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Clinical outcome of postchemotherapy retroperitoneal lymph node dissection in advanced nonseminomatous germ cell tumors

Swedish Title:

Kliniskt utfall av postkemoterapi retroperitonal lymfkörtelsutrymning av avancerade icke-seminomatös testikelcancer

Degree Project in Medicine

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Abstract

Clinical outcome of postchemotherapy retroperitoneal lymph node dissection in advanced nonseminomatous germ cell tumors

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Background: Nonseminomatous germ cell tumors (NSGCT) which have not responded adequately to chemotherapy requires subsequent surgical removal of the residual tumor (post chemotherapy retroperitoneal lymph node dissection, PC-RPLND).

Following PC-RPLND about 40% of the patients present fibrosis/necrosis in the final pathology report. Yet no truly satisfactory model is available to select patients where PC-RPLND treatment would improve prognosis.

Objectives: To evaluate perioperative and long-term clinical outcome of PC-RPLNDs performed between 2004-01-01 and 2017-12-13 at Sahlgrenska University Hospital and to analyze predicting factors for final pathology.

Methods: A retrospective analysis was made on patients who underwent PC-RPLND at Sahlgrenska University Hospital between the years 2004 and 2017. χ^2 test was used to analyze associations between tumor shrinkage and final pathology results.

Results: A total of 114 procedures were performed of which 85 were eligible for analysis. After a median follow up time of 6.8 years, 81 (95.3%) patients were alive. A total of 4 (4.7%) patients had died, 3 (3.5%) of which due to NSGCT. Regarding the safety of the procedure, 5 (5.9%) patients experienced complication grade IIIa (Clavien-Dindo classification). Six (7.1%) patients suffered from relapse of which 3 (3.5%) subsequently died

as mentioned above. In the final pathology report, 37 (43.5%) displayed fibrosis/necrosis 40 (47.1%) teratoma and 8 (9.4%) viable cancer. Tumor shrinkage of ≥50% was associated with fibrosis/necrosis at PC-RPLND.

Conclusions: Perioperative complications were low, with only 5 Clavien-Dindo IIIa complications. With greater shrinkage levels after chemotherapy, the probability of finding fibrosis/necrosis in the residual mass increased. However, a substantial proportion of patients with the greatest tumor size decrease would still benefit from the procedure.

Keywords: Nonseminomatous germ cell tumour; Retroperitoneal lymph node dissection; Testicular cancer

Background

Testicular cancer (TC) is a rare form of malignancy constituting about 1% of all cancers. Nevertheless, it is the most common malignancy among men aged 15-35 years. Approximately 380 cases of testicular cancer are diagnosed each year in Sweden (1). The incidence of TC has doubled worldwide in white men during the last 40 years with an annual increase of 3% to 6% (2, 3). In the Nordic countries this increase is even greater. In Sweden the incidence has increased from about 3/100 000/year in 1970 to about 8/100 000/year in 2015, and in Norway it has more than tripled during the same time period (4, 5). The cause of this increase in not known.

TC can be divided into two major groups: tumors originating from germ cells and tumors developing from the gonadal stroma such as the Sertoli or the Leydig cells. Germ cell tumors make up the majority (95%) and can be further divided into seminomas, embryonal carcinoma, yolk sac tumor, chorioncarcinoma, teratoma or mixed tumors (6). Yet another dichotomy is made between pure seminomas and nonseminomatous germ cell tumors (NSGCT). If the tumor consists of anything other than seminoma it is considered a NSGCT. The groups differ in histopathologic features and the fact that pure seminomas have normal levels of alphafetoprotein (AFP) in contrast to NSGCT. In addition, the two groups differ in prognosis and treatment regimens. Radiation therapy has been preferred historically for pure seminomas and chemotherapy for NSGCT. However, due to the risk of cardiovascular decease and secondary cancers chemotherapy has become the preferred treatment for seminomas as well(7, 8).

About 50 % of patients diagnosed with NSGCT will have clinically detectable metastases at diagnosis. Yet about one third of the patients in the group without clinically detectable metastases will reveal metastases during the 6 week long surveillance period (6).

The most common metastatic site for NSGCT is lymph nodes in the retroperitoneum. This is due to the testes "path of descent" from the superior posterior fetal abdomen through the inguinal canal and into the scrotum. When spread hematogenous the most common site of visceral metastases is the lungs (9).

