The role of postchemotherapeutic lymphadenectomy in the treatment of testicular germ cell tumors

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Objectives: To review the role of postchemotherapy retroperitoneal lymph node dissection (PC - RPLND) in patients with the advanced testicular germ cell tumors (TGCT) with special attention to indication, surgical technique and oncological outcome.

Methods: A structured review of the literature until June 2012 using the PubMed database was carried out.

Results: According to current guidelines and recommendations, PC - RPLND in advanced seminomas with residual tumors would be indicated only if PET scan performed 6 - 8 weeks after chemotherapy was positive. In nonseminomatous TGCT, PC - RPLND is indicated for all residual radiographic lesions with negative or plateauing markers. Loss of antegrade ejaculation represents the most common long-term complication, which can be prevented by nerve - sparing or modified template resection. The relapse rate after PC - RPLND is around 12%; however, it increases significantly to about 45% in cases with re - do RPLND and late relapses. Patients with the increasing markers should undergo salvage chemotherapy. Only selected patients with elevated markers who are thought to be chemorefractory would undergo desperation PC - RPLND if all radiographically visible lesions were completely resectable.

Conclusion: PC - RPLND represents a major part of the management of patients with the advanced TGCT undergoing inductive chemotherapy. Complete resection of all residual masses after primary chemotherapy results in a long - term disease - free survival of 95%. PC - RPLND requires complex surgical approach and should be performed in the experienced, tertiary referral centers only.

Introduction
Testicle tumors are the most malignant tumors in males aged from 15 to 35 years. The largest number of tumors (95 - 98%) includes tumors of germinal epithelium, while the rest are stromal tumors (leydigeoma, sertolioma and other rare tumors). Germ cell tumors are divided by their histological characteristics in two large groups - seminomatous and nonseminomatous tumors. The incidence of these tumors is different in world - they are extremely rare in Africa (0.1/100000), similar in Asia, while the incidence in the Scandinavian countries is up to 8/100000. In our country, the incidence accounts for about 3/100000. Earlier, these tumors were detected mostly in metastatic phase (in up to 60% of patients) while today the situation is quite different, meaning that almost 80% of all tumors are detected.

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in clinically initial stage of disease (CS - I). In the last 30 years, treatment of these patients was improved by development of effective multimodal therapy and significant success has been achieved in curing the majority of these patients, with the rate from 60% in 1970s to almost 98% at the beginning of 21st century1,2,3. Introduction of chemotherapeutical cisplatin protocols has considerably contributed to complete cure of these patients. On the other hand, detailed anatomical studies have confirmed primary sites of tumor spread to retroperitoneum. Retroperitoneal lymphadenectomy (RPLND) has become an integral part of management and one of the most important components in curative treatment of patients with the advanced stage and whose residual postchemotherapeutic metastatic tumor mass remained in retroperitoneum4,5,6. Introduction of modified plan of operative field and nerve sparing approach produced minimal morbidity when the procedure was performed by experienced surgeon in tertiary - level centers addressing this problem. Nevertheless, RPLND is a challenging surgical technique requiring good knowledge of RP anatomy, expertise in surgical techniques of vascular and intestinal structures as well as huge experience in management of patients with testicular tumors.

Detailed histological studies have contributed to identification of patients at high risk of metastatic diseases. The percentage of embryonal cancers and lymphovascular invasion (LVI) signs in primary tumors appeared to be independent risk factors of recurrence1,2,8. CS - I patients with over 80% of embryonal cancer (EC) and present lymphovascular invasion (LVI) in histological specimen of testicular tumor will be in stage II in 88% and patients with less than 45% of EC and negative LVI in histological specimen of testicular tumor will be without metastatic disease in 91.5%. The Testicular Cancer Intergroup study has shown that EC and LVI percentage precisely predict pathological stage (PS - II) of patients in 86% of the time. These data significantly helped in choosing the method of treatment and contributed to better positioning of RPLND in treatment of these patients.

