Author’s response to reviews

Title: Neo-adjuvant treatment of adenocarcinoma and squamous cell carcinoma of the cervix results in significantly different pathological complete response rates.

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Author’s response to reviews:

Gent, October 16th

Dear Editor-in-Chief,

We would like to thank the editor and both the reviewers for considering our manuscript for publication and for the valuable comments and questions.

In this point-by-point response letter we will provide a detailed response to each comment or question posed by the reviewers.
Sincerely,

Prof. Dr. Katrien Vandecasteele,

On behalf of all co-authors

Reviewer 1 (Kathleen Gong Essel, M.D.):

Aim: To determine the clinicopathological characteristics of patients with cervical cancer treated at a single university center and to investigate the differences in survival and relapse rates between AC and SCC of the cervix.


1. Primary goal compare survival rates & relapse pattern between AC & SCC
2. Secondary goal: evaluate a difference in survival, relapse pattern, & pathological tx response to NA-CRT between AC & SCC in the NACRT group.

N=179. AC = 36. SCC 143. 40% stage IB.

Significant overall findings:

1. 5 yr DSS NA-CRT group -AC 100% vs SCC 75.5%
   a. Univariate analysis revealed +LN, tumor size, and advanced FIGO stage influenced DSS.
   b. Thrombocytosis, tumor differentiation, LVSI did not affect DSS
   c. Multivariate analysis revealed only FIGO stage had significant impact on DSS

2. 5 yr DFS Entire cohort - AC 73.8% vs SCC 79.2 % p=0.8
   NA-CRT group - AC 61.5% vs SCC 72.3% p=0.56

3. pCR NA-CRT group - AC 7% vs SCC 43% (p=0.02)
4. Relapse rate Entire cohort -- AC 22% vs SCC 20% (p=0.90)
a. Site of 1st relapse AC v SCC (N.S.)
   locoregional 12.5% v 39%,
   distant nodal 12.5% v 4%,
   distant non-nodal 50% v 18%,
   combo 25% v 39%

5. NACRT Relapse rate AC 36% v SCC 27% (p=0.74)
a. Site of 1st relapse AC v SCC (N.S.)
   locoregional 0% v 42%,
   distant nodal 20% v 5%,
   distant non-nodal 60% v 16%,
   combo 20% v 37%
   No changes

Other comments:
1. Page 12 line 14 Please clearly define early vs late stage AC & SCC. The reason as to why 5 yr DSS was utilized was well described.
   The definition of early and late disease was already stated in the materials & methods section (page 6 line 13) and also included on page 11 line 2-4 for the ease of the reader.

2. Page 13, lines 1-5 - This was one of the secondary goals of the study. Recommend breaking up this sentence so that it is easier to read.
   We broke the sentence up as suggested by the reviewer in page 11 line 18-20.
   This paper explores a novel concept - the ability of chemoRT to result in a pathological CR amongst patients with adenocarcinoma vs SCC of the cervix. This article specifically explores
differences in outcomes in patients who are treated with neoadjuvant chemoRT followed by surgery. This currently is not a widely-accepted standard of care. This warrants an explanation regarding this alternative and why it was selected as a treatment strategy in this hospital, particularly in patients with advanced disease for whom the current standard of care if ChemoRT.

We addressed the choice for NA-CRT in the introduction section page 4 line 20-22 and page 5 line 1-7 as follows: Definitive CRT is a 2-step process consisting of external beam RT ± chemotherapy (if possible cisplatin) and a brachytherapeutic boost. Even with the use of image-guided dose-intensified brachytherapy, local relapse arising from CRT-resistant foci is high (3y-local pelvic control rates of 73% up to 96%, depending on stage and treating center) and remains a major cause of treatment failure (1-3). In exchange for an improved overall survival (OS), adding chemotherapy to conventional EBRT has doubled the risk of severe acute hematological and gastro-intestinal toxicity and tripled platelet toxicity (4). Triggered off by both the high local recurrence and the toxicity rates we challenged the gold standard by investigating the role of surgery after definitive CRT [5-7], allowing a pathological evaluation of treatment response in this specific group of cervical cancer patients.