The most common symptom a TC patient presents with is a palpable resistance in one of the testicles. This is sometimes accompanied by scrotal pain but more often than not the pain is absent. Through ultrasound the diagnosis is either to confirmed or ruled out. If diagnosis is confirmed a subsequent unilateral radical orchiectomy of the afflicted testicle is performed. It is important that the procedure is radical i.e. that the spermatic cord is also removed. The spermatic cord sometimes houses potentially malignant cells therefor the removal of this structure reduces the risk of relapse. The procedure is done through an incision in the inguinal region where subsequently the testicle and spermatic cord are evacuated.

After a diagnosis is confirmed a clinical staging will ensue. The model most commonly used are Royal Marsden which consists of 4 stages. The clinical staging procedure includes: serum levels of AFP, β-HCG, LDH and CT of thorax, abdomen and pelvis with IV and oral contrast. Clinical stage (CS) I shows no evidence of metastases.

In CS II patients have metastatic disease restricted to abdominal nodes. This stage will hold the majority of patients. This is due to the testes "path of descent" from the superior posterior fetal abdomen through the inguinal canal and into the scrotum. Therefore, the most common site for NSGCT to metastasize is lymph nodes in the retroperitoneum.

In CS III patients have supradiaphragmatic node involvement.

CS IV is the most advanced stage and these patients present with extra-lymphatic metastases. When spread hematogenous the most common site of visceral metastases is the lungs (9).

About 50 % of patients diagnosed with NSGCT will have clinically detectable metastases at diagnosis. If a patient is at CS I a later definitive staging is performed 6-8 weeks after orchiectomy. This is due about one third of the patients in the group without clinically detectable metastases will reveal metastases during the 6 week long surveillance period (6).

As mentioned earlier the primary treatment of metastatic NSGCT is cisplatin-based chemotherapy. In the 1970's this new drug revolutionized the treatment of TC with radically improved prognoses. Prior to the cisplatin era the outlook for patients with TC was very bleak. The response to the chemotherapy is evaluated radiologically and by repeated tumor marker measurements. Although cure rates are remarkably high following this treatment, surgical removal of residual tumor is sometimes required. If the residual tumor is situated within the retroperitoneal space a post chemotherapy retroperitoneal lymph node dissection (PC-RPLND) is performed.

Open PC-RPLND is extensive and requires a large incision and can be associated with significant morbidity. To limit the scale the surgeon focuses on specific areas of the retroperitoneum. These areas are determined by patterns of dissemination, the laterality of the primary testis tumor and radiological findings showing the extent of the disease.

The number of PC-RPLNDs performed in Sweden each year is approximately 35-40 (Figure 1)

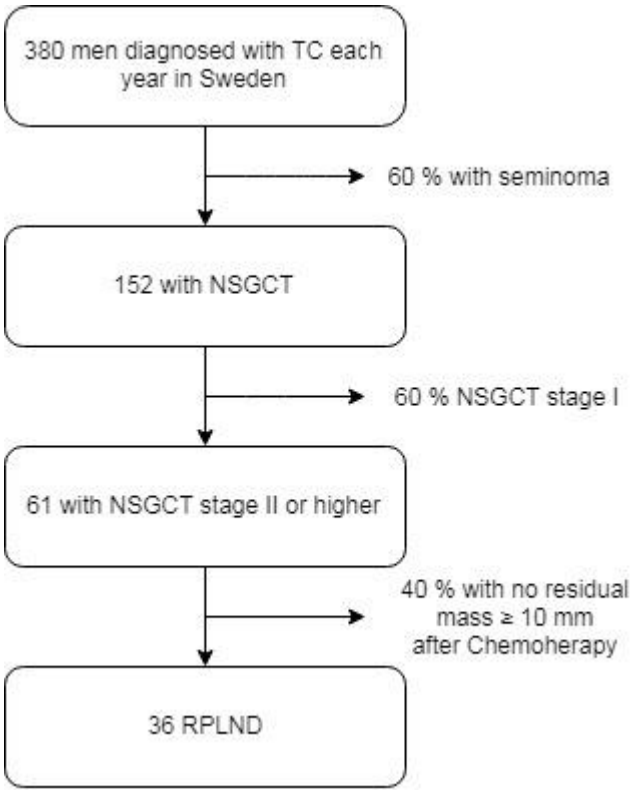

Figure 1. Flowchart over the approximate number people diagnosed with TC that ultimately goes through PC-RPLND in Sweden each year(10).