Approach to treatment of patients with postchemotherapeutic residual metastatic mass largely depends on histology of primary tumor. All patients with NSGCTT who have postchemotherapeutic residual metastatic mass in retroperitoneum larger than 1 cm should undergo RPLND because they are at higher risk of mature teratoma finding in 40% - 45% and vital tumor in 10% - 15% of cases1,3,7,8,9,10,11,12. The patients with the finding of teratoma in tissue obtained by RPLND have disease - free survival (DSF) in 80%, while the presence of live tumor in specimen is associated with lower odds for survival12,13. In residual seminoma tumor changes in retroperitoneum, the size of the tumor (smaller or bigger than 3 cm) and FDG - PET scan results play a crucial role in their management. In spite of the above mentioned, there have been controversies on the issue of PC - RPLND. The first question is what to do with small residual tumor growth smaller than 1 cm, and second, if there was a possibility of anticipating the histology of residual mass, what would be the role of PET CT in decision - making for RPLND, how much this RPLND should be extensive, and finally, should RPLND be done under conditions of higher serum tumor marker (STM) level.

Although PC - RPLND is a routine procedure in the experienced medical centers, this procedure is associated with significant complications, because it is not rare (about 25% of cases) that it requires additional surgical interventions such as nephrectomy and major blood vessels surgery1,3,5.

PC - RPLND in seminoma
The patients having residual mass after CHT used for the advanced seminoma would be candidates for PC - RPLNDif only the growth was larger than 3 cm in diameter and had positive FDG - PET scan result. In all other cases, the residual tumor mass will not be resected, but its strict monitoring by STM determination and imaging techniques is necessary. Another indication is late recurrence of seminoma tumor in retroperitoneum.

After the applied induction CHT, vital cancer will be seen in about 12% - 30% of patients with residual mass larger than 3 cm, and in less than 10% of patients with mass smaller than 3 cm. Nevertheless, according to CHT protocols in manuals, the incidence of vital cancer in residual seminoma masses is up to 20% of the time independently from its size16.

Key words
testicular germ cell tumors; chemotherapy; postchemotherapeutic lymphadenectomy
Following the recommendations that masses larger than 3 cm in diameter should be resected, there will be almost 80% of unnecessary treatment without any benefit for patients. In order to make the right choice of patients who will have benefit from PC - RPLND, the role of PET - CT in prediction of vital tumor in residual masses of seminoma tumors was analyzed prospectively. In this study, the patients with residual mass after CHT underwent PET CT and surgery or monitoring - if the growth increased, it was considered malignant, and if it was stable or decreased within 24 months, vital tumor was considered absent. PET CT sensitivity and specificity to detect vital cancer was 80% and 100%, respectively, and there were no false positive and false negative findings\textsuperscript{17,18}.

In accordance with EGCCCG (European Germ - Cell Cancer Consensus Group) recommendations, upon completion of CHT or RT, residual tumor growth in seminoma need not to be resected independently from their size, but must be strictly clinically followed by imaging techniques and measurement of tumor markers. In patients with residual mass smaller than 3 cm, PET CT is optional. If PET CT scan results were negative, regular follow - up would be sufficient, but if PET CT done after 4 - 6 weeks of therapy was positive, it would be a good and accurate indicator of vital tumor in residual mass. In such case, histological confirmation by biopsy or tumor resection is required. Further treatment is based on the obtained histological findings (monitoring, surgical treatment, radiation, CHT). The patients with progression of disease are advised to have “salvage” CHT\textsuperscript{19,10}.

On the other hand, surgical resection of residual seminoma is technically challenging procedure due to extensive desmoplastic reaction of residual mass and adjacent vascular and visceral structures. Retrospective studies have demonstrated high incidence of complications and need for additional surgical procedures during PC - RPLND for seminomatous tumors. Additional nephrectomies and vascular procedures (partial or complete resection of vena cava and placement of aortic prostheses) are necessary in even 38% of patients in distinction from 25% of cases of PC - RPLND patients with NSGCTT.

**PC - RPLND in nonseminomatous germ cell testicular tumors (NSGCTT)**

In NSGCTT patients, PC - RPLND is indicated in cases where normalization or STM plateauing is achieved and residual mass is over 1 cm\textsuperscript{2,10}. In patients with small residual mass smaller than 1 cm, there would be higher risk of residual teratoma if teratoma was present in the initial histology. For this reason, these patients are also candidates for PC - RPLND, because although the residual mass is small, there is a predisposition to local growth, malignant transformation of teratoma and late recurrence. Residual mass with vital tumor inside reflects internal or external resistance to CHT, meaning that these changes would definitely progress if left in place in spite of later second - line or salvage CHT. The following indication for PC - RPLND is a recurrence with negative STM at the site of previously done RPLND, or negative residual STM or STM maintaining mass after salvage CHT. There is one additional, though rare, indication for so - called desperation PC - RPLND when there is CHT resistant tumor and potentially resectable tumor mass. If surgeon succeeded in removing the tumor in toto during surgical intervention, the probability for five - year survival would rise to 60% of the time.

