradiation has been described by DEAN (1956), WILSON et coll. (1958) and HÖST & STOKKE (1959). If the whole renal parenchyma be irradiated with more than about 2 000 rad in 30 to 35 days definite damage of the kidney parenchyma slowly develops, with increasing fibrosis, endarteritis, finally resulting in vascular renal cirrhosis. Clinical complications such as hypertension, albuminuria, progressive anemia and uremia may develop if both kidneys are irradiated. This can however be avoided by individual planning of the radiation therapy, careful assessment of the actual tumour area and distribution of high dose levels to only one kidney (Figs 3, 4, 6 and 7).

Irradiation damage of the kidneys was observed in three of our patients.

Case 1. A 48-year-old patient with seminoma developed metastases in the epigastric nodes 2 months after the primary operation, in the iliac nodes 16 months later, and in the lungs and mediastinum 10 months later. All metastases were irradiated and disappeared. The epigastrium was irradiated through relatively large right and left ventral and dorsal portals. The absorbed dose in the left kidney was calculated as about 4 000 rad in 7 months, the dose in the right kidney as 2 700 rad in 9 months.

Ten years after the irradiation the patient developed chronic nephritis, severe hypertension and progressive retinopathia, and died 3 years later of these complications.

Case 2. A 47-year-old patient with seminoma, stage I, received postoperatively a dose of 2 500 rad to the left kidney with roentgen radiation. Six years later he developed vascular renal cirrhosis and the kidney was resected. The patient is now living without complications.

Histologic examination of the operation specimen revealed no inflammatory changes but destruction of the parenchyma and blood vessels and interstitial fibrosis.

Case 3. A 41-year-old patient with teratocarcinoma and periaortic lymph node metastases. The right kidney received a dose of at least 3 600 rad in 35 days with ^{60}Co. Chronic inflammation and progressive damage of the kidney function developed on the irradiated side two years later.

Sedimentation rate and clinical prognosis. That an increased blood sedimentation rate to over 25—30 mm/1 h is of prognostic importance after orchidectomy was pointed out by AHLBOM (1947). This was also reported by NOTTER (1956) and MÜLLER (1962); the latter further reported a highly significant difference between the sedimentation rates of patients with clinically manifest and latent metastases and patients without metastasis at the primary treatment. This was particularly evident in seminomas. A high sedimentation rate is therefore of special prognostic and clinical interest in seminomas without known metastases at primary treatment.

Fig. 10. Lead shield used for protecting the remaining testicle when irradiated with ^{60}Co.

Non-germinal tumours. The non-germinal tumour group contains 3 cases only: two tubular androblastomas and one interstitial cell tumour. None of these patients had metastases at the commencement of treatment or later. Their periods of observation are 9, 3 and 2 years.

A tubular adenoma was discovered in a hydrocele operation on a 5-month-old boy. After removal of the testis, 1 050 R (skin dose) was administered during 8 days to the epigastrium through an anterior and a posterior portal (170 kV, FHD 50 cm, HVL 0.7 mm Cu). The urinary excretion of hormones was not examined. He is without signs of tumour more than 9 years after operation.

The other patient with a tubular adenoma was 23 years of age. The excretion of hypophyseal gonadotrophin, steroids and estrogens was normal. There were no signs of tumour more than 3 years after operation.

Neither of these two patients exhibited clinical evidence of hormonal disturbance.

The patient with the interstitial cell tumour was 57 years of age. Bilateral gynecomasty, present before operation, soon disappeared following it. The gonadotrophin excretion was normal, but the excretion of estrogens was slightly increased. He received no irradiation after orchiectomy and is now, more than 2 years afterwards, without signs of tumour.

Radiation protection of the testis. Irradiation of the pelvic region, in particular, though also of the epigastrium, results in a considerable radiation dose to the testis remaining after semi-castration unless this is protected by a special shield. The dose received varies considerably, however, owing to the individual variations in the shape of the scrotum. In a small, short scrotum the testis lies close to the perineal skin and may be difficult to place in a lead shield; in such cases protection will therefore be insufficient. If the scrotum is large, on the other hand, protection will be much more efficient.