The figure below displays the different areas commonly used by surgeons. Anatomical landmarks such as the renal vessels, aorta, vena cava and arteria mesenterica inferior are used to determine the different areas (Figure 2).

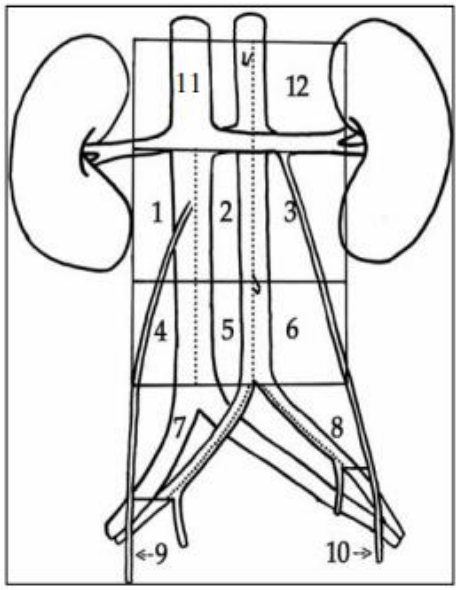

Figure 2. Schematic picture of the different areas of evacuation in retroperitoneal lymph node dissection.

These areas are then combined into certain templates. For example, the left unilateral template consists of areas 2+3+6+8+10 and the right 1+2+3+4+5+7+9. The right unilateral template is more comprehensible due to the path of the descending testes during development. Areas 11 and 12 are only occasionally evacuated.

Previous studies have shown that a substantial portion of patients, 35-50%, will have necrosis/fibrosis in the resected specimen following PC-RPLND. About 35-60% will have teratoma and only 2-15% will have viable cancer (11-14). Since necrosis/fibrosis is benign these patients do not benefit clinically from the procedure. Moreover, the proportion that reveals viable cancer is slowly dropping as better chemotherapy regimes continues to develop (6). Yet no truly satisfactory model is at hand for the selection of patients where PC-RPLND treatment would improve prognosis.

Teratomas are generally seen as a benign entity and does not frequently metastasize. However, they can grow in size and the mass can cause problems locally. Furthermore, there is a small risk of malignant transformation (2.9%) although rare (15).

A number of predictors for necrosis/fibrosis in the final pathology report has been identified. These include primary tumor histology, prechemotherapy AFP, prechemotherapy human chorionic gonadotropin (HCG), prechemotherapy lactate dehydrogenase (LDH), mass size and reduction in size (12).Other factors that have been suggested is the appearance of choriocarcinoma and absence of teratoma in the orchiectomy pathology report (16).

SWENOTECA (Swedish and Norwegian Testicular Cancer Group) changed their guidelines for the procedure with the release of SWENOTECA VIII in May 2012. Prior to this change every patient who initially had abdominal lymph nodes >2 cm before chemotherapy underwent the procedure irrespective of size of residual mass. The current guidelines state that the procedure is only mandatory for those with a residual mass of ≥10 mm after chemotherapy.

Being a technically demanding, and relatively infrequent procedure, PC-RPLND should be performed by experienced surgeons in dedicated referral center. Since 2017, Sahlgrenska University Hospital is one of two Swedish treatment centers for PC-RPLND.

Aim

To evaluate perioperative and long-term clinical outcome of PC-RPLNDs performed between 2004-01-01 and 2017-12-31 at Sahlgrenska University Hospital and to analyze predicting factors for final pathology.

Method

A retrospective analysis was made on all patients who underwent PC-RPLND due to advanced NSGCT at Sahlgrenska University Hospital during 2004-01-01 through 2017-12-31. The procedures were identified via the Sahlgrenska surgical database. Patient and tumor characteristics (age, testicular tumor pathology, laterality, tumor marker status, clinical stage and IGCCCG group) were gathered from medical records. Perioperative data (operation time, hospital stay, abdominal drainage, surgical complications, and any additional surgical procedures) as well as long-term clinical outcome (relapse and mortality) were registered. Surgical complications were classified according to the Clavien-Dindo system (17). In accordance with current guidelines, extent of retroperitoneal masses was evaluated based on appearance on CT, with the greatest transverse diameter as the size estimate. Post-chemo residual masses were classified into 5 size groups (<10mm, 10-<20mm, 20-<50mm, 50-<100mm and ≥100mm), and 3 groups based therapeutic response to chemotherapy (progression, shrinkage <50% and shrinkage ≥50%). Final pathology of RPLND specimen were classified as necrosis/fibrosis, teratoma or viable cancer.

