



Review

Surgical treatment of metastatic germ cell cancer



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Abstract Among young men between the ages of 15 and 40 years, germ cell cancer is the most common solid tumor [1]. The worldwide incidence of germ cell cancer is 70 000 cases. Compared to all solid tumors of men, germ cell cancer accounts for 1% of all male tumors. Nevertheless, the mortality of this rare tumor entity is about 13% since 9507 patients died worldwide of germ cell cancer. The improvement in survival of germ cell cancer patients is due to a multimodal treatment of germ cell cancer including cisplatin-based chemotherapy and surgery leading to higher cure-rates even in advanced stages [1], whereas the increasing incidence of germ cell cancers cannot be thoroughly explained. In this article we review the current indications for surgery in metastatic germ cell cancers, highlight the strength and weaknesses of techniques and indications and raise the question how to improve surgical treatment in metastatic germ cell cancer.

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1. Introduction

Retroperitoneal lymphnode dissection (RPLND) for metastatic germ cell cancer has always been an essential part of the treatment of germ cell cancer with its description in the early 1900s [2]. Where surgery for metastasis could improve the oncological outcome for patients with meta-

static germ cell cancer, the introduction of cisplatin revolutionized the treatment and outcome in metastatic patients, increasing the cure rate of all germ cell cancer patients to over 95% [3].

In 1997, the International Germ Cell Cancer Collaborative Group (IGCCCG) published a classification for germ cell cancers, defining three groups based on 5-year progression-

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free survival (PFS) and overall survival rates (OS) [4]. In patients classified as good-risk, 5-year PFS was 88% and OS 91%. Intermediate risk patients' 5-year PFS was 75% and OS 79%. Patients defined as poor-risk presented with a 5-year PFS of 41% and an OS of 48% [4,5]. Irrespective of tumor features, and thus of the IGCCCG classification, it was shown that oncological outcomes were improved in any of the aforementioned groups, when patients were referred to high-volume centers [6–8]. Together with IGCCCG risk classification, germ cell cancer is described also according to clinical stage, which represents the metastatic spread of the disease. Stage 0, IA and IB represent non-metastatic germ cell cancer; instead stage IS, stage II and stage III represent metastatic germ cell cancer (Table 1).

Surgery plays a major role in the multimodal curative treatment of patient with germ cell cancer. According to the current guidelines of the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN), RPLND is crucial in the post chemotherapy setting (PC-RPLND) where PC-RPLND is subsequently performed after inductive chemotherapy [1,9]. However, as shown in Fig. 1, RPLND also has its place in the primary setting. An additional indication for surgery without prior chemotherapy is late relapse of germ cell cancer without elevated tumor markers. Late relapse is defined by relapse of disease more than 2 years after last termination of platin-based chemotherapy [10].

2. Anatomical boundaries for RPLND

The site, extent and technique performed for PC-RPLND have been discussed and described by several working groups. As both the EAU and NCCN guidelines on testicular cancer recommend a fully bilateral resection [1,9], several study groups have shown that unilateral template resection

might achieve equal oncological results than a bilateral resection [11–13]. Reason not to perform bilateral resection might be a better functional outcome measured by higher rate of antegrade ejaculation. A modified template resection of the right side includes the precaval, caval, paracaval, retrocaval and inter-aortocaval regions, as well as the region lateral of the common iliac vessels. The ipsilateral ureter represents the caudal and lateral boundary of resection. In patients without retrocrural or supra-hilar lymph nodes, the renal vein is described as the cranial and the crus of the diaphragm as the posterior resection boundary.

On the left side, a modified template resection includes the pre-aortic, retro-aortic and para-aortic lymph nodes. The cranial and posterior boundary is the left renal vein and the crus of the diaphragm. Medially, the superficial inter-aortocaval and preaortal lymph nodes up to the inferior mesenteric artery are removed with nerve-sparing (ns) of the right sympathetic nerves. Lateral and caudal boundary is represented by the ureter and the ureter crossing the vessels. In patients with radical template resection, both sides are removed as described above (Fig. 2). If possible, ipsilateral sympathetic nerves in all approaches should be preserved in order to improve the rate of antegrade ejaculation.

