Author's response to reviews

Title: Comparison of laparoscopic and open postchemotherapy retroperitoneal lymph node dissection in patients with advanced testicular cancer a single center analysis

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Version: 2 Date: 10 March 2012

Author's response to reviews: see over
Revision remarks

New title: “Laparoscopic and open postchemotherapy retroperitoneallymph node dissection in patients with advanced testicular cancer a single center analysis”

Berlin, March 1\textsuperscript{st} 2012

Dear editors, dear reviewers,

Thank You for Your multiple and very helpful comments. Please find our reply to both reviewers below every remark and our changes marked in yellow within the revised manuscript.

We hope that our extensively revised article is now suitable for publication in BMC Urology.

Yours sincerely

J. Busch
S. Hinz

Reviewer #1: Philippe Spiess

Reviewer's report:
The present study compares open and laparoscopic approaches for postchemotherapy RPLND in patients with residual masses tin the clinical context of testicular cancer. The authors have compared intraoperative parameters, complications and post-operative tumor recurrence between these 2 subgroups, with a large subset undergoing a laparoscopic approach (n=43) versus an open approach (n=24). Overall, this is an interesting study but needs a host of revisions before it would be suitable for publication:

1. Within the abstract, there is no Methods section which would need to be included.
   \textbf{Authors' reply}: The instruction for authors of BMC Urology does not include a Methods section for the abstract. Therefore we did not include it in our initial version. We now added a methods section in the revised version of the abstract.

2. Within the manuscript, the methods section is at the end of the manuscript following the conclusions which should be re-arranged.
   \textbf{Authors' reply}: We agree with the reviewer that the disposition of the methods section is unusual. However the instruction for authors of BMC Urology requires the methods section at the end of the manuscript. Therefore we made no changes to our initial version regarding this remark.

3. Were the open and laparoscopic cases performed concurrently? and if so, what were the selection criteria for either approach?
   \textbf{Authors' reply}: This is an important aspect. The Charité department of urology is performing surgery in two different locations. On one campus all residual tumor resections were performed laparoscopically on the other campus all by the open approach. Therefore open
and laparoscopic cases were performed concurrently and consecutively. This information was added to the methods section.

4. The Clavien system was described to address postoperative complications. The authors have used it as a system to classify intraoperative complications. What was the type and incidence of perioperative complications in the two subgroups? **Authors' reply:** This is an important aspect. A detailed analysis of postoperative complications according to Clavien was added to the table 2. One O-PCLND patient underwent a relaparotomy due to a suspected bowel obstruction three days postoperatively. This information was also added to the results section of the revised version.

5. Was there any difference in the lymph node yield between the two approaches? Was there cancer in any of the nodes removed and what was their respective histology? **Authors' reply:** The point of the reviewer is well taken. Unfortunately a detailed analysis of the lymph node count was not part of the study design. Therefore this information is missing. The percentage of patients with viable cancer, mature teratoma or fibrous scar is given in table 2. A further detailed analysis of the viable cancer histology was not done during study planning and data acquisition. This could be a future project of ours.

6. In how many laparoscopic cases was dissection performed behind the great vessels and complete lumbar vessel clipping/cutting using a traditional "split and role" technique? **Authors' reply:** Complete resection behind the great vessels has at least been performed in all cases with a radical bilateral resection (L-PCLND: n=12; 26%). For the modified unilateral approach the extend of resection is defined by the template boundaries described in material and methods. This part was updated. The dissection of the lumbar vessels is quite delicate and demands very experienced laparoscopic surgeons. With the laparoscopic approach the lumbar vessels were clipped either by Hemolok clips (5mm or 10mm) or by 5 mm titan multifire endoclips. In some of the cases a intracorporal suture with a 4/0 Lahodny suture was necessary. Most of the times dissection behind the vessels was performed with the help of a small laparoscopic swab to role the great vessel therefore this technique is quite similar to a traditional split and role technique. Unfortunately the detailed technique is not described in our surgical report we just have the information of the extend of the dissection. Please also see the second reviewers comment regarding this issue.

7. The authors should state how many recurrences were in field and how many were distant. **Authors' reply:** In order to address this issue we added a new table 7 with details of all relapse patients. The corresponding text (section oncological outcome) in the results section was removed. Please also see the second reviewers corresponding remark and our reply.