We used the statistic tool SPSS to perform descriptive and inferential analyses. The χ^2 test was used to explore relationships between tumor shrinkage and necrosis/fibrosis in final pathology.

Ethics

Approval for the data collection has been given by the head of the urology department. National identification number and information regarding the patients have been handled in accordance to laws and regulations. The individuals were made unidentifiable upon analysis outside the Sahlgrenska server.

Results

Patient and tumor characteristics

During the 14-year study period, a total of 114 RPLNDs, on 109 men, were performed. Of those, 5 were lumpectomies due to seminoma metastases, 13 had not received prior chemotherapy, 6 had other NSGCT malignancies in the final RPLND pathology report, and 5 had missing data, leaving 85 procedures and patients eligible for analysis. The median follow up time was 6.8 years with an interquartile range (IQR) of 1,7-10,9. Median age at time of RPLND was 27 years (IQR 23-34). Further details are shown in Table 1 below.

Table 1 - Patient and tumor characteristics (n = 85)		Median	Interquartile range	Min	Max	No.	%
Age, y		27	(23-34)	16	53		
ASA	1					31	36.5
	2					44	51.8
	3					6	7.1
	4					1	1.2
	Missing data					3	3.5
Laterality	Extragonadal					5	5.9
	Right					37	43.5
	Left					43	50.6
Primary histology	NSGCT					70	82.4
	Teratoma					35	41.2
	Seminoma					4	4.7
	Missing Data					2	2.4
Royal Marsden staging	1					3	3.5
	1 Mk+					1	1.2
	2					47	55.3
	3					3	3.5
	4					31	36.5
IGCCCG prognosis classification	good					56	65.9
	intermediate					12	14.1
	poor					17	20.0

ASA = American Society of Anasthesiologists; NSGCT = Nonseminomatous Germ Cell Tumor; Mk+ = Tumor markers AFP/β-hCG persistently elevated; IGCCCG International Germ Cell Cancer Collaboration Group

At diagnosis, the majority of patients (55.3%) were at stage 2 (metastatic disease restricted to abdominal nodes). About one third (36.7%) were at stage 4 (extra lymphatic mestastases in i.e. brain, liver or bone). Four patients had no evidence of metastases (stage 1) but eventually revealed a mass on CT scan during surveillance.

In 4 cases only seminomatous cells could be found in the primary histology report. But due to elevated tumor markers these were treated as NSGCT.

Perioperative parameters

The perioperative parameters are shown in Table 2. Less than one third (29%) of the patients received a drain at the end of the procedure. However, four patients needed drain insertion sometime after the main surgery due to signs of lymph leakage. Totally 5 (5.9%) patients (including those who had a drain after surgery) suffered from severe complications (class IIIa according to Clavien-Dindo classification), no patient having higher grades. Other associated interventions during RPLND were rare; in one case a combined unilateral nephrectomy and adrenalectomy was performed to ensure radicality. In two cases the ureter was sutured and in one case the bladder was repaired due to iatrogenic injury. Other minor associated interventions are shown in Table 2.

The operation time had a median of 184 min (IQR 152-229). Postoperative stay had a median of 7 days (IQR 6-8). The median blood loss during the operation was 500 ml (IQR 300-100)

Table 2 - Perioperative parameters (n = 85)		No.	%
Blood transfusion		12	14.1
Peritoneal drain	Intraoperative	25	29.4
	After discharge	4	4.7
Clavien-Dindo complication classification	Grade 0/I	75	88.2
	Grade II	5	5.9
	Grade IIIa	5	5.9
	Grade IIIb	0	0
Associated interventions	Thrombectomy in vena cava inferior	2	2.4
	Suture of the urinary bladder	1	1.2
	Suture of the ureter	2	2.4
	Open insertion of ureteral stent	1	1.2
	Nepherctomy and adrenalectomy	1	1.2
	Appendectomy	3	3.5
	Extirpation of tumor of the small intestines	2	2.4
	Resection of the small intestine	1	1.2
	Open surgery of inguinal hernia	1	1.2
	Testicular biopsy	2	2.4
	Unilateral orchiectomy	3	3.5
	Implantation of testicular prosthesis	1	1.2

Tumor characteristics

Table 3 shows the distribution of tumor size change, residual tumor size and final RPLND pathology result.