In patients who had, after the initial CHT, normalization of STM values independently from the size of residual tumor in RP, the histological finding of resected residual tumor mass will be necrosis in 40% - 50%, mature teratoma in 35% - 40% and vital cancer in 10% - 15% of patients. PC - RPLND carried out after salvage CHT showed that the specimens of removed residual tumors would contain vital cancer in about 50% of the time.

The patients in good prognostic group according to IGCCCG criteria, after the complete resection of residual tumor containing less than 10% of vital cancer, have excellent odds for positive outcome of disease. If more than 10% of vital tumor was found or radicality of surgical treatment was questioned, the patients should undergo two additional CHT cycles. The patients in whom complete resection of residual tumor is not possible or only partial resection of tumor is done along with the increase of tumor markers, should receive a full dose of salvage therapy\textsuperscript{9,20}.

The patients with residual mass smaller than 1 cm are also candidates for PC - RPLND because different studies have shown that up to 20% of patients have mature teratoma and 8% have vital cancer as well. Increased risk of mature teratoma was also found when teratoma was present in primary testicular histology.
There have been suggestions, if technically feasible, to resect all locations where tumor mass was initially present independently from the fact whether any tumor mass remained after the CHT. However, this approach should be the issue of serious considerations and review following the publication of three retrospective studies completed in different centers. The group led by Kollmannsberger, upon analysis of 276 patients who had received CHT due to initial metastatic NSGCTT tumors and responded to therapy by reduction of tumor mass to less than 1 cm, found recurrence in 6% of patients and no lethal outcome after salvage therapy within the follow-up period of 40 months on average (8-128). Among them, 94% of subjects were in good IGCCCG prognostic group and only 3% in moderate and poor prognostic group. In a similar study on 141 patients during 15-year follow-up, Ehrlich et al. reported 9% of patients with recurrence and 3% of cases with lethal outcome. IGCCCG classification appeared to be the best predictor of response because the recurrence-free survival (RFS) and cancer specific survival (CSS) were 95% and 99%, respectively, for patients in good prognostic group, and 91% and 73%, respectively, for patients in moderate and poor prognostic group. However, the disease recurred in RP only in 6 of 12 patients, and accordingly, only 50% patients would benefit from PC-RPLND. Recently published study (2011) by German group for testicular cancer analysis (GTSCG) analyzed the results of 392 patients who had undergone PC-RPLND for residual masses of all sizes; thereupon, definitive histopathology was compared with the size of residual tumor mass and IGCCCG risk profile. The patients with residual tumor smaller than 1 cm had vital cancer and mature teratoma in 9.4% to 21.8% ratio. This proportion has increased to 21% and 25% in patients with tumor sized 1-1.5 cm, and to 36% and 42% in patients with tumor bigger than 1.5 cm. IGCCCG risk profile has not appeared as an independent significant predictor of final histology in small tumor growths, and therefore, the authors concluded that all patients, irrelevant from the size of their tumors, should undergo PC-RPLND in referral tertiary centers.

The role of diagnostic procedures
Six to eight weeks upon completion of the initial CHT, all patients should undergo CT scanning of the chest, abdomen and small pelvis, STM determination, and lung function tests should be done in patients with higher risk of pulmonary toxicity (4 PEB cycles, age over 40, smoking, renal failure). The condition of major blood vessels should be especially examined in patients with large tumor masses in RP because the involvement of the walls of vena cava and aorta ranges from 6% to 10% of these patients. If the infiltration of the walls of large blood vessels were suspected, MRI would be the right choice for examination. If the interior vena cava (IVC) and/or aorta were involved, their resection would be required because 2/3 of patients have vital cancer or mature teratoma in tumor mass. It is usual to use grafts designed only for aorta; venous complications in case of resection without IVC graft are seen in less than 5% of the time.

Extensiveness of surgery
The question of surgical approach and need for the extensiveness of surgery has been raised. There are two options to approach the residual tumor - classical open surgery and laparoscopic surgery. By so far published experiences, the classical open approach has been still the method of choice, while the laparoscopic method is reserved for the centers practicing exclusively laparoscopy and in the event of small residual masses.