8. What was the mortality rate (if any) in the two subgroups? **Authors' reply:** This is another important aspect since there was no intervention-associated death during hospitalization. This information is included in our analysis of intraoperative complications according to Clavien. Any death would have been mentioned there as a grade V complication.

9. The manuscript would benefit from scientific editing prior to being reconsidered for publication. **Authors' reply:** Thank You for this remark. We reviewed the manuscript with regard to language and grammar aspects and included the required corrections in the revised version of the manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests  
**Quality of written English:** Needs some language corrections before being published
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Reviewer #2: Wade Sexton**

**Reviewer’s report:**
Dr. Busch and colleagues report the clinical outcomes of patients undergoing open or laparoscopic post-chemotherapy retroperitoneal lymph node dissection (PCRPLND) for metastatic testis cancer. Those of us who manage advanced testis cancer patients would certainly agree that PCRPLNDs can at times be quite challenging requiring experienced surgeons with expert skill and knowledge of dissection techniques. In the post-chemotherapy setting, patient candidates for a laparoscopic approach have to be selected carefully due to the inherent difficulties associated with nodal and vascular dissection. A more important consideration is the premise that the first opportunity to cure (surgically) in the post-chemotherapy setting is absolutely the best opportunity to cure as re-do PCRPLNDs are even more challenging with greater risks for vascular injury and inferior surgical outcomes. To the authors’ credit, they correctly emphasize patient selection. However, the purpose of this study is to compare the outcomes between patients undergoing Lap-PCRPLND and Open-PCRPLND. In order to compare these patient groups, they should be similar in their clinical characteristics. Unfortunately, the two groups are not comparable which limits any conclusion the authors suggest other than stating that a Lap-PCRPLND is feasible in highly selected patients with very limited post-chemotherapy tumor volume. Furthermore, in many instances, the authors’ reporting of the data appears incomplete and at times is misleading.

**Major Compulsory Revisions:**
1. The groups undergoing PCRPLND and O-PCRPLND are not comparable. This poses the biggest problem with the manuscript and substantially biases the authors’ results. The authors should further address the following points and possibly reassess the aims of the study.

**Authors’ reply:** We agree with the reviewer. Our study certainly suffers from the bias related to the imbalanced distribution of the two groups. We changed the title of our study into “Laparoscopic and open postchemotherapy retroperitoneal lymph node dissection in patients with advanced testicular cancer a single center analysis”. Please also see comment on remarks # 1e, 15 and 16.

a. A significantly greater percentage of patients with good prognosis disease was managed with lap vs open PCRPLND.

**Authors’ reply:** We agree with the reviewer. Our study certainly suffers from the bias related to the imbalanced distribution of the two groups. The higher percentage of good prognosis patients in the L-PCRPLND cohort is one potential bias. Please also see comment on remarks # 1e, 15 and 16.

b. The median tumor diameter was significantly less in the lap group (2.2 cm) compared to the open group (6.7 cm). Most certainly, residual tumor size is associated with Clavien grade III complications, need for subsequent procedures, organ or vascular resection.

**Authors’ reply:** We agree with the reviewer. Our study certainly suffers from the bias related to the imbalanced distribution of the two groups. The smaller median residual tumor diameter of patients in the L-PCRPLND cohort is one potential bias. Please also see comment on remarks # 1e, 15 and 16.

c. The extent of the retroperitoneal dissection was significantly greater in the open group (61.9% of open patients undergoing full bilateral dissection vs. 26% of lap patients undergoing full bilateral dissection). Obviously, the surgical times would have been impacted tremendously if patient groups were comparable (longer operative times in the lap group).
Authors’ reply: We agree with the reviewer: Our study certainly suffers from the bias related to the imbalanced distribution of the two groups. The different extent of retroperitoneal resection of patients in the L-PCLND cohort is one potential bias. We can only speculate that in case of equally balanced groups the surgical times would be longer. Please also see comment on remarks # 1e, 15 and 16.

d. Two patients in the lap cohort underwent a simple lumpectomy – a procedure clearly recognized to not reflect the standard of care for the management of testis cancer. **Authors’ reply:** We agree with the reviewer that lumpectomy is not the standard of care. These two patients received an individualized treatment concept fully aware of the potential downsides of this surgical approach. Both patients had S0 marker levels and about 1cm residual tumor diameters at easily accessible locations. Both patients experienced no recurrence during follow-up and an uncomplicated hospital stay.