Table 3 - Retroperitoneal tumor characteristics (n = 85)		No.	%
Tumor size change*	Increased	13	15.3
	Decreased <50%	31	36.5
	Decreased ≥50%	41	48.2
Residual tumor size	<10 mm	15	17.6
	10-<20 mm	28	32.9
	20-<50 mm	26	30.6
	50-<100 mm	12	14.1
	≥100 mm	4	4.7
RPLND pathology result	Necrosis/fibrosis	37	43.5
	Teratoma	40	47.1
	Viable cancer	8	9.4

* = As a result of chemotherapy; RPLND = Retroperitoneal Lymph Node Dissection

In the final RPLND pathology analysis of the tumor, 37 (43.5%) had benign tissue, 40 (47.1%) had teratoma, and 8 (9.4%). had viable cancer. Figure 3 shows the distribution of final histology depending on therapeutic response to chemotherapy. With greater shrinkage came an increase in the portion of necrosis/fibrosis and a decrease in the portion of viable cancer.

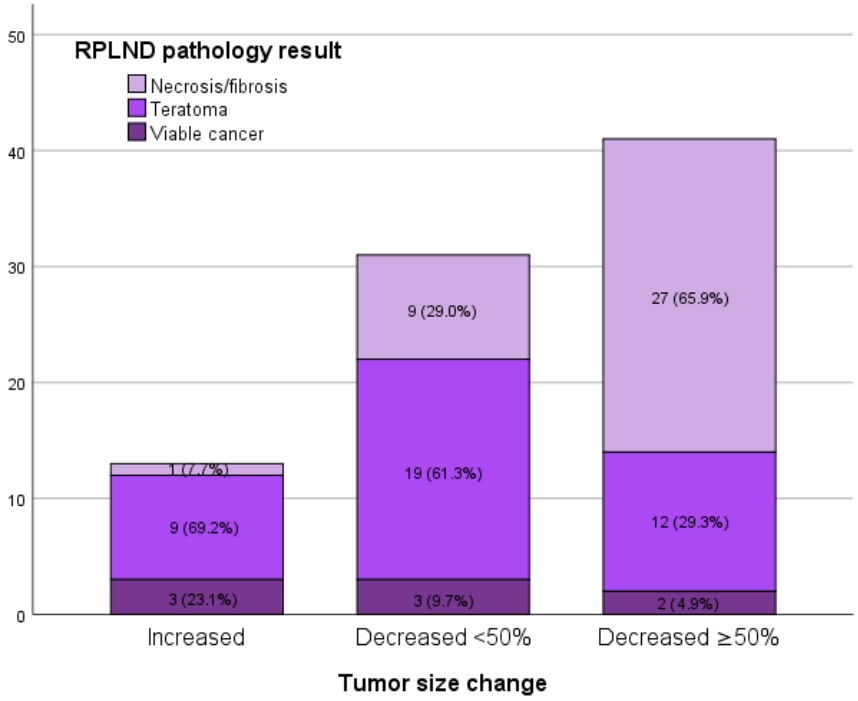

Figure 3. Distribution of Retroperitoneal Lymph Node Dissection (RPLND) pathology result in relation to tumor size change

Figure 4 shows the distribution of final histology depending on size of residual mass. It shows that no viable cancer was found in the group that had a residual tumor mass of less than 10 mm.

