

CHAPTER V

**COMPLICATIONS OF THE POSTCHEMOTHERAPY RESECTION OF  
RETROPERITONEAL RESIDUAL TUMOR MASS IN PATIENTS WITH  
NONSEMINOMATOUS TESTICULAR GERM CELL TUMORS**

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## ABSTRACT

*The objective of this study was to evaluate the resection of the retroperitoneal residual tumor mass (RRTM) for histological examination after chemotherapy in patients with disseminated nonseminomatous testicular germ cell tumors (NSTGCT), with particular attention to surgical morbidity. From 1979 to 1995, 112 patients (mean age 28 years, range 16-53) with disseminated NSTGCT had residual disease after chemotherapy for which surgical evaluation was indicated; the histology of the residual tumor and the surgical complications were assessed. Possible associations between the occurrence of surgical complications and the age of the patient, size the residual tumor, operative duration, previous laparotomy and pathological findings were evaluated. The median size of the residual tumor was four cm (range 0-18); histological examination revealed viable cancer in 9.0%, mature teratoma in 44.1% and necrosis/fibrosis in 44.1% of the patients. In 3 patients (2.8%) no residual tumor mass was found at laparotomy. There were 26 complications in 20 patients (18.0%); urinary tract infection was the most common, occurring in nine patients (8.1%). One patient died during the induction of anesthesia. There were no significant relationships between the occurrence of complications and age, size of the residual tumor, operative duration, previous laparotomy or pathological findings. The resection of RRTM after polychemotherapy treatment for disseminated NSTGCT is a safe surgical procedure, with low treatment morbidity, mainly consisting of urinary tract infection. Knowledge of the potential complications may help to prevent morbidity. However, the surgical evaluation of the ultimate effect of polychemotherapy remains the gold standard.*

## INTRODUCTION

The initial treatment of patients with disseminated nonseminomatous testicular germ cell tumors (NSTGCT) is cisplatin-based polychemotherapy. The previously dismal prognosis of these patients has been improved dramatically with the development of this effective treatment.<sup>1</sup> However, on completion of the remission-inducing polychemotherapy, retroperitoneal residual tumor mass (RRTM) is still found regularly. Shrinkage of metastases may cease due to

necrosis and fibrosis or they may persist as mature teratoma.<sup>2,3</sup> Sometimes viable cancer is present. All mature teratoma tissue has to be removed to prevent the occurrence of the growing teratoma syndrome<sup>4</sup> or the development of a secondary malignancy in residual mature teratoma.<sup>5-7</sup> If malignant tumor tissue is still found to be present in the postchemotherapy resected specimen, salvage chemotherapy is indicated. Nevertheless postchemotherapy resection of RRTM has an important role in patients with retroperitoneal residual disease following normalisation of tumor markers with polychemotherapy. Resection of all the residual lesions for histopathology is necessary to evaluate the ultimate response. If no pathological mass is visible on the postchemotherapy computed tomogram (CT scan), some authors still advocate resection in the following situations: if a teratomatous component was present in the primary tumor;<sup>3</sup> if prechemotherapy retroperitoneal lymph node metastases were larger than 30 mm;<sup>8</sup> or if laparotomy is performed routinely as part of the treatment policy.<sup>9</sup>

At the University Hospital Groningen, the Netherlands, laparotomy is performed on all patients with a disseminated NSTGCT who become serum tumor marker-negative following remission-inducing polychemotherapy and who show evidence of retroperitoneal residual disease, or had mature teratoma in the primary tumor. The current paper describes the experience with postchemotherapy resection of RRTM and attention is focused on postoperative morbidity.