3. How long after completing chemoRT did patients undergo surgery?

This was clarified in the material and methods section page 7 line 21-22 by adding following part of the sentence (underlined): Surgery consists consisted of type II Wertheim hysterectomy with pelvic lymphadenectomy performed within 6 to 8 weeks after ending NA-CRT.

4. Was there a difference in survival amongst patients w adenocarcinoma who received surgery alone vs chemoRT vs neoadjuvant CRT f/b surgery? This could shed light on the optimal method of treatment for adenocarcinoma of the cervix.

Although this is an excellent suggestion by the reviewer, we are not able to perform this comparison.

Off all adenocarcinoma patients:

1. None of the AC patients was treated with primary chemoradiation.

2. Twenty-two patients were primarily operated upon, without (n=10) or with (n=12) adjuvant (chemo)radiation in case of adverse prognostics factors
3. Fourteen patients were treated with neo-adjuvant chemoradiation intent, all patients were operated upon.

Above that, only 3 of the adenocarcinoma patients deceased, of which one death was not cancer-related. Although it is not the primary question of the reviewer, also comparing the survival of group 2 and 3 is not useful due to lack of events. We believe the best next step is a matched case-control study to address the question of the reviewer, which will be performed in future research but is beyond the possibilities of this patient cohort study.

Reviewer 2 (Tomasz Banas, MD, PhD, MPH):

1. Abstract should contain brief information about all study groups and treatment modalities not only focus on NA-CRT group although results in NA-CRT are the core and novel finding.

We did not have the intention to just focus on the NA-CRT group only. We describe both the DSS and relapse pattern in both groups. Pathological complete response rate can only be described in the NA-CRT because the other groups did not receive neo-adjuvant treatment (surgery group) or surgery (chemoRT group). The clarify the fact that we discuss both groups we added: “... in the entire cohort, or in the NA-CRT group.” to the first sentence of the conclusions in the abstract (page 2 line 21).

2. The statement: "To date, management of cervical cancer is independent of its histological subtype but merely guided by staging at diagnosis" revalidated as is based on NCCN guideline from 2015 and current guidelines include Version 1.2019- August 2018. Additionally in an everyday clinical practice women with cervical adenocarcinomas in low clinical stages are more likely to be treated with radical surgery compared to RT or CRT compared to cervical squamous cell carcinoma due to increased risk of adnexal metastases and/or lymph node involvement. Therefore this issue needs elucidating according to current guidelines and state-of-art.

The reviewer is correct that we refer to an old NCCN guideline. We changed this to an up-to-date version: NCCN Guidelines Version 1.2019 – September 2018. We referred to the only recommended treatment difference between AC and SCC with the following sentence: Only for fertility-sparing surgery (not recommended for patients with small cell neuroendocrine tumors, gastric type adenocarcinoma or adenoma malignum), recommendations differ between AC and SCC (page 4 line 17-19). The reference was updated (page 23 line 25-26).
3. In the Material and method section the Authors write: "The patient cohort was classified according to histological type and FIGO stage: adenocarcinoma (AC) including adenosquamous subtypes (n= 36) versus squamous cell carcinoma (SCC; n= 143)" while in the Results is written: "Thirty-six out of 205 patients were excluded due to various reasons, including metastatic disease at diagnosis, treatment for recurrent (and not primary) disease and histological types other than AC and SCC." A cohort of 179 women was included (36+143) according to the Material and method section while 205-36 is 169 - this discrepancy needs elucidating and recruiting process should be clearly described in the Material and methods including numbers and reasons for patients exclusions. Statement "due to various reasons" is not enough for high-quality research.

We agree with the reviewer that a mistake was made. We corrected the data: 28 out of 207 patients were excluded and moved this text to the material and methods section. This resulted in the following paragraph on page 6 line 5-10: Twenty-eight out of 207 patients were excluded due to following reasons: treatment for recurrent disease or metastatic disease at diagnosis (n=9 and n=8, respectively), treatment received in another center (n=7), treatment interrupted according to patients’ wish (n=1) or general non-cervical cancer (or its treatment) related problems (n=3). Independent checks were performed for patient, tumor, treatment and outcome characteristics to identify and correct reporting errors.