3. ns-RPLND without prior chemotherapy

3.1. Stage I non-seminomatous germ cell tumor (NSGCT)

RPLND in stage I NSGCT is one treatment option that is recommended both in the EAU as well as in the NCCN guidelines and the guidelines on early stage testicular cancer of the American Urological Association (AUA) [1,9,14]. To avoid long-term toxicity of chemotherapy, Albers et al. [15] investigated the role of ns-RPLND versus one cycle of chemotherapy with bleomycin, etoposide and cisplatin (BEP) in patients with stage I NSGCT. Three hundred and eighty patients were randomized to undergo ns-RPLND or one cycle of BEP independent of the presence of risk factors like lympho vascular infiltration. The recurrence rate for patients with RPLND was 8% whereas the recurrence rate of one cycle of BEP was only 1%. Beside the oncological outcome of primary RPLND in stage I NSGCT, Heidenreich et al. [16] presented that 7% of men suffer from loss of antegrade ejaculation due to unilateral modified surgery. Mano et al. [17] claimed to achieve similar results by ns bilateral primary RPLND for clinical stage I NSGCT.

Nevertheless, RPLND holds its place in the adjuvant treatment of stage I NSGCT especially in cases of teratoma or somatic transformations on histopathological findings of primary tumor.

3.2. Stage II NSGCT

Men with NSGCT after orchiectomy and clinical stage IIA without elevated markers represent a complex and rare group of patients, since a retroperitoneal mass of less than 2 cm and absence of tumor markers leaves the uncertainty of metastatic disease. Beside benign cause of this small

Table 1 Stage grouping for germ cell cancer (European Society of Medical Oncology, ESMO) [37].

Stage	Characteristics			
Stage 0	pTis	N0	M0	S0, SX
Stage I				
Stage IA	pT1	N0	M0	S0
Stage IB	pT2-pT4	N0	M0	S0
Stage IS	Any pT	N0	M0	S1-3
Stage II				
Stage IIA	Any pT	N1	M0	S0, S1
Stage IIB	Any pT	N2	M0	S0, S1
Stage IIC	Any pT	N3	M0	S0, S1
Stage III				
Stage IIIA	Any pT	Any N	M1a	S0, S1
Stage IIIB	Any pT	N1-N3	M0	S2
	Any pT	Any N	M1a	S2
Stage IIIC	Any T	N1-3	M0	S3
	Any T	Any N	M1a	S3
	Any T	Any N	M1b	Any S
	Primary mediastinal Extragonadal germ cell cancer	Any N	Any M	Any S

All abbreviations are shown in the [Supplemental Table 1](#).

