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Review

Neoadjuvant chemotherapy in woman with early or locally advanced cervical cancer

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ABSTRACT

Cervical cancer is a major global health problem for women. Despite the screening and vaccines available today, it continues to be the fourth most common cancer in women worldwide with 85% of cases occurring in developing countries. Standard treatments for early or locally advanced cervical cancer are surgery (S) or concomitant chemo-radiotherapy (CT-RT). Neoadjuvant chemotherapy (NACT) prior to surgery or radiotherapy has been proposed and tested in clinical trials and has been included in clinical practice in some countries.

In order to determine the true role of NACT either prior to S or RT in terms of achieving benefits in OS or DFS, randomized clinical trials and meta-analyses published from its beginnings to the present have been searched and analyzed in this study.

The analysis of published clinical trials shows that NACT followed by S and NACT followed by RT have failed to demonstrate benefits in OS or DFS. Clinical trials comparing NACT followed by S versus exclusive RT have also been analyzed, where NACT followed by S could not show benefits for RT either.

Conclusion: Adding neoadjuvant chemotherapy to S or RT cannot be recommended outside the context of clinical trials.

1. Introduction

Cervical cancer is a major global health problem for women. Despite the screening and vaccines available today, it continues to be the fourth most common cancer in women worldwide[1,2] with 85% of cases occurring in developing countries.[3,4] Radiotherapy (RT) and surgery (S) are equally effective in early stages (FIGO IA-IBI), each giving 5-year survival rates of around 80–90%.[5] Historically, the standard treatment for IA and IB1 is surgery.[6] For more advanced stages the primary treatment for cervical cancer is either surgery or radiotherapy. Even in stages IB2 and II A2 radiotherapy offers better results than surgery.[7] Radical radiotherapy comprises external beam and intracavitary treatment and is treatment of choice for locally advanced disease stage IIB, III and IVA offering an alternative to radical surgery for patients with tumors larger than 4 cm confined to the cervix (stage IB bulky).[8] RT has also been used for patients not being candidates for hysterectomy. 5-year-survival using radiotherapy ranged from around 60% for patients with stage IIB disease to approximately 20% for patients with stage IV disease.[5]

Due to the lack of progress in results during decades of surgery and radiotherapy and based on the results of cytostatic agents in patients with disseminated disease, the idea of incorporating chemotherapy into other strands began to be reflected in clinical trials.

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One of the ways to investigate the effect of CT in non-disseminated cervical cancer patients is as neoadjuvant treatment to the traditional treatments, that is, to S and/or RT with the intention of finding out if neoadjuvant chemotherapy (NACT) could diminish the size of the tumor and thus increase the operability and/or eradicate the possible micro-metastasis and/or increase tumor vascularization reducing the number of hypoxic cells, making the tumor more sensitive to radiation. Specifically, agents available in early trials were fluorouracil and hydroxyurea.

In 1981 treatment results of cisplatin as a single agent chemotherapy for recurrent or metastatic cervix cancer patients were published.[9,10] The showed 50% of response rate in patients who had received no prior CT and an overall response rate of 38%.

Given response rates to cisplatin in recurrent or metastatic cervical cancer patients reported in those times, its use was tested in 2 neoadjuvant settings: either before S or before RT as an attempt to improve survival.

2. Neoadjuvant chemotherapy followed by surgery versus surgery alone

Possible advantages of giving NACT prior to S include the potential for reducing tumor volume, increasing operability and helping to control micro-metastatic disease.[10–13]

Four data base systematic reviews concerning NACT were published by Cochrane Library (1999, 2004, 2010 and 2012). Latest version of Cochrane Data Base Systematic Review for NACT followed by S versus S alone was published in 2012.[14] The first published review was published in[15] and updated with more recent searches and additional data in 2012. The review included six trials[16–21] randomized between 107 and 291 women with FIGO stages IB to IIIB from 1987 to 2005. One trial[20] included only women with FIGO IB2 (bulky) disease. Two trials[16,18] recruited women with both IB1 and IB2 disease. Of the remaining three trials, two[19,21] randomized women with stage IB2 to IIB disease, where most were classed as stage IB to IIA (66%), and one[17] randomized women with stage IB to IIIB disease, very heterogeneous population. Cisplatin-based CT was used in all trials, with some variation in the treatment regimens and platinum dose. The type of S varied from pelvic lymphadenectomy and both pelvic and para-aortic lymphadenectomy. Two trials gave RT to patients with inoperable tumors.[16,17] In four trials[16,17,20,21] between 36% and 61% of women who underwent radical hysterectomy also received post-operative RT. No information was available for one trial[19] about how many women had received post-operative RT. All five of these trials gave post-operative RT (with or without brachytherapy) to resected patients because of risk factors for recurrence found at the time of surgery. In one trial,[16] 100% of women who underwent radical hysterectomy also received post-operative RT, regardless of risk factors and they were clinically stage IB. Trials gave total external beam RT doses ranging from 45 to 60 Gy in 1.7 to 2.0 Gy fractions, and three of these also gave brachytherapy in doses ranging from 25 to 60 Gy. Information available from the trial report for one further trial[21] stated that post-operative pelvic RT consisted of 3 Gy to the entire pelvis and an additional 2 Gy for parametrial tissue, but it was unclear whether this referred to total dose or dose per fraction given. In one trial of bulky IB patients,[20] radical RT was given to patients both on and off protocol and furthermore, patients whose disease had progressed beyond the cervix during NACT were treated with standard CT-RT. Outcomes of survival and PFS found a significant improvement with NACT for both. As reported, much more than 50% of the patients analyzed received RT. The impact of this treatment is not analyzed and the toxicity of receiving all three treatments is not reported. A significant benefit with NACT was observed in terms of reduced local recurrence rates, but not for distant recurrence. It is not possible to attribute this reduction in local recurrences solely to the administration of NACT, particularly since a proportion of patients in all trials also received post-operative RT. Neither is an intention to treat results analysis performed. However, the conclusions were: both OS and PFS were improved with NACT. Although the effects were less clear on all other pre-specified outcomes, they all tended to be in favor of NACT. Whilst these results appear to indicate that NACT may offer a benefit over S alone for women with early-stage or locally advanced cervical cancer, the evidence is based on only a small number of trials, and further research may be warranted.