The greater part of the energy absorbed in the testis comes from the radiation

Table 9

Radiation dose to remaining testicle as a percentage of tumour dose

Treated area	Cobalt 60		Roentgen rays, HVL 2 mm Cu	
	Without shield	With shield	Without shield	With shield
Epigastric portal anterior	ca 1.0 %	0.01—0.1 %	ca 1.1 %	0.01—0.1 %
» » posterior	ca 1.0 %	0.01—0.1 %	ca 1.0 %	0.01—0.1 %
Iliac portal anterior	ca 4.0 %	0.10—0.4 %	ca 5.0 %	0.15—2.0 %
Whole treatment (three fields)	6.0 %	0.12—0.6 %	7.1 %	0.17—2.2 %

scattered in the irradiated parts of the body. The dose in the testis has been determined by measurements with a type of ionization chamber designed for radiation protection measurements by R. M. Sievert and R. Walstam. These dosemeters are of suitable size and their response is quite independent of the energy and angle of incidence of the radiation.

The lead shield, designed by L. Sundbom, used in irradiation with ^{60}Co, consists of two lead hemispheres with 25 mm walls (Fig. 10). For conventional roentgen radiation the testis is easily protected by bedding the scrotum in lead rubber.

The dose to the testis after irradiation through anterior and posterior epigastric portals and an anterior pelvic portal is given in Table 9. If treatment is administered with ^{60}Co through all three portals the dose to the testis may be decreased from 6 % to between 0.1 and 0.6 % by the lead shield. If the patient is roentgen irradiated (2.0 mm Cu HVL) the dose can be reduced from 7 % to between 0.2 and 2 % by lead rubber.

Examination of the sperma disclosed that irradiation of the pelvic region is followed by slight or severe oligo-astheno-terato-spermia, sometimes even by total sterility. Fertility may be impaired for many months and even years, though it is mostly completely restored after one or two months. Since, however, the surgical trauma and psychosomatic factors may influence the spermogenesis, conclusions as to the prognosis of fertility after operation and irradiation must be drawn with considerable caution. Disturbance in ejaculation is also observed after retroperitoneal lymphadenectomy, resulting in total and often therapeutically resistent aspermia. Nothing is known today about what radiation dose may be regarded as genetically harmless and the question therefore arises as to whether fertility is still desirable in these irradiated patients. It may be stated that 5 patients in the present series have had healthy, well developed children born to them after semi-castration and irradiation. A long-term genetic study of these patients and their descendents — similar to that proposed in England (SMITHERS 1962) — is most important and should be performed in several countries.

Dicussion

The indications for irradiation. The value of irradiation in the therapy of testicular carcinomas has long been discussed, some authors ascribing it no

importance at all, others reporting a clear effect on metastases and holding that carcinomas should not be described as generally radioresistant, even if they do require higher doses than seminomas (LINDGREN 1951, NOTTER 1956, MÜLLER 1962). These varying opinions are partly due to differences in histologic features and radiosensivity of the carcinomas. Most of them are not specially radiosensitive, but particularly carcinomas with several tumour types — above all with seminoma structures — may react very favourably to irradiation. Unfortunately, the metastases of carcinomas are often far more widely spread than can be demonstrated clinically, so that treatment of one region has often not been concluded before new metastases appear elsewhere.

Since metastases have been found to develop subsequently in the lumbar nodes, even in cases without retroperitoneal metastases at lymphadenectomy, the question arises whether postoperative radiation therapy ought not to be given to all cases. This has not been the routine to date but it might be justified especially in mixed tumours where the primary tumour presents radiosensitive structures.

DEAN (1956) proposed preoperative irradiation with 4 000 to 4 500 rad over 4 to 5 weeks to the retroperitoneal lymph nodes, a suggestion that has not been followed as far as can be gathered from the literature. However, it is not impossible that irradiation may be more effective and will be better tolerated by tissue with normal lymph drainage than after traumatizing lymphadenectomy.

Irradiation of the retroperitoneal lymph nodes is, on the other hand, generally recommended for all seminomas. Tumour doses between 700 and 3 000 rad are accepted at different irradiation centres and may be given with suitable techniques without endangering the surrounding tissues.