e. Comparing and analyzing the differences in Clavien complications (vascular injuries, nephrectomies, etc.) is difficult as again the groups are simply not comparable. **Authors’ reply:** Thank You for these very important and detailed remarks. Our study certainly suffers from the bias related to the imbalanced distribution of the two groups. Therefore we tried to perform a subgroup analysis of all small residual tumors. However this approach still did not generate an equal distribution of patients’ characteristics between both groups. We additionally performed a detailed univariate analysis of predictors of grade III intra and postoperative complications and could demonstrate that the residual tumors’ size (RR 1.24; CI 1.05-1.47; p=0.010) and the number of chemotherapy cycles (RR 2.90; CI 1.50-5.63; p=0.002) were the only two significant predictors. The surgical approach was not a significant predictor. This information was added to the results section. At last we present our data on L-PCLND and O-PCLND, provide for the best analysis with these data and clearly indicate the bias and weakness of our study. One future project could be a multicenter approach for both groups comparing exclusively small residual tumors. Also see reply to comment #15 and #16.

2. The abstract should be revised to reflect both methods and results sections standard to almost all journal formats. **Authors’ reply:** The instruction for authors of BMC Urology does not include a Methods section for the abstract. Therefore we did not include it in our initial version. We now added a methods section in the revised version of the abstract.

3. Unless specified by the journal, the methods section in the manuscript should be inserted following the background section. **Authors’ reply:** We agree with the reviewer that the disposition of the methods section is unusual. However the instruction for authors of BMC Urology requires the methods section at the end of the manuscript. We tried to follow these instructions very closely.

4. Results section first sentence. If 26% and 28.5% of 18 patients with seminomatous elements in the primary orchietomy specimen underwent L-PCRPLND and O-PCRPLND respectively, what transpired with the remaining 45.5% of patients? Maybe the authors have worded this sentence incorrectly? **Authors’ reply:** Thank You for this helpful comment. The first sentence was corrected as follows: “At orchietomy a total of 18 patients showed evidence of seminomatous fractions in the primary histology report (L-PCLND: n=12; 26.0% and for O-PCLND: n=6; 28.5%).” For further details of histologies at orchietomy please see table 1.

5. The authors never defined the modified templates they chose to utilize. For instance, in the modified right template, did they respect reports reflecting potential for right to left crossover of nodal involvement and resect the left paraaortics? For left sided templates, did they resect
the interaortocaval nodes? In the post-chemotherapy setting, did they completely mobilize the aorta and vena cava by dividing lumbar arteries and veins?

**Authors’ reply:** Thank You for this comment. We indicated the boundaries of resection by citing Heidenreich’s study of 2009. Due to space limitation we did not extensively repeat these definitions. In order to address comment #5 properly the following sentences were added to the manuscript: “The Right-sided modified template resection consisted of the precaval, paracaval, retrocaval, and interaortocaval regions as well as the area lateral to the common iliac vessels with the crossing of the ureter as a caudal boundary. The ureter served as the lateral and the renal vein as the cranial boundary. Similarly the left-sided modified template resection included the preaortic area down to the inferior mesenteric artery, the para-aortic and retroaortic regions with the ureteral crossing of the iliac artery as the caudal and the lateral boundaries of dissection. A radical template resection was performed in case of contralateral spread, interaortocaval location, or larger residual tumors completely mobilizing the aorta and vena cava.”

6. Did the authors perform nerve preservation – especially given that the median tumor volume reported for the lap cohort was only 2.2 cm. Thus, approximately ½ of the patients had tumor volumes less than 2.2 cm.

**Authors’ reply:** Almost 74% of our L-PCLND patients received a modified template resection or lumpectomy. Unfortunately the study protocol did not include a detailed documentation of preoperative and postoperative erectile function. The vast majority of these 74% received nerve preservation. Due to missing erectile function data we are unable to answer this question profoundly.

7. How many patients in each of the groups had a complete response following chemotherapy (defined as normal tumor markers with a residual mass less than 1 cm or no residual mass)? In the setting of a complete response, retrospective data from two recent reports support observation following chemotherapy rather than PCRPLND.

**Authors’ reply:** Unfortunately none of our patients fulfills these complete response criteria. All patients had residual tumor diameters ≥1 cm. The median and IQR values are indicated in table 2. Therefore a comparison of the above mentioned series with our data appears not to be applicable.