## PATIENTS AND METHODS

In the period July 1979 to March 1995, 112 consecutive resections of RRTM were performed at the University Hospital Groningen, the Netherlands, in patients with disseminated NSTGCT. All patients were treated with cisplatin-based polychemotherapy; in all cases it was the first operation after chemotherapy treatment. Initial clinical staging was performed by physical examination, chest X-ray, serum tumor markers alpha-fetoprotein (AFP) and human chorionic gonadotrophin (hCG) levels and CT scans of the chest and abdomen.<sup>10</sup> Until 1989, staging laparotomy was performed in patients with disseminated NSTGCT in conjunction with orchidectomy, to make a definite diagnosis regarding the size of the retroperitoneal lymph node metastases. On the basis of previous analyses, it was decided from that time onwards to perform this staging laparotomy only if radiological findings were inconclusive.<sup>11</sup> Since then

patients have been clinically staged with CT scans of the chest and abdomen. Patients with Stage I disease were treated according to the wait-and-see policy.<sup>12</sup> Patients with Stage II or higher were treated with cisplatin-based polychemotherapy: cisplatin, vinblastine and bleomycin (PVB) or bleomycin, etoposide and cisplatin (BEP). A total of four remission-inducing courses were administered; each course had a duration of three weeks. Up to 1982, patients were given maintenance treatment, as was usual at that time. This policy was changed on the basis of data that became available in the early eighties.<sup>13</sup> After completion of the polychemotherapy, the patients were clinically restaged with CT scans of the chest and abdomen and monitored for serum tumor markers. If serum tumor markers were still high or failed to decrease according to the known serum half-life times, supplementary salvage chemotherapy was administered. Otherwise any residual tumor was removed surgically and examined pathologically. This treatment strategy has been described previously by Donohue and Rowland.<sup>14</sup>

Over eighty percent of the resections of RRTM were performed by, or in the presence of the same surgeon. In total, four surgeons were involved in the treatment. The technique of trans-abdominal and thoraco-abdominal resection of RRTM used at the University Hospital Groningen had been described by Wobbes.<sup>15</sup> Generally, partial retroperitoneal lymph node dissection was performed. Standard preoperative procedures included subcutaneous heparin injection to prevent thrombosis, introduction of a gastric tube to prevent stomach dilatation and aspiration, and the introduction of a urinary catheter to monitor urine production during the operation. The urinary catheter also ensured collapse of the bladder and thus facilitated surgery in the pelvic area. Anesthetic management included continuous monitoring of oxygen saturation and intermittent arterial blood gas analysis. After induction, the  $\text{FiO}_2$  was maintained at the lowest level possible to still allow adequate oxygenation (21-25%).<sup>16</sup> The patients did not receive any perioperative antibiotics. Postoperative pain medication was not standardised. The histology of the resected residual tumor mass was compared to that of the primary testicular tumor, using the nomenclature of the World Health Organisation.<sup>17</sup>

Complications of postchemotherapy resection of RRTM were studied. A possible association between the occurrence of complications and the age of the patient, size of the residual tumor, operative duration, previous laparotomy and pathological findings was evaluated. Differences between subgroups of patients

with and without complications were analysed by means of the Mann-Whitney U-test for continuous data; for categorical variables, the Chi-square test was used or Fisher's exact test in case of small numbers.

## RESULTS

The mean age of the 112 patients was 28 (range 16-53) years; 77 of them had undergone staging laparotomy before remission-inducing polychemotherapy was initiated. Clinical staging at the time of diagnosis was as follows: Stage IIa, eight patients (7.1%); Stage IIb, 38 patients (33.9%), Stage IIc, 16 patients (14.3%); Stage III, 23 patients (20.6%); and Stage IV, 27 patients (24.1%). The median interval between the last dose of combination chemotherapy and resection of the RRTM was 38 (range 6-467) days. Of the 112 patients, 111 eventually underwent surgery. One patient (0.9%) died during induction of anesthesia. He experienced asphyxia, bradycardia and despite resuscitation efforts cardiac arrest. This patient was excluded from the analyses. The trans-abdominal technique was used in 109 patients. In two patients who also had residual pulmonary disease, the thoraco-abdominal approach was used, i.e. laparotomy with median sternotomy in one patient and laparotomy with left posterolateral thoracotomy in the other patient. The median operative duration, defined as time from incision to skin closure, was 150 (range 30-550) minutes. Median size of the residual tumor mass was four (range 0-18) centimetres. To enable the removal of all residual tumor tissue, partial resection and reconstruction of the aorta had to be performed in one patient and nephrectomy in four other patients.