The calculated tumour dose in the lumbar nodes given at Radiumhemmet is about 1 600 rad in 14 days which, it would appear, is sufficient to destroy metastases of pure seminoma. HÖST & STOKKE (1959) consider an absorbed dose of at least 2 700 rad as superior, and SMITHERS & WALLACE (1962) are of the same opinion. These different experiences may perhaps have an explanation in a varying histologic definition of 'seminoma'. FRIEDMAN (1962) was able to demonstrate different radiosensitivity in seminoma by preoperative irradiation with varying doses. The typical pure seminoma was destroyed by a tumour dose of 1 000 rad in 14 days, but other types of seminoma, especially those with mixed structures, and of different testicular carcinomas, needed 2 500 rad in 14 days or 3 500 rad in 45 days. These atypical carcinomas are however classified in the present series as carcinomas, in accordance with DIXON & MOORE.

Prophylactic irradiation of the mediastinum and the supraclavicular regions has been attempted, for instance by PENDERGRASS (1946), SAUER et coll. (1948) and MÜLLER (1962), though no improvement in the form of increased survival rates has as yet been demonstrated. The impossibility of diagnosing small

lumbar and mediastinal metastases means that the dividing line between stages I and II, and between II and III is vague. Hence the question arises as to how often irradiation of the mediastinum is in fact prophylactic. In the present material metastases developed in the mediastinum and supraclavicular fossae in 8 % of seminomas stage I, 30 % of seminomas stage II and 25 % of carcinomas stage I. There may therefore be justification for irradiating the mediastinum and the supraclavicular regions in cases with epigastric metastases, especially in the radiosensitive seminomas. Metastases may however sometimes be missed when considering primary treatment. This has been investigated in 168 seminomas and 73 carcinomas stage I, i.e. supposedly metastasis-free cases. Of the seminomas, 32 (19 %) subsequently developed metastases and were thus in reality cases with metastases at the primary treatment. Together with the 44 cases diagnosed from the start, this makes 76, or 35.8 %, of the total number of seminomas. Of the carcinomas stage I, 46 out of 73 (63 %) presented metastases later; with the 59 cases with primary metastases, 80 % of all the carcinomas had metastasis at the primary treatment. This then would seem to be the true reason for the poor results of treatment.

The indications for retroperitoneal lymphadenectomy. The therapeutic value of lymphadenectomy in carcinomas with metastases, selected at random, has not yet been proved. Patients without metastases will be cured by orchiectomy alone. Nineteen of 73 patients with carcinoma, stage I, in this series have survived for more than 10 years without lymphadenectomy and relatively small doses of roentgen irradiation. Presumably the tumours were totally extirpated at operation. The three 10-year-survivors with carcinoma, stage II, should be regarded with some scepticism. The lumbar metastases were diagnosed clinically but not confirmed histologically, and the diagnoses may have been wrong. These three patients are alive 29, 22 and 13 years after the primary treatment.

Some patients with testicular carcinoma and lumbar metastases in whom surgery alone effected a cure for more than five years are reported however by WHITMORE (1962), demonstrating the definite value of lymphadenectomy in carcinomas.

Most of the lymphadenectomized patients have also received radiation therapy. Even though retroperitoneal metastases have not been found in as many as 50 to 60 % of the operated patients, 25 to 40 % of them die later of metastases (LEWIS 1948, PATTON & MALLIS 1959, DOWD et coll. 1959, THOMPSON 1961 and WHITMORE 1962). Lymphadenectomy therefore probably does not improve the prognosis of those without clinical metastases. On the other hand, it is difficult to avoid unnecessary lymphadenectomy as long as methods for diagnosing metastases are uncertain and limited.

There appears to be justification under these circumstances in performing lymphadenectomy, even in cases without clinically confirmed metastases, because of the general bad prognosis and relatively high radioresistance of these tumours.