In the same year, Gong et al.[22] published a retrospective clinical study comparing NACT-S versus S alone. Data were analyzed from 414 patients stage IB2-IIB who underwent treatment between January 2008 and November 2009. The 2-year progression free survival rates were 93% and 95% in the NACT-S group, and 94.5% and 97% in the S group ($p > 0.05$). The conclusion was that NACT-S did not show a significant advantage for patients with locally advanced cervical cancer.

In 2013, Kim et al.[23] published a review on articles published between January 2007 and September 2010. 5 randomized controlled trials and 4 observational studies involving 1784 patients out of 523 potentially relevant studies were included. Overall and loco-regional recurrences and progression-free survival rates were not different between the 2 treatments. On the other hand, NACT before S was associated with poorer overall survival in observational studies when compared with primary surgical treatment (HR, 1.68; 95% CI, 1.12–2.53). Conclusion of the study was that although NACT before S reduced the need for adjuvant RT by decreasing tumor size and lymph node metastasis, it failed to improve survival when compared with primary S in patients with FIGO stage IB1 to IIA cervical cancer. It should be mentioned that the criteria for the indication of adjuvant RT are not mentioned and that at the time of the study they were not standardized as they are at present.

The results of all these studies are very difficult to compare with the results of the currently standard treatments because they are small series, with very short follow-up and unclear selection criteria. However, none showed a significant advantage with NACT.

More than 50% of operated patients received subsequent RT. This represented a significant morbidity and a substantial increase in the cost of treatment without significant benefits.

GOG started a randomized trial in patients with bulky stage IB cervical cancer comparing NACT followed by radical hysterectomy and pelvic/para-aortic lymphadenectomy versus

radical hysterectomy and pelvic/para-aortic lymphadenectomy. The study was closed early because of slow accrual. Nevertheless, they concluded that: for patients bulky IB (≥4 cm) that undergo radical hysterectomy, approximately 50% will require adjuvant radiation; NACT followed by radical hysterectomy did not improve PFS or OS as compared to radical hysterectomy alone and the GOG recommends, based on this study, against NACT for patients with stage IB2 cervical cancer.[24]

Due to all the data presented and in accordance with the meta-analyses and the published reviews, adding NACT to S cannot be recommended outside the context of clinical trials.

3. Neoadjuvant chemotherapy followed by RT

Seven first randomized trials comparing RT vs. NACT followed by RT have been published: Sardi et al.,[16] Chang et al.,[25] Benedetti-Pacini,[26] Chauvergnet et al.,[27] Kumar et al.,[28] Leborgne et al.,[29] Souhami et al.,[30] Sundford et al.,[31] Tattersall et al.,[32] Tattersall et al.[33] Of these 7 trials, 5 do not show benefits with NACT, 2 demonstrated a significantly better survival rate with exclusive RT. None compared with CT-RT. The results of these uncontrolled studies are very difficult to compare with the results of traditional treatments because they are small series, with very short follow-up and unclear selection criteria. However, none showed a significant advantage with NACT. And more than 50% of operated patients received subsequent RT. This represented a significant morbidity and a substantial increase in the cost of treatment without significant benefits.

In 2004 a Cochrane Review was published,[34] aimed to assess the effect of NACT followed by RT compared to the same RT. They report data from 18 trials and 2074 patients but are unclear if 18 or 15 met the necessary requirements to be included. Considering these trials together, there was a high level of statistical heterogeneity, a substantial amount of which was explained by analyses of trial groups. Both the external beam RT dose and intracavitary RT dose varied (40–60.8 and 18–80 Gy, respectively), with a total dose in the range of 55–80 Gy. The author declares that for each of the outcomes measured, when all trials were combined, a highly significant level of statistical heterogeneity was evident, such that it is inappropriate to combine the trials in this way, which in fact suggests that these trials may not be addressing exactly the same questions. Considering all trials together, there was no evidence of an effect of NACT on survival, or any of the other endpoints. Variation in the duration of radiotherapy amongst the trials in this meta-analysis could contribute to the differences seen in local control and survival. Furthermore, the author suggests that if there is combined CT and RT cross-resistance, the duration of CT, the delay to RT and the duration of RT making up the overall treatment time, could each have an impact on prognosis. Interestingly, the trials giving more prolonged CT tended to be those with longer delays to RT and longer durations of RT and vice versa. However, the control group survival of these two groups of patients is very similar and within these groups, there is no evidence that particular types of patients benefit more or less from CT. Conclusions were: overall results do not support the use of cisplatin-based NACT prior to RT for women with locally advanced cervical cancer.