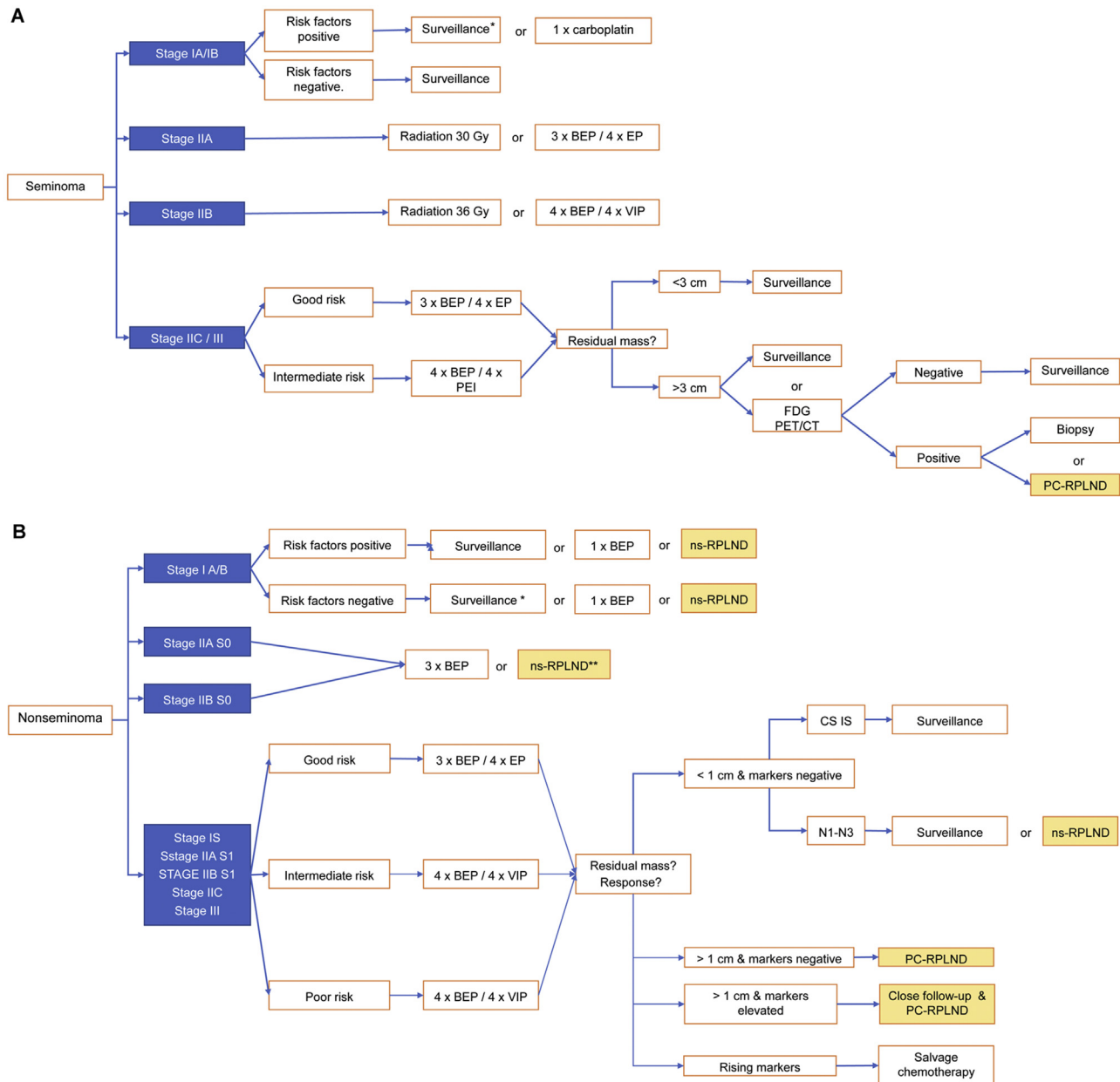


Figure 1 Flow chart of treatment of germ cell cancer according to the NCCN and EAU Guideline [1,9]. The indications for surgery are highlighted (yellow). (A) The clinical and diagnostic work-up of seminoma patients; (B) The clinical and diagnostic work-up of non-seminoma patients. BEP, bleomycin, etoposide, cisplatin; EP, etoposide, cisplatin; PEI, cisplatin, etoposide, ifosfamide; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PC-RPLND, postchemotherapy retroperitoneal lymphnode dissection; ns-RPLND, nerve-sparing retroperitoneal lymphnode dissection; CS IS, clinical stage 1S; VIP, vinblastine, ifosfamide, cisplatin; N1-N3, lymphodal metastasis WHO classification; NCCN, the National Comprehensive Cancer Network; EAU, the European Association of Urology. *preferred; **only selected cases.

retroperitoneal mass, teratoma or marker negative germ cell tumor can be cause of retroperitoneal mass. Stephenson et al. [18,19] could show that up to 48% of patients with tumor marker-negative clinical stage IIA have pN0 disease on histopathological report and 17% show teratoma. Therefore, ns-RPLND in this indication can be diagnostic and therapeutic in the same step. Since only 35% of patients seem to reveal vital tumor on marker negative clinical stage IIA and relapse rates after ns-RPLND

are as low as 2%–3%, surgery is a valid option in marker negative clinical stage IIA [20] and should be taken into account when patients are advised in treatment options. Whether RPLND has to be performed bilateral or unilateral is matter of ongoing discussion.

In cases of positive findings on histopathological report (pN1/pN2), chemotherapy or surveillance is an option. In pN1 patients without adjuvant chemotherapy, relapse rates are 10%–20% and in pN2, relapse rates after ns-RPLND

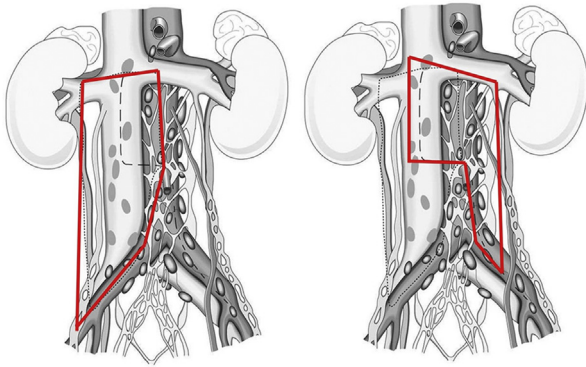


Figure 2 Graphical description of anatomical boundaries of right and left template PC-RPLND. Template resection of the right side includes the precaval, caval, paracaval, retrocaval and inter-aortocaval regions, as well as the region lateral of the common iliac vessels. Template resection of the left side includes pre-aortic, retro-aortic and para-aortic lymph nodes. The ipsilateral ureter represents the caudal and lateral boundary of resection; in patients without retrocrural or suprahilar lymph nodes, the renal vein is described as the cranial and the crus of the diaphragm as the posterior resection boundary. PC-RPLND, post chemotherapy setting retroperitoneal lymphnode dissection.