8. Did any of the patients have elevated markers at the time of PCRPLND?

**Authors’ reply:** We added tumor marker levels before and after chemotherapy to table 1 and the following sentence to the results section: “After chemotherapy ten patients revealed S1 tumor marker levels. All of these patients had a massive decline in marker levels from S3/S2 to S1 and a radiological response with decreased tumor diameters.” Additionally we added tumor marker analysis to the material and methods section: “…as well as tumor marker levels before and after chemotherapy”.

9. What criteria did the authors utilize to determine which patients would undergo open vs. lap PCRPLND?

**Authors’ reply:** This is an important aspect. The Charité department of urology is performing surgery in two different locations. On one campus all residual tumor resections were performed laparoscopically on the other campus all by the open approach. Therefore open and laparoscopic cases were performed concurrently and consecutively. This information was added to the methods section.

10. Table 1, the percentages of good, intermediate, and poor risk IGCCCG donot account for 100% of the patients in either of the lap or open groups. Either data are missing or the reporting of the results is inaccurate.

**Authors’ reply:** This is another important remark. We recalculated the distribution of IGCCCG prognostic stratae and analyzed the missing values. Table 1 was updated now providing the missing information.
11. Table 2, data is missing for residual tumor histology in at least one or more of the patients undergoing open surgery. Furthermore, please specify whether you are reporting lap patients with more than one histology (totals 50 patients).

Authors’ reply: Table 2 was updated in order to address this comment sufficiently. Missing values are given, multiple histologic subtypes were possible in the L-PCLND cohort.

12. Table 3. Grouping patients by clinical stage IIa through IIc and IIIa through IIIc and then comparing the patients with statistical analysis is terribly misleading—especially when comparing lap vs. open surgical approaches. The authors should divide into separate stages (i.e. IIa, IIb, IIc, IIIa, etc) and simply show the numbers. There is a tremendous difference between a IIa patient with a 1.5 cm residual paraaortic mass and a IIc patient with a 10.0 cm interaortocaval mass (± S1 markers).

Authors’ reply: We updated table 3 providing for the exact number of patients of each clinical stage according to Lugano.

13. Report the number of chemotherapy cycles in both groups. How many patients in each group were treated with salvage chemotherapy regimens following induction chemotherapy prior to undergoing PCRPND?

Reply by the authors: This is another interesting aspect of the study. We analyzed the number of cycles as well as the number of patients receiving salvage chemotherapy and included this information into the results section.

14. Table 5. In regards to further treatment, there must be 10 patients in the Lap group lost to follow-up and at least 2 patients in the open group lost to follow-up. The authors make no comment in this regard and do not explain the results. Although they errantly include a “surveillance group” in the “further treatment” section of this table, it seems that they should indicate the status of these other unaccounted for patients.

Authors’ reply: It is quite difficult to follow-up every patient especially in these young and very mobile patient cohort. In fact we contacted all local urologists who admitted the patients to our clinic, sent a letter to the last known patient’s address and tried to track the patients via their health insurance companies and a local tumor center network. Unfortunately a total of 10 patients had an incomplete follow-up (L-PCLND n=9 and O-PCLND n=0) and a total of three patients were completely lost to follow-up with no information available on life status (L-PCLND n=1 and O-PCLND n=2). This information was added to table 5 and the results section in order to clarify this point.

15. Table 6. The subgroup analysis is still non-comparable due to significantly different post-chemotherapy median tumor sizes and other unknown clinical factors.

Authors’ reply: This observation is already included in the first paragraph of our discussion section. The first section of our discussion section was enlarged by two sentences: “Due to all of these remaining confounding factors a profound comparison of our O-PCLND and L-PCLND patients does not seem feasible in spite of the data presented above. Larger multicentre studies focussing on small residual tumors are urgently needed to sufficiently compare the two surgical approaches.”

16. Discussion section. The first sentence needs to be revised. In addition, the authors’ data do not support their statement that long-term oncological outcomes were comparable due to many treatment biases as described, although the authors briefly discuss the study biases in the early part of the discussion section.

Authors’ reply: Thank You for this additional remark. We discussed this issue in our reply to remark #1e and #15, revised the first part of the discussion section and added the above mentioned two sentences: “Due to all of these remaining confounding factors a profound comparison of our O-PCLND and L-PCLND patients does not seem feasible in spite of the data presented above. Larger multicentre studies focussing on small residual tumors are urgently needed to sufficiently compare the two surgical approaches.” Additionally, we changed the title into “Laparoscopic and open postchemotherapy retroperitoneal lymph node
dissection in patients with advanced testicular cancer – a single center analysis” avoiding the term “comparison”. We also revised the abstract regarding this issue.