### **Evaluation of the response to polychemotherapy**

Of the 111 patients operated on, 67 (60.4%) had a mature teratoma component in the primary tumor. This mature teratoma component was also present in the retroperitoneal residual tumor mass in 42 out of these 67 patients (63%), as well as in the residual tumor in 11 out of the 44 patients (25%) who did not have mature teratoma in the primary tumor. Thus, a total of 53 patients (47.7%) had residual mature teratoma. Despite normalisation of the serum tumor markers, histological examination still revealed viable cancer in 10 (9.0%) patients

(Table 1), among whom four also had a mature teratoma component in the residual tumor. Forty-nine patients had only residual mature teratoma in the resected tumor tissue (44.1%). In 49 other patients (44.1%) only necrosis and/or fibrosis was found. Although CT scans of the abdomen had identified a small retroperitoneal residual tumor mass, in three patients (2.8%) no residual retroperitoneal tumor mass was found at laparotomy, therefore resection was not performed.

**Table 1. Histological composition of the retroperitoneal mass in the ten patients with residual viable cancer (n=111)**

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Components	No.	%
E	2	1.8
Y	2	1.8
E+C	1	0.9
E+M	1	0.9
E+Y	1	0.9
M+I	1	0.9
E+M+I	1	0.9
E+Y+M+I	1	0.9
Total	10	9.0

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Abbreviations: C, choriocarcinoma; E, embryonal carcinoma; I, immature teratoma; M, mature teratoma; Y, yolk sac tumor

### **Complications of resection of RRTM**

There were 26 complications in 20 patients (18.0%). Three patients had two complications and one patient had four complications. Median hospitalization for uncomplicated resection of RRTM was seven (range 4-14) days, compared to 11 (range 5-33) days in patients with complications (P=.005). Table 2 shows a list of these complications, compared to the current literature.

**Table 2. Complications of retroperitoneal surgery**

<b>Complication</b>	Skinner'82 <sup>18</sup>	Moul'89 <sup>19</sup>	Jewett'91 <sup>20</sup>	Wahle'94 <sup>21</sup>	Baniel'95 <sup>22</sup>	Gels'96
<b>No. patients</b>	149*	148*	100*	40**	603**	112***
Wound infection	3	4	7	1	29	1
Wound dehiscence	2	2	2	1	-	1
Paralytic ileus < 6 days	-	0	2	-	1	3
Paralytic ileus > 6 days	-	3	1	-	13	0
Ileus; laparotomy	3	8	6	2	0	0
Chylous ascites	-	1	2	-	12	1
Lymphocele	1	2	3	2	10	2
Pancreatitis	-	1	-	-	6	0
Gastro-intest. bleeding	-	-	3	-	3	0
RP bleeding; laparotomy	-	-	1	-	1	1
RP/abdominal abscess	1	1	-	-	-	0
RP/abdominal hematoma	-	1	1	-	1	1
Colon necrosis	-	-	-	-	1	0
Ureteral injury	-	1	-	-	6	0
Ureteral stricture/obstruction	-	-	5	-	-	0
Urinary tract infection	-	-	1	-	5	9
Ischemic damage kidney	-	2	4	-	1	0
Renovasc. hypertension	1	2	1	-	2	0
Atelectasis/Pneumonia	2	2	4	-	34	0
ARDS	-	1	-	-	6	0
Prolonged ventilation	-	-	-	-	5	2
Pulmonary embolism	-	-	-	-	1	0
Femoral neuropathy	-	-	-	1	3	2
Other neural injury	-	-	-	-	4	0
Other complications	7	19	6	-	-	3
<b>Total complications</b>	20	50	49	7	144	26
in number of patients	19	45	35	6	125	20
	(13.0%)	(30.4%)	(35.0%)	(15.0%)	(20.7%)	(18.0%)
Mortality post-operative	2	0	0	0	5	0
	(1.3%)	(0%)	(0%)	(0%)	(0.8%)	(0%)
Mortality anesthesia	-	-	-	-	-	1
						(0.9%)

\* pre- and postchemotherapy retroperitoneal lymph node dissection (RPLND)/resection of residual retroperitoneal tumor mass (rRRTM); \*\* postchemotherapy RPLND/rRRTM; \*\*\* postchemotherapy rRRTM; - not described; RP, retroperitoneal; ARDS, Adult Respiratory Distress Syndrome

*Wound infection.* This complication occurred in only one patient, who also developed wound dehiscence four days after the infection.