without adjuvant chemotherapy are up to 50% [21]. With two cycles of etoposide and cisplatin (EP) chemotherapy relapse rate in pN+ patients can be lowered to <2% [22–24]. In order to reduce chemotherapy toxicity, ns-RPLND with subsequent two courses of BEP chemotherapy in case of pN2 may be a treatment option in clinical stage IIA patients with NSGCT. pN1 patients should be left without adjuvant treatment.

4. Postchemotherapy RPLND

Germ cell cancer is a curable disease, even in metastasized patients. This excellent prognosis can only be achieved by a multidisciplinary treatment with chemotherapy and subsequent surgery is necessary. About 70% of metastasized patients show complete response after cisplatin based chemotherapy with normalized serum tumor markers and residual mass <1 cm. According to the current EAU and NCCN guidelines on testicular cancer, PC-RPLND is mandatory in non-seminoma patients with a residual mass larger than 1 cm in transverse CT diameter [1,9]. The aim of adjuvant surgery after chemotherapy is to remove all vital tumor cells including teratoma. In 7%–30% of all cases, histopathology reveals vital cancer and in 35%–65% post-pubertal teratoma. Necrosis can be found in 22%–50% depending on chemotherapy-regime [25,26]. In patients with residual mass less than 1 cm after chemotherapy, PC-RPLND and surveillance are optional recommendations. However, relapse rate under surveillance amounts to 6%–10% and mature teratoma is seen in about 40% of cases if surgery is performed [1,27].

As both EAU and NCCN guidelines recommend a fully bilateral resection of residual mass, several study groups

could show an improved functional outcome regarding antegrade ejaculation by achieving equal oncological outcomes after first-line chemotherapy for NSGCT [11–13].

To evaluate the extend of PC-RPLND and following the question whether PC-RPLND in strictly unilateral mass has always to be performed bilateral, we evaluated 171 consecutive patients undergoing PC-RPLND for non-seminoma germ-cell cancer after cisplatin-based chemotherapy. Ninety and 81 patients underwent unilateral template resection and fully bilateral resection respectively after first-line chemotherapy for NSGCT. The decision whether to perform a unilateral template or a fully bilateral resection was taken on the base of size and location of initial and residual tumor. Patients with a residual mass of less than 5 cm were considered for unilateral template resection as it was demonstrated that larger masses bear a higher risk of contralateral teratoma. Patients with a residual mass greater than 5 cm were considered for radical bilateral resection.

We could show that unilateral template resection of strictly unilateral residual mass of less than 5 cm could achieve ns in 87% vs. 40% resulting in a preservation of antegrade ejaculation in 94% of patients whereas in the bilateral resection antegrade ejaculation was only seen in 37%. In terms of functional outcome and midterm-oncological outcome, Hiester et al. [11], Heidenreich et al. [13] and Beck et al. [12] could show that unilateral template resection does not necessarily harbor higher recurrence rates but surely improves rates of antegrade ejaculation. Limiting to this conclusion, it must be mentioned that treatment of all three studies took place at a high volume tertial referral center and patients for unilateral template resection have been highly selected.

However, since 50% are overtreated with PC-RPLND and up to 50% of patients reveal necrosis on histological report of RPLND, questions have been raised for a predicting tool to avoid unnecessary RPLND in patient with high likelihood of necrosis. Paffenholz et al. [28] validated two models of predicting necrosis/fibrosis after inductive chemotherapy. The discriminatory accuracy of both models was not sufficient for clinical use, so that at the current time no investigation can rule out RPLND after chemotherapy.