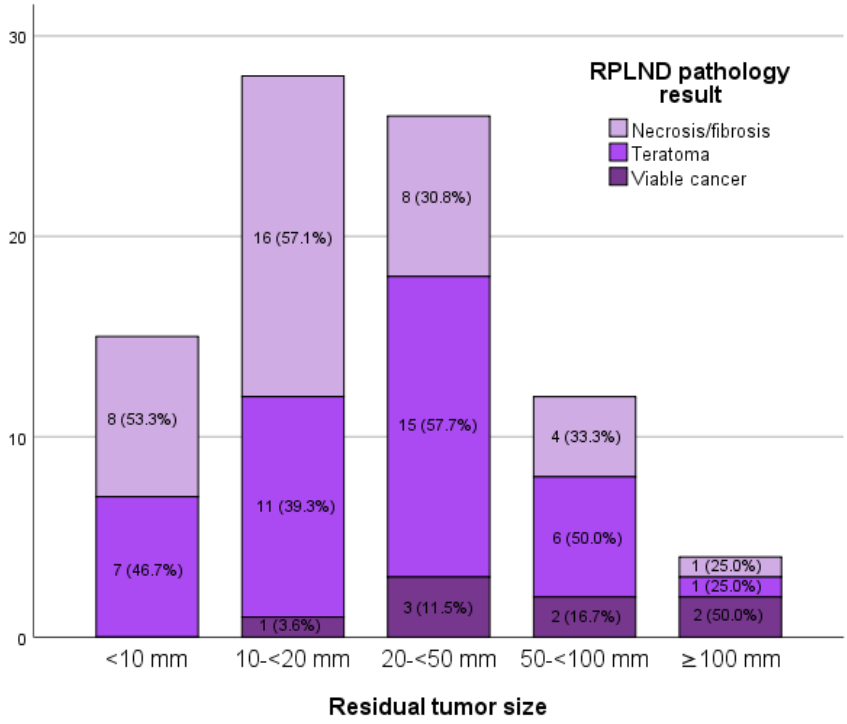

Figure 4. Distribution of Retroperitoneal Lymph Node Dissection (RPLND) pathology result in relation to residual tumor size

Through χ^2 analysis we found that a tumor shrinkage of ≥50% was associated with necrosis/fibrosis at PC-RPLND (*p<0.005)*

Clinical outcome

Up until 2017-12-31, 95.3% of the patients were alive at end of follow-up. Only 4 were deceased, 3 of which as a result of NSGCT yielding a 3.5% disease-specific mortality at 6.8 years. Those who died due to NSGCT did so within one year after the time of surgery, 5, 10 and 11 months respectively. These three patients displayed necrosis/fibrosis, viable cancer and mature teratoma in the final RPLND pathology report respectively. All patients were diagnosed at stage 4 (Extra-lymphatic metastases) and had poor prognosis according to IGCCCG.

An additional three patients had nonfatal cancer recurrence during follow-up leaving 6 (7.1%) with recurrence in total. Of these three patients two had mature teratoma and one had necrosis/fibrosis in their final RPLND pathology report after the first procedure. All three patients underwent subsequent surgery (resection of residual mass/lumpectomy) and were alive at the end of the study period.

Discussion

According to current guidelines on TC, patients with residual masses ≥1 cm after chemotherapy for NSGCT should undergo PC-RPLND due to the risk of teratoma or viable cancer in the resected specimen. In this study, the risk of teratoma was 47% and viable cancer 9%, which is in line with previous studies (11, 18, 19). The remaining 44% revealed benign histology meaning that a substantial portion of patients underwent the procedure without a clinical benefit. However, 59 of the 85 patients in this study were treated before May 2012, when SWENOTECA (Swedish and Norwegian Testicular Cancer Group) changed the indication for the procedure to only be mandatory for those with a residual mass of ≥10 mm. A total of 15 patients with a residual mass of <10 mm underwent the procedure, none of which had viable cancer in the final pathology report. Of these 15 patients 7 presented with teratoma and 8 with necrosis/fibrosis. This supports the most recent SWENOTECA guidelines from May 2012. Hence, the indication for PC-RPLND has sharpened over the years, but still a significant portion of TC patients need to undergo extensive surgery with no benefit.

While awaiting further diagnostic and molecular models to better predict final histology we need to minimize the risk of complications and negative effects of treatment. In November 2017, RPLND for metastatic TC was centralized to two national centers in Sweden in an

attempt to improve the quality of this relatively rare procedure. In addition, minimally invasive techniques have evolved and in the present study two patients were operated robot assisted laparoscopically. With a low rate of complications (5.9% Clavien-Dindo grade IIIa complications and no grade IIIb or above) and a 92.9% disease free survival this study supports previous reports from high-volume centers. These indicate that RPLND after primary chemotherapy for advanced NSGCT is safe and results in long-term disease-free survival.

