Gynecologic Oncology xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review Article

Concurrent chemoradiotherapy *vs.* radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis

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HIGHLIGHTS

- Systematic review and meta-analysis in locally advanced cervix cancer (IIB – IVA).
- Included 14 randomized trials comparing concurrent chemoradiotherapy *vs.* radiotherapy alone.
- Chemoradiotherapy significantly improves all key therapeutic endpoints.
- Chemoradiotherapy also significantly increases the incidence of acute toxicities.
- Both efficacy and toxicities are independent of the chemotherapeutic agents used.

ARTICLE INFO

Article history:
Received 9 December 2016
Received in revised form 24 January 2017
Accepted 31 January 2017
Available online xxxx

Keywords:
Cervix cancer
Chemoradiotherapy
Radiotherapy
Systematic review
Meta-analysis

ABSTRACT

The efficacy of concurrent chemoradiotherapy (CTRT) in locally advanced cervix cancer (LACC, stages IIB-IVA) is contentious. This is due to the variable extent of therapeutic benefit reported in different randomized clinical trials and meta-analyses that usually include all stages of cervix cancer. A systematic review and meta-analysis was therefore conducted to evaluate the efficacy of concurrent CTRT over radiotherapy (RT) alone, predominantly in LACC for the key endpoints; complete response (CR), long-term loco-regional control (LRC), overall survival (OS), grade III/IV acute and late toxicities. Six databases namely - PubMed, EMBASE, SCOPUS, Web of Science, Google Scholar and Cochrane library were explored and supplemented by hand-searching. Only prospective randomized trials conducted in LACC between concurrent CTRT and RT alone with no surgical interventions were included. Fourteen English language articles from 1788 citations were shortlisted for the final analysis. Of the 2445 patients evaluated (CTRT: n = 1217; RT: n = 1228), 95.7% had LACC and 96% had a squamous cell histology. Eight studies used cisplatin alone, 4 had cisplatin-based combination chemotherapy (CT) while 2 used mitomycin-C, either alone or in combination. CTRT improved the CR (+10.2%, $p = 0.027$), LRC (+8.4%, $p < 0.001$) and OS (+7.5%, $p < 0.001$) over RT alone. However a 10.4% higher incidence of grade III/IV acute toxicities ($p < 0.001$) was also evident with CTRT. Late toxicities in both groups were equivalent. Subgroup analysis and meta-regression did not reveal any significant advantage in outcomes between the 3 CTRT regimens. Thus, although concurrent CTRT provides conclusive therapeutic benefit over RT alone in LACC, the choice of CT agents should be based on their cost-effectiveness and the anticipated expenses for the management of any associated acute toxicities. This assumes importance particularly in resource-constrained low-middle-income countries with the highest burden of LACC, where majority of the patients meet the treatment costs as out-of-pocket expenses.

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http://dx.doi.org/10.1016/j.ygyno.2017.01.033
0090-8258/

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1. Introduction

Management of locally advanced cervix cancer (LACC, stages IIB-IVA) is a major therapeutic challenge. Globally, it is the fourth commonest cancer in women with an estimated 528,000 new cases of cervix cancer reported in 2012 [1]. Of these, around 85% arise in the less developed regions of the world. It is estimated that 9 out of 10 deaths (87%) due to cervix cancer occur in low- and middle-income group countries (LMICs). This could be attributable not only to an advanced tumour stage at presentation but also to the lack of adequate radiotherapy (RT) infrastructure and allied human resources in LMICs [2–4].

Traditionally, the RT management of LACC involved a planned combination of external beam RT (EBRT) and intracavitary brachytherapy (BRT). However, following the National Cancer Institute (NCI), USA announcement in 1999 [5] that, "*strong consideration should be given to adding chemotherapy (CT) to RT in the treatment of invasive cervical cancer*," there has been a worldwide adoption of concurrent chemoradiotherapy (CTRT) in the management of all stages of cervix cancer. A closer perusal of the five randomized trials on which the NCI recommendations were based reveals that none of these trials were exclusively designed for LACC. They included patients with all disease stages (two had patients only in early stages), all had surgery or surgical staging and in two studies, hydroxyurea was administered with RT in the control arm [6–10]. The mixed outcomes of the prospective randomized trials undertaken following the NCI announcement have resulted in uncertainties regarding the efficacy of CTRT in LACC [11–24]. The Cochrane meta-analysis for concurrent CTRT *vs*. RT reported a stage-dependent advantage of CTRT, with benefit decreasing as the stage of the disease increased [25,26]. Consequently, the 10% benefit in 5-year survival in stages IB to IIA fell to 7% in stage IIB and to merely 3% in stages III-IVA [25].

Although the various meta-analyses suggested a benefit of CTRT over RT alone in cervix cancer, the extrapolation of these results to LACC is fraught with uncertainties due to the variable inclusion criteria and treatments offered in the different trials. These were: inclusion of various stages of cervix cancer; use of surgery or surgical staging; inclusion of trials with neoadjuvant or adjuvant CT along with CTRT; inclusion of trials with hydroxyurea (a known radiosensitizer) in the RT control arm and incorporation of unpublished data, abstracts or retrospective studies [25–29]. A systematic review and meta-analysis including only patients with LACC who received either concurrent CTRT or RT as primary therapy is therefore necessary to truly evaluate any benefit of CTRT over RT alone in this setting. This data could be particularly significant, as most trials and meta-analyses have shown that CTRT increases grade III/IV acute toxicities. Moreover, as LACC is a major problem in LMICs, it is essential to consider the safety and cost-effectiveness of CTRT to maximize therapeutic benefit in the context of limited resources.

The present systematic review and meta-analysis has therefore been conducted exclusively in LACC with treatment strategies involving either concurrent CTRT or RT only. The efficacy has been evaluated for the key therapeutic end points along with the grade III/IV acute and late toxicities. In addition, an attempt has been made to identify the most appropriate CT regimen for CTRT, using subgroup analysis and outcome predictors by meta-regression for each of the above endpoints.

2. Material and methods

2.1. Search strategy

The systematic review was conducted in accordance with the PRISMA guidelines [30] (Fig.1). Six databases, namely PubMed, EMBASE, SCOPUS, Web of Science, Google Scholar and the Cochrane library were searched. The last search was performed on August 29, 2016. The Medical Subject Headings (MeSH) terms used were, "Uterine Cervical Neoplasms," "Radiotherapy" and "Drug therapy." The search was not limited to any date or language. Additional papers were retrieved through hand-searching. The lead authors were contacted for updates and clarifications where required.

2.2. Inclusion criteria

The inclusion criteria were (a) patients exclusively/predominantly with LACC, (b) prospective randomized trials with concurrent CTRT *vs*. RT alone, (c) no surgical intervention in the form of a hysterectomy or surgical staging and (d) full length publications in English. Unpublished results, abstracts or retrospective studies were not included. Studies using neoadjuvant or adjuvant CT or hypoxic cell sensitizers or immunomodulators in either of the treatment arms were excluded.

2.3. Study selection

From a total of 1788 citations, 1510 records remained after removing the duplicates. An additional 1471 articles were omitted on the basis of their titles and abstracts (Fig.1). Finally, 39 articles were subjected to full

Please cite this article as: N.R. Datta, et al., Concurrent chemoradiotherapy *vs*. radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis, Gynecol Oncol (2017), http://dx.doi.org/10.1016/j.ygyno.2017.01.033