PC-RPLND is a very complex surgical procedure requiring profound knowledge of surgery of vascular and intestinal structures as well as specificity in treatment of testicular tumors. In relation to the size and expansion of residual tumor mass in RP, a surgeon may modify the approach to RP space. Medial laparotomy from the processus xiphoideus to symphysis may be applied in the majority of patients with unilateral infradiaphragmatic, while Chevron incision may be used in supradiaphragmatic and bilateral disease. Thoracoabdominal approach is used in 10% of patients with the persistent retrocrural disease and it requires brilliant knowledge of retroperitoneal anatomy for avoiding significant surgical complications.

The extensiveness of surgery has been analyzed pretty much in literature, and the conclusion is that in some cases (tumor smaller than 5 cm) a surgeon may use so-called modified plan of operative field both for the right-side and left-side tumors, which will not interfere with the oncological treatment result, but will have a significant effect on reduction of morbidity of...
operation. To what extent a modified plan of operative filed may “miss” a residual tumor was shown by study of Carver and associates\textsuperscript{13}. The study analyzed 532 patients who had PC - RPLND, and followed the localizations of residual tumors in relation to modified plan of operative field. Residual tumor or teratoma was found in 7% - 32% of patients depending upon how modified plan of operative field was defined. In the right - side modification, residual tumors or teratoma were found in 32% of paraortic and 23% of preaortic nodi, while in the left - side in 29% of interaortocaval, 11% of precaval and 10% of paracaval specimens. Residual disease in contralateral iliac nodi was found in 4% of both left - and right - side specimens. This study is only a confirmation that the decision on the extensiveness of surgery must be made by an urologist with great experience in treatment of testicular tumors.

Illustration of modified plan of operative field
A special entity is teratoma “growing” syndrome. It appears in patients during the initial chemotherapy who have growing tumor mass in RP with normal or normalization of STM values. It is the question of chemoresistant teratoma. An adequate mode of treatment is a complete surgical resection in the form of complete bilateral lymphadenectomy since this teratoma is chemoresistant and no “salvage” or other chemotherapy will produce good response. Although teratoma is a benign tumor, it may cause a serious morbidity by its growth, and eventually mortality. Early recognition of this form of tumor will bring about early surgical resection of RP mass what will finally result in complete cure. If tumor resection was not complete, this tumor would recur in very high percentage (up to 83%)\textsuperscript{31}.

Abdominal MSCT - Teratoma growing syndrome

Special forms of pc - rplnd
Two forms of PC RPLND are singled out, termed as “salvage” and “desperation” PC - RPLND. They are applied in patients who, after the initial CHT, still have increased STM values independently from radiological response of the enlarged RP lymphatics, so they subsequently receive “salvage” CHT which will result in restoration of STM to normal. In these patients, the probability of the presence of vital cancer in residual mass is as high as 55% of cases in comparison with patients after the initial CHT. Probability of vital cancer will be lower if “salvage” therapy is based on taxanes (14% vs 42%), while teratoma incidence is approximately the same and accounts for 30% - 35%\textsuperscript{26}.

A special group includes patients with residual tumor mass without any normalization of STM values even after the “salvage” CHT. The patients, who undergo “desperation” PC - RPLND, have teratoma and necrosis in 20% - 40% and 10% - 20% of specimens, respectively. One should be aware of the fact that some conditions, which are not directly associated with tumor, may consequently manifest the persistence of STM values such as liver dysfunction (AFP), marijuana abuse and hypogonadism (hCG)\textsuperscript{27}.

PC - RPLND is not recommended in patients in whom hCG level rises in spite of performed measures of treatment because their prognosis of disease is very poor.

Two - year survival of patients with vital tumor found in residual mass is 44%, and with increased AFP and hCG levels is 17%\textsuperscript{28}.

Complications of pc - rplnd
In comparison with primary RPLND, PC - RPLND results in higher level of complications ranging from 7% to 30%, and mortality is around 1%. The complications after this surgical intervention are most often minor (wound infection, paralytic ileus, transient hyperamylasemia, lung atelectasis), while serious complications appear in less than 2% of cases (injuries to renovascular structures, acute renal failure, obstructive ileus, chylous ascites...). Retrograde ejaculation with consequential sterility is well known complication in patients with the complete bilateral lymphadenectomy. Tumor size, its localization and postchemotherapeutic desmoplastic reaction significantly affect the level of complications. Fortunately, advancement of surgical techniques and perioperative treatment has led to reduction of complications over time\textsuperscript{32}.