Patients in the present material have undergone lymphadenectomy on the homolateral side only via the dorsolumbal approach by the HINMAN, KIMBROUGH & LLOYD LEWIS method. However most operators to-day recommend the thoracoabdominal approach which gives better exposure to the subdiaphragmatic region and allows simultaneous dissection on both sides (PATTON & MALLIS 1959, DOWD et coll. 1959, WHITMORE 1962). Metastases above the renal pedicles, which cannot be detected at operation by the dorso-lumbal approach, may easily be excised at reoperation by the thoracoabdominal approach. Two patients have been cured for more than five years by this procedure and a third died 2 1/2 years after operation without retroperitoneal metastases at the post-mortem examination (DOWD et coll. 1958).

A series of 60 patients was collected from three Swedish hospitals. Thirty-two had no metastases at lymphadenectomy, 20 of them are still living without signs of metastases and and 12 have developed metastases (5 pulmonary, 1 mediastinal and 5 abdominal); 7 of these 12 patients have died. Seven of the 28 patients with metastases at operation are still living after an average of more than 3 years (range 1 to 5 years); 6 of these 7 were operated unilaterally and one bilaterally. Twenty-one of the 28 patients with metastases at operation died; 5 of them were operated upon bilaterally and 16 homolaterally. Bilateral dissection could not avoid subsequent development of retroperitoneal metastases in 2 of 6 patients. All six have died with metastases.

No difference, such as that reported by MÜLLER (1962), has been found in the present series as regards the results of treatment in relation to varying intervals between orchiectomy and the start of radiation therapy.

Prognosis in seminoma and testicular carcinoma. The following signs are generally held to worsen the prognosis:

1. Primary tumour more than 4 cm in size, or invasion of the testicular tunics.
2. Tumour growth beyond the resection of the spermatic cord.
3. Invasion of the blood vessels by tumour cells.
4. Metastases at primary treatment, especially metastases above the diaphragm.
5. Visceral metastases.
6. Leidig cell hyperplasia in extratumoral testicular tissue.
7. High ESR before and after treatment.
8. Urinary excretion of choriogonadotrophin.

Conditions without importance for the prognosis. These are considered to be: duration of the history (as reported by the patient), gynecomasty, trauma, infiltration of the testicular tunics without breakthrough, infiltration of the epididymis, infiltration of the spermatic cord near the testis and epididymis.

Since approximately 80 % of all carcinomas have metastases already at primary treatment, it would seem logical to initiate cytostatic treatment as early as possible in conjunction with the primary operation, lymphadenectomy and irradiation. Naturally, the patient's general condition as well as the state of the bone marrow have to be taken into account. It may be that the early

use of cytostatics in connection with operation and irradiation is preferable to the late use of cytostatics when fibrotic damage of the blood supply and radiation necrosis impair the transport of the cytostatic agents and hence their action on the tumour cells.

SUMMARY

The treatment of 355 malignant tumours of the testicles, about 60 % of which were seminomas and 37 % carcinomas, is reviewed. Orchiectomy and irradiation, combined in some instances with homolateral retroperitoneal lymphadenectomy, formed the standard treatment. The prognostic importance of hormonal factors, trauma and metastases, as well as some practical aspects of operation and irradiation, are discussed.

ZUSAMMENFASSUNG

Die Behandlungsmethoden von 355 malignen Tumoren der Hoden, etwa 60 % Seminome und etwa 37 % Karzinome, wurden revidiert. Die normale Behandlungsweise war Exstirpation des Hodens mit Bestrahlung, kombiniert in einigen Fällen mit der gleichseitigen Exstirpation der retroperitonealen Lymphdrüsen. Die prognostische Bedeutung von hormonalen Einflüssen, von Trauma und Metastasen, sowie einige praktische Faktoren der Operations- und Bestrahlungstechnik werden besprochen.

RÉSUMÉ

Les auteurs ont passé en revue le traitement de 355 tumeurs malignes du testicule, dont environ 60 % étaient des séminomes et 37 % des cancers. L'orchidectomie et l'irradiation, associées dans certains cas à une lymphadénectomie rétropéritonéale homolatérale, ont constitué le traitement habituel. Ils examinent l'importance pronostique des facteurs hormonaux, du traumatisme et des métastases, ainsi que certains aspects pratiques de l'opération et de l'irradiation.

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