In line with previous reports we found that a greater shrinkage levels after chemotherapy increased the probability of finding necrosis/fibrosis in the final RPLND histology. However, a substantial proportion of patients with the greatest decrease (≥50%) in tumor size would still benefit from the procedure (2 with viable cancer and 12 with teratoma out of 41).

Due to lack of time no further inferential analysis were made. But even though the χ^2 analysis is rudimentary it shows an important statistical relationship.

In recent years the overtreatment of this patient group has sparked an interest among clinicians and researchers to come up with better models for the selection of these patients (20, 21). By identifying determining factors and applying appropriate models there is a hope to change the paradigm of advanced testicular cancer treatment and avoid unnecessary retroperitoneal lymph node dissection.

Populärvetenskaplig sammanfattning på svenska

Testikelcancer är en sällsynt sjukdom som utgör ca 1% av all cancer. Den är emellertid den vanligaste typen av cancer bland män i åldern 15–35 år. Antalet som drabbas av sjukdomen har dubblerats världen över, och nästan tredubblats i Sverige, under de senaste 40 åren. Vad orsaken till denna ökning beror på vet man inte.

Det finns olika flera typer av testikelcancer. Den typ vi har studerat kallas icke-seminomatös och är den vanligaste, den utgör ca hälften av fallen. Sjukdomen sprider sig vanligtvis till lymfkörtlarna i rummet bakom bukhålan och den primära behandlingen är cellgifter. Även om de allra flesta blir friska efter cellgiftsbehandlingen krävs ibland operation för att avlägsna kvarvarande tumörmassa.

Efter utrymningen skickas den borttagna vävnaden till analys. I cirka 40% av fallen visar det sig att vävnaden bara består av ärrvävnad, dött material eller annan godartad vävnad. För dessa patienter är alltså operationen onödig. Än så länge finns det ingen tillfredsställande modell för att välja ut patienter där ingreppet är nödvändigt och förbättrar prognosen.

Vi gick igenom medicinska journaler och fann 85 lämpliga operationer att analysera som utförts på Sahlgrenska sjukhus mellan åren 2004 och 2017. Det vi var intresserade av att veta var hur det gick för dessa patienter både på kort och lång sikt. Vi ville även analysera faktorer som skulle kunna förutsäga om operationen var nödvändig eller ej.

Uppföljningstiden av patienterna var i genomsnitt ca 7 år. Fem patienter drabbades av allvarligare komplikationer i samband med operationen och sammanlagt fick 6 patienter återfall i sin cancer, varav 3 avled och 3 överlevde.

I den slutliga analysen av tumören hade 37 godartad vävnad, 40 hade teratom (som oftast är en godartad tumör) och 8 hade kvarvarande cancer.

Med tanke på ingreppets omfattning får komplikationerna, endast 5 allvarligare, i anslutning till operationen i denna studie anses vara låg. Även återfall och efterföljande död på grund av sin testikelcancer (6 respektive 3) var få till antalet.

Vi fann ingen kvarvarande cancer hos patienter som genomgick ingreppet och hade en återstående tumörmassa på mindre än 10 mm. Detta stödjer de senaste riktlinjerna från SWENOTECA (Swedish and Norwegian Testicular Cancer Group) från 2012. Då ändrade man sig och ansåg att utrymning endast vara obligatorisk för personer med en återstående massa på mer eller lika med 10 mm. Före detta skulle varje patient som hade förstorade lymfkörtlar före kemoterapibehandlingen genomgå operationen.

Vi fann också genom statistiska analyser att med större krympningsnivåer efter kemoterapibehandlingen ökar sannolikheten för att hitta godartad vävnad i restmassan. Dock är det emellertid så att en stor del av patienterna i gruppen med den största minskningen av tumörstorleken fortfarande drar nytta av utrymningen.

Fortsatt forskning inom området är nödvändigt. Skulle man kunna hitta en krympningsgräns kombinerat med andra faktorer där man kan avstå operation utan att man missar någon med kvarvarande cancer? Det behövs göras mycket för att förbättra urvalet av patienter och på så sätt slippa onödiga och dyra operationer samt minska onödigt mänskligt lidande.

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