In different series, a percentage of complications depended on the experience of centers where operations were performed. In a German series from Dusseldorf, a total proportion of postoperative complications was less than 12% (out of which, even 55% of patients with moderate and poor ICGCCCG risk factors, 14% in late recurrence and 10% in “redo” PC - RPLND)\textsuperscript{6,16}.

Conclusion
PC - RPLND is an integral part of interdisciplinary man-
agement of patients having testicular germ tumors with the advanced metastatic disease upon the completion of CHT. Unfortunately, in spite of all attempts and performed studies until these days, there are no clinical parameters that may determine the histological characteristics of residual tumor mass after the end of CHT.

In patients with metastatic seminoma, PC - RPLND would be indicated only if the finding of residual mass over 3 cm was positive upon PET CT examination done 6 - 8 weeks after therapy. In NSGCTT, PC - RPLND should be done in all patients with the remaining residual mass larger than 1 cm, and even in those with growth smaller than 1 cm, depending upon the initial histology of testicular tumor. PC - RPLND is a complex surgical procedure, which should be performed in tertiary centers with great experience in treatment of testicular tumors.

**Σκοπός:** Η διερεύνηση του ρόλου της μεταχημειοθεραπευτικής λεμφαδενεκτομής (ΜΧΘ - ΛΕ) σε ασθενείς με προγραμμάτισες αρχικούς όγκους γεννητικών κυττάρων με έμφαση στις ενδείξεις, χειρουργικές τεχνικές και οικολογικό αποτέλεσμα.

**Μέθοδος:** Μια ανασκόπηση της βιβλιογραφίας μέχρι τον Ιούνιο του 2012 από τη βάση δεδομένων του PubMed.

**Αποτέλεσμα:** Σύμφωνα με τις υπάρχουσες οδηγίες, η ΜΧΘ - ΛΕ σε προγραμματισμένα σεμινώματα υπολειπόμενη μάζα ενδείκνυται μόνο σε θετικό PET scan 6-8 εβδομάδες μετά τη χημειοθεραπεία. Σε μη σεμινωματώδεις όγκους, η ΜΧΘ - ΛΕ ενδείκνυται σε όλες τις υπολειπόμενες ακτινολογικές βλάβες με αρνητικώς ή σταθερούς δείκτες. Η απώλεια της εκσπερματικής εμφάνισης είναι η πιο συχνή μακροχρόνια επιπλοκή, και μπορεί να αποφευχθεί με προγραμματισμένη λεμφαδενεκτομή. Το ποσοστό υποτροπής μετά τη ΜΧΘ - ΛΕ είναι περίπου 12%, όμως αυξάνεται σημαντικά σε 45% σε περιπτώσεις re - do Λεμφαδενεκτομών με όψεις υποτροπής. Ασθενείς με αυξημένους δείκτες πρέπει να υποβληθούν σε χημειοθεραπεία διάσωσης. Μόνο επιλεγμένοι ασθενείς με αυξημένους δείκτες που θεωρούνται χημείο - ανθεκτικοί μπορούν να υποβληθούν σε ΜΧΘ - ΛΕ, αν όλες οι ακτινολογικές εμφανείς βλάβες είναι πλήρως εξαιρετικές.

**Συμπέρασμα:** Η ΜΧΘ - ΛΕ αποτελεί ένα βασικό όπλο στην αντιμετώπιση ασθενών με προγραμματισμένους αρχικούς όγκους με προγραμματισμένες ακτινολογικές βλάβες με αρνητικούς ή σταθερούς δείκτες. Η μακροχρόνια επιπλοκή είναι η πιο συχνή μακροχρόνια επιπλοκή, και μπορεί να αποφευχθεί με προγραμματισμένη λεμφαδενεκτομή. Πλήρης εξαιρέσεις τοποθετούνται σε ασθενείς με αυξημένης επιπλοκής ακτινολογικές εμφάνισες βλάβες, και μπορεί να αποφευχθεί με προγραμματισμένη λεμφαδενεκτομή.
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