4. Repainting information from the Materials and methods in the Result section (eg. Data of 179 cervical cancer patients were analyzed, of which 36 were AC and 146 were SCC.) should be avoided.

146 was changed into 143 on page 10 line 3.

5. The Authors say that: "Mean tumor size was significantly larger for SCC (4.3 cm) than AC (3.3 cm) (p=0.03); ACs were more often stage IB1 (50% versus 25% for SCC; p=0.01) and well differentiated (41% versus 7% in SCC; p=0.001). Squamous cell carcinomas were more often moderately differentiated than AC (48% versus 25% resp.; p=0.02)." and that "The treatment regimens were not significantly different between AC and SCC (table 2). 14/36 (39%) AC and 70/143 (49%) SCC patients were treated with NA-CRT intent respectively (NA-CRT group)." This issue should be discussed (perhaps in the context of the comment no 2) how to explain lack of differences in the treatment modalities while the study groups differed significantly in clinic-pathological features. Such a discussion might be very interesting and improve the overall quality of the manuscript. By the way the issues concerning pCR and locoregional control in AC and SCC were very detailly disused by the Authors.
This is indeed a very interesting point of discussion. We added following observation and text on page 14 line 2-8:

Despite the overrepresentation of FIGO stage IB1, small and well differentiated tumors in the AC population, we failed to observe a difference in treatment regimen between AC and SCC. We assume that this lack of difference is due to the small patient sample size and high amount of treatment options. If we reduce the treatment options to primary surgical (including adjuvant CRT or fertility sparing neo-adjuvant chemotherapy and conization) and primary RT intent (including NA-CRT; definitive CRT and brachytherapy alone) we do find more AC (22/36) than SCC (60/143) patients primarily operated upon (p=0.039).

6. "The 5y OS rate for early AC and SCC was 100% and 89.4% (p=0.40) respectively." How early and advanced AC and SCC are defined according to the Authors (ie. Stage I and II vs. III+?)?

The definition of early and late disease was already stated in the materials & methods section (page 6 line 13) and also included on page 11 line 2-4 for the ease of the reader.

7. As in NA-CRT AC numbers are low did the Authors used Yeates correction for chi-square tests as presented results: "Seventy-seven patients treated with NA-CRT intent were operated upon. A pCR was obtained in 7% (1/14) and 42% (27/63) of the AC and SCC patients respectively (p=0.027). This difference remained statistically significant when all non-operated tumors (n=7, all SCC) were considered as incomplete pathological response: 7% (1/14) versus 39% (27/70) pCR for AC and SCC respectively (p=0.049)." may differed if corrected for low number group. Statistical consultation may be required to resolve this issue.

We can confirm that we have applied Yates’ continuity correction. We’ve used the standard test for equality of proportions from R, which can be used for testing the null hypothesis that the proportions in several groups are the same. This test applies Yates’ continuity correction by default.

Further information below addresses the concern of the reviewer.

Without non-operated tumours (total SCC = 63)

2-sample test for equality of proportions with continuity correction

data: c(1, 27) out of c(14, 63)
X-squared = 4.8647, df = 1, p-value = 0.02741

With non-operated tumours (total SCC = 70)

2-sample test for equality of proportions with continuity correction
data: c(1, 27) out of c(14, 70)
X-squared = 3.8679, df = 1, p-value = 0.04922

8. P-value should preferably be presented as 0.000 (3 digits after the decimal)
This was adapted throughout the manuscript.

9. In the Discussion presenting results should be avoided ie. "Table 3 shows the results of studies reporting on survival differences between AC and SCC [3, 4, 6-8, 30-34]."
This sentence was removed. Table 3 was referred to in the next sentence: In contrast to this study, several studies did report a worse prognosis for AC (table 3) [3, 4, 6-8, 34-38] on page 14 line 9.

10. The limitation of this study were detailedly discussed and its retrospective character and low number of women with AC as well as single-center localization do not decrease its value. In my opinion further prospective studies should be designed to confirm this interesting and novel findings. Overall, the work appears to be of high quality and provides a novel insight to the field of cervical cancer research.

No changes