*Gastrointestinal complications.* Ileus of less than six days duration was noted in three patients and was of a paralytic nature. All recovered after conservative treatment. Significant ileus for six days or longer postoperatively was not observed.

*Lymphatic complications.* Complications related to the lymphatic system were observed in 3 patients. Chylous ascites appeared in one patient after nine days. This patient responded well to conservative treatment with a low fat diet and diuretics. In two patients lymphocele occurred; both were diagnosed within one month after surgery. In one patient the lymphocele was aspirated under ultrasonographic guidance and did not recur. In the other patient, the lymphocele appeared to be infected. This necessitated puncture under ultrasonographic guidance and drainage for 9 days.

*Retroperitoneal bleeding or hematoma.* A significant decrease in the hemoglobin level was noted in one patient, with the clinical suspicion of retroperitoneal bleeding. This required relaparotomy. However, except for some oozing, no significant source of bleeding was found. One patient on anticoagulation therapy for pulmonary embolism (before surgery) complained about abdominal pain after 12 days. Ultrasonographic imaging showed a solid mass in the retroperitoneum, which after puncture turned out to be a hematoma. This patient responded well to conservative treatment.

*Urinary tract complications.* Urinary tract infection was the most common complication in this study: nine patients (8.1%). These patients were treated successfully with antibiotics.

*Pulmonary complications.* Two patients needed prolonged postoperative ventilation because of inappropriate oxygenation for two and five days, respectively. Respiratory failure due to pneumonia, the adult respiratory distress syndrome or pulmonary embolism was not observed.

*Neurological complications.* Femoral nerve neuropathy occurred in two patients. Both patients recovered early in the convalescent phase.

*Other complications.* Two patients developed moderately severe postoperative diarrhoea of undetermined etiology. One patient developed a bacterial infection in both eyes, due to insufficient care during anesthesia. No significant differences were found in the age of the patient, size of residual tumor, operative duration, previous laparotomy or pathological findings between the patients with and without postoperative complications.

## DISCUSSION

Surgical resection is widely accepted as the treatment of choice for retroperitoneal residual masses after polychemotherapy for metastatic NSTGCT.<sup>1</sup> Resection enables histological diagnosis of the residual mass, which may be purely benign with necrotic and/or fibrotic remnants only, or may contain mature teratoma elements or viable cancer. Resection of masses containing necrosis or fibrosis only is assumed to be of no therapeutic benefit and is usually not followed by additional treatment. Resection of mature teratoma is considered to be beneficial as it prevents growth of potentially malignant cells.<sup>8</sup> If resection is not performed, masses that contain mature teratoma may start to grow during follow-up (growing teratoma syndrome).<sup>4</sup> Resection may then be more complicated than it would have been shortly after the completion of chemotherapy. Finally, leaving masses with residual viable cancer unresected involves a serious risk. The presence of viable cancer in the residual mass directs the decision to administer additional chemotherapy.<sup>14</sup>

In this series, histological examination revealed viable cancer in only ten out of the 111 patients (9.0%); four of these patients also had a mature teratoma component in the residual tumor. Mature teratoma without viable cancer was found in 49 patients (44.1%). In 49 other patients only necrosis and/or fibrosis was found (44.1%) and in three patients resection was not performed because no residual tumor mass was found at laparotomy. The incidence of necrotic debris, mature teratoma, or viable cancer varies in different studies. In general, pathology reports revealed necrosis and/or fibrosis in about 40%, teratoma in another 40% and viable cancer in the remaining 20%.<sup>2</sup>

As histology determines the need for of resection, attempts have been made to predict the postchemotherapy histology.<sup>23-25</sup> Steyerberg found that predictors of necrosis were the absence of teratoma elements in the primary tumor, prechemotherapy normal AFP, normal hCG and elevated lactate dehydrogenase (LDH) levels, a small prechemotherapy or postchemotherapy mass and large shrinkage of the mass during chemotherapy. However, mature teratoma cannot easily be distinguished from viable cancer. The value of Magnetic Resonance Imaging (MRI) in the treatment evaluation of retroperitoneal lymph node metastases from NSTGCT was studied by Hogeboom et al.<sup>26</sup> They found that MRI was unable to predict the outcome of chemotherapy treatment.