In none of these trials NACT followed by radical radiotherapy was compared with a concomitant CTRT control arm, which is not only the standard treatment but the concomitant CTRT increases survival compared with exclusive RT.

Due to all the data presented and in accordance with the meta-analyses and the published reviews, adding neoadjuvant chemotherapy to radiotherapy cannot be recommended outside the context of clinical trials.

4. Neoadjuvant chemotherapy followed by surgery versus RT

In 2003, a meta-analysis was published that includes only 5 trials of NACT plus S versus RT.[35]

The conclusions of this meta-analysis were favorable for NACT plus S (14% increase in OS at 5 years, from 50% to 64%). In none of these five trials NACT followed by S was compared with a CT-RT control arm, which is not only the standard treatment but the concomitant CT-RT increases the survival compared with exclusive RT in a similar percentage (≥12%).

Furthermore, in all five trials, RT was suboptimal, either due to insufficient total dose or due to the prolongation of treatment time. In one of these trials, 27% of the patients did not perform brachytherapy, 11% received less than 60 Gy at point A, and the average dose at point A was 70 Gy whereas recommended total dose should be 80–90 Gy.

In 2012, a meta-analysis comparing NACT plus S versus exclusive S was published.[14] This meta-analysis includes a small number of trials, only 5, some of them are very old, with large variations in the use of adjuvant RT and great disparity of results,

For a significant percentage of patients assigned to NACT arms followed by S, S could not be performed due to toxicity caused by CT or by insufficient response

In the results, the author notes that the number of patients (872) and events (368) is not large and the results need to be interpreted with caution. Also, some of the patients included in these trials would be considered as having localized disease (FIGO stage IB-IIA) and others would be considered locally advanced (FIGO stage IB bulky, IIB-IIIB) and, as such, clinically, they would not often be considered together. This comparison is further complicated by the fact that intra-arterial CT was used in one trial and by the use of postoperative pelvic RT in the NACT plus S arm. In two trials,[36,37] almost all patients received pelvic RT and in other two trials,[25,38] it was given to around of 30% of patients. The risk factors that determined the indication of adjuvant RT is not clearly defined in the studies and differs between them. Therefore, there are a number of possible confounding factors. Although the HR of 0.65 indicates a 14% absolute overall improvement in 5-year survival, because baseline survival differs considerably by stage, this relative benefit translates into absolute improvements ranging from 8 to 14% at 2 years and 12 to 16% at 5 years. It is noteworthy that the meta-analysis does not evaluate the impact of the insufficient total dose of RT administered in some studies or the impact of the prolongation of the total time of the radiation treatment while it does on the CT administered. In

none of these five trials NACT followed by S was compared with a concomitant CT-RT control arm, which is not only the standard treatment, but the concomitant CT-RT increases the survival compared with exclusive RT in a similar percentage (≥12%).

During the ESMO Congress 2017, published later, a randomized clinical trial comparing NACT followed by S versus concomitant cisplatin and radiation therapy in patients with stage IB2, IIA or IIB squamous carcinoma of the cervix was presented.

635 patients were randomized between both arms, planned cross-over from NACT-S to CT-RT arm was performed in patients with unresectable disease after 2 or 3 cycles of CT, intraoperative inoperability or lymph node positive on frozen section intraoperative.

DFS at five years in intention-to-treat population was 69.35 in NACT plus S vs. 76.7% in the CTRT arm.

Conclusions of the trial were: RT concurrent with weekly cisplatin resulted in a higher DFS compared with NACT using paclitaxel and carboplatin followed by radical surgery in patients with locally advanced squamous cell cervical cancer. CT-RT should continue to be the standard of care in locally advanced cervical cancer.

5. Conclusions

During the last 19 years, CT-RT is generally the primary treatment of choice for stages IB2 to IVA disease based on the results of 5 randomized clinical trials that have shown that the use of CT-RT results in a 30% to 50% decrease in the risk of death compared with RT alone. In 1999 the NCI issued an alert stating that a strong consideration should be given to using chemoradiation instead of RT alone. Commonly, platinum based regimens are used, although a meta-analysis published in 2008 reported significant benefits with non-platinum-based agents. This result was confirmed by several trials and a meta-analysis.

Due to the above, the treatment of CT-RT with platinum base regimens continues to be the standard for patients with stage IB2 to IVA of cervical cancer. The NACT should not be used outside clinical trials.

Conflict of interest

None declared.

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