17. Table 3 and Table 6. In the manuscript, the authors suggest that no drainage tubes were inserted in the lap group, but in these two tables data show that drains were indeed placed in some patients undergoing Lap PCRPLND. (see results section , operative characteristics, duration of drainage tube 0 days). Why were drains placed in some and not in others? Is this a common practice for this group of surgeons? What criteria did the authors use to select patients for drains?

Authors’ reply: This is another helpful comment, thank You. We clearly stated that drainage tube were indeed used within the L-PCLND group providing details in table 3 and 6. For the whole laparoscopic cohort in 12 cases a drainage tube was put in place. A comparison of duration of drainage tubes was done counting every patient without a drainage tube as zero days and counting the exact number of postoperative days for patient with drainage tubes. Given the higher percentage of patients without tubes in the L-PCLND group (26% vs. 71%) the median duration is zero days compared to 3.5 days for O-PCLND. For the subgroup analysis six L-PCLND patients with drainage tubes and larger residual tumors were excluded further lowering the IQR values for drainage tube duration.

We believe that the observation criticized above is a statistical phenomenon also associated to the imbalanced group characteristics.

The rationale for using drainage tubes in the L-PCLND cohort largely depended on the surgeon’s intraoperative impression of wound secretion and residual tumor’s volume. This last information was added to the material and methods section.

18. Last sentence of the results section: Were the authors surprised by the findings that neither the IGCCCG classification nor the clinical stage correlated with survival? This is contrary to what has been reported for patients with good, intermediate, and poor prognosis disease. The discussion should be expanded in this regard.

Authors’ reply: This is an important notion. Therefore we expanded our discussion section by the following sentences: “These findings are in contrast to our findings - in a univariate cox regression analysis neither the surgical technique, the IGCCCG risk score, the clinical stage nor the residual tumor diameter were predictors of relapse-free and OS. Probably this difference reflects the large differences in our study cohort primarily consisting of good prognosis L-PCLND patients with small residual tumors.”

Minor Essential Revisions:
19. 18/67 primary tumors were pure embryonal carcinoma (a higher percentage than what would normally be expected). Was a urologic pathologist utilized for this study to re-review the specimens and standardize pathologic analysis?

Authors’ reply: Histologic evaluation of the specimens was initially done by senior uropathologists of the Charité University Medicine Berlin or under their supervision. In defined cases with open questions regarding the primary histology a retrospective re-evaluation could be performed. No changes were made to the manuscript.

20. Table 4, how can the estimated overall survival be significantly greater than the median followup?

Authors’ reply: This is a correct observation and probably reflects the difference between two statistical tests. The estimated overall survival was calculated as a mean value. For the determination of mean-estimated overall survival the Kaplan-Meier-method was applied censoring patients with short follow-up periods or a positive life status. For analysis of follow-up time all patients with a given follow-up period were included to measure the median value.

21. In the Results section, Outcome characteristics subheading, it is difficult to determine in which group patients 1-7 belong (lap vs open). The details regarding relapse would be presented better in a table format.
Authors’ reply: In order to address this comment we added an additional table 7 with details of relapse patients to the manuscript and removed the text in the results section.

22. Table 4. Correct several misspelled words.
Reply by the authors: Thanks for this notice. We corrected several misspelled words.

Discretionary Revisions:
23. In the two patients with pure seminoma in the primary tumor that subsequently underwent L-PCRPLND (table 1), did they undergo surgery for tumors greater than 3 cm in diameter or for a positive post-chemotherapy PET scan?
Authors’ reply: Unfortunately this issue remains unresolved due to a paucity of data.

24. Table 3. Why were there more major vascular injuries in the Lap group and what was the outcome?
Authors’ reply: This interesting question that will probably remain unresolved. We can only speculate that a reduced tactile feedback during L-PCLND could account for the higher percentage of vascular injuries. Due to the significantly imbalanced patients’ characteristics, the single center nature and other unknown confounding factors we cannot answer this point profoundly. Regarding outcome we already described the conversion of three L-PCLND cases (6.5%) to laparotomy due to uncontrollable bleeding. All other vascular injuries could be managed laparoscopically as stated in our manuscript.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.