Recently, Stephens et al have described a study to assess the ability of Positron Emission Tomography (PET-scanning) to differentiate between residual radiographic abnormalities in postchemotherapy NSTGCT patients. They found that PET could not differentiate necrosis/fibrosis from teratoma, but it could differentiate viable cancer from residual necrosis/fibrosis or teratoma.<sup>27</sup> Until now, the only procedure which gives optimal and accurate information regarding the histology of a residual retroperitoneal mass is pathological investigation of resected specimens obtained by surgery. However, the great advantage of surgery must be weighed against the disadvantages, i.e. complications.

Postoperative complications after resection of RRTM can be divided into two groups: general complications of the type that can develop after any laparotomy and specific complications of retroperitoneal lymph node dissection (RPLND). General complications include: postoperative haemorrhage, pneumonia, thromboembolism, urinary infection and disturbed wound healing. Although chylous ascites and lymphocele cannot be regarded as specific complications of RPLND, they are nevertheless conditions caused by damage to the retroperitoneal lymph node plexus. Infertility due to the loss of emission as a result of resection of the sympathetic nerves that traverse the area of resection, is a specific and common complication in patients who undergo full bilateral postchemotherapy RPLND. Less frequently it occurs in patients who undergo resection of RRTM after polychemotherapy. This complication has recently been assessed specifically by Van Basten et al.<sup>28</sup> They found that after resection of RRTM the prevalence rate of absence of ejaculation was 25.9%. The volume of the retroperitoneal residual masses was higher (95 cm<sup>3</sup>) in the patients with absence of ejaculation than in those without ejaculatory dysfunction (40 cm<sup>3</sup>). The absence of ejaculation was reported significantly more often in patients with right paracaval/inter aorta-caval located tumor (34.5%) than in those with left para-aortal located tumor (16.7%).

Overall, the number of complications did not differ essentially from the numbers reported in the recent literature (Table 2). It should be realized that the acute and long-term toxicity of chemotherapy can give rise to complications during surgical procedures. For instance bleomycin produces acute interstitial pneumonia and chronic fibrotic changes in the lung. Its use in standard testis cancer protocols places all such patients at risk for pulmonary insufficiency after long periods of anesthesia.<sup>16</sup> However, we did not observe an increased number of pulmonary complications, which may have been due to the low level of FiO<sub>2</sub> during

anesthesia. Although most authors did not report urinary tract infections, this complication occurred fairly frequently in this study. This may have been due to the fact that a urinary catheter was always introduced prior to the operation and a sample of urine was taken for culture directly after removal. Whenever pathogenic micro-organisms were found in the culture, antibiotics were given on the basis of the antibiogram and the urinary infection was documented as a complication.

It should be taken into account that resection of RRTM was well-tolerated by all of these patients, despite prior chemotherapy. The relatively young age and the vigorous premorbid condition enabled the patients to endure the major surgical procedure relatively well and with only a short postoperative period of hospitalisation. Depending on the volume as well as on the location of the residual tumor, adjacent structures or organs may have to be resected. In this study, nephrectomy had to be performed in four patients, while partial resection of the aorta followed by reconstruction had to be performed in one patient. Hendry et al described a series of 231 postchemotherapy RPLNDs. The ipsilateral kidney was removed with the lymph node mass in 12.5%; the aorta or iliac artery was resected or grafted in 4% and the vena cava was resected or tied off in 3%.<sup>29</sup> Operative mortality rates of between 0% and 1.3% have been reported in the literature (Table 2). In our study none of the postoperative complications resulted in mortality. However, one patient died during the induction of anesthesia. Obduction did not reveal any explanation for the sudden death of this patient.

The prognosis after the resection of residual disease is generally favourable, with a 5-year recurrence-free survival of over 85% after resection of necrosis or mature teratoma and of between 50% and 80% after the resection of viable cancer followed by additional chemotherapy.<sup>8,30</sup> Increased awareness of potential complications may help to prevent morbidity in patients with disseminated NSTGCT. However, surgical resection of RRTM remains the only procedure that gives optimal and accurate information about the histology of the retroperitoneal residual mass. The long-term remission rate obtained with surgery in adjunct to chemotherapy still justifies complete resection whenever it is indicated and possible.

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