5. Salvage RPLND

A special position in PC-RPLND is RPLND after salvage chemotherapy. About 30% of patients with metastatic germ cell cancer will experience refractory disease and will need salvage chemotherapy [29]. In this case, these patients have to be evaluated for salvage chemotherapy either with conventional dose chemotherapy (CDCT) such as paclitaxel-ifosfamide-cisplatin (TIP) or high dose chemotherapy (HDCT) mainly performed with paclitaxel-ifosfamide followed by high-dose carboplatin-etoposide (TI-CE) [30]. Independent of chemotherapy regimen used for salvage chemotherapy residual mass seems to harbor significantly higher percentage of viable tumor cells than after first-line chemotherapy. Miller et al. [31] and Lorch [29] describe viable tumor cells in about 30% of RPLND after salvage chemotherapy which is up to three times higher than after inductive chemotherapy [31,32]. Since residual mass after

salvage chemotherapy contains higher percentage of vital tumor, it seems to be reasonable to perform RPLND even in residual mass <1 cm in all former areas of tumor.

The rare case of persistently elevated tumor markers after salvage chemotherapy indicates that chemotherapy refractory cells survive salvage therapy. In this case, a desperation surgery is indicated. Several study groups could show that in patients with no marker normalization retroperitoneal histopathological findings reveal viable germ cell cancer in up to 84%. In this case, only few patients show long-term survival especially when viable cancer is found in the specimen [33].

6. Later relapse

Late relapse of germ cell cancer is defined as a recurrence of disease more than 2 years after completion of cisplatin-based chemotherapy with complete response after chemotherapy or complete RPLND.

The incidence of late relapse in germ cell cancer is low. After 20 years the incidence of late relapse is about 1.4% [34]. The median time to relapse is between 4.7 and 6.9 years.

The most common localization of relapse for both, seminoma and non-seminoma is the retroperitoneum (51% and 55%). In patients with seminoma, the second most location is the mediastinum while non-seminoma late relapse occurs in the lung the second most often [34]. In 2008, Sharp et al. [35] presented a single center study with 75 patients with late relapse. Fifty-three percent presented a unifocal and 44% a multifocal relapse. Only 3% presented with exclusively elevated tumor markers. The same study group examined possible risk factors for cancer specific survival. On multivariate analysis, two factors could be described as independent risk factors, bad clinical condition and multifocal recurrence [35].

In another study, Shahidi et al. [36] could show that the presence of teratoma on histopathological report of PC-RPLND increases the risk of late relapse by 3.4 fold. Another risk factor of suffering from late relapse is an inadequate first-line treatment especially missing out on RPLND with residual mass after chemotherapy.

The recommended treatment of late relapse germ cell cancer depends on localization, serum tumor markers and clinical condition of the patient. In case of marker negative late relapse and resectable findings primary surgery is recommended. Patients with unresectable late relapse have a poor prognosis regarding their cancer specific survival and require chemotherapy (CDCT or HDCT) and if possible surgical resection afterwards [1].

7. Conclusion

In general, germ cell cancer patients are young and do not present with a lot of comorbidities. Even in metastatic stages cancer specific survival rates are >90% and germ cell cancer patients present with a highly curable disease, depending on stage and treatment. Studies all over the world could show that thorough and guideline-adherent treatment of these men is of the utmost importance to achieve the highest cure rate possible. These cure rates are only to be achieved by multimodal treatment consisting of chemotherapy and subsequent surgery.

In this review we showed the strength of surgery through different stages of germ cell cancers. In case of marker negative nonseminoma with a clinical stage IIA, ns-RPLND is a valid option to avoid toxicity of chemotherapy since >50% do not harbor vital tumor.

In the PC-RPLND setting, surgery is crucial for survival in case of residual mass >1 cm for patients after cisplatin-based chemotherapy for metastatic NSGCT.

However, not only in first-line treatment of patients, surgery holds its place. Especially in advanced stages like salvage treatment surgical removal of all residual mass after salvage chemotherapy is mandatory for long-term survival.

Late relapse is a rare phenomenon and occurs only in 1.4% of patients. Surgical removal of marker negative relapse goes along with a higher long-term survival than patients presenting with unresectable findings.

Treatment of germ cell cancer patients is a highly specialized procedure whose outcome depends to a significant extent on excellent surgical provision.

Author contributions

Study concept and design: Andreas Hiester, Peter Albers

Data acquisition: Andreas Hiester

Data analysis: Andreas Hiester, Peter Albers

Drafting of manuscript: Andreas Hiester

Critical revision of the manuscript: Peter Albers

Conflicts of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ajur.2020.05.007>.

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