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TOPIC HIGHLIGHT

Different strategies of treatment for uterine cervical carcinoma stage ⅠB2-ⅡB

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Core tip: There is no currently demonstrated the best option of treatment for women with locally advanced cervical cancer Federation of Gynecology and Obstetrics stage ⅠB2-ⅡB. This article describe the evidence as well as the advantages and disadvantages of the main strategies of treatment.

Abstract

Uterine cervical cancer is the second most common gynecological malignancy. It is estimated that over 35% of tumors are diagnosed at locally advanced disease, stage ⅠB2-ⅡB with an estimated 5-year overall survival of 60%. During the last decades, the initial treatment for these women has been debated and largely varies through different countries. Thus, radical concurrent chemoradiation is the standard of care in United Sated and Canada, and neoadjuvant chemotherapy followed by radical surgery is the first line of treatment in some institutions of Europe, Asia and Latin America. Until today, there is no evidence of which strategy is better over the other. This article describe the evidence as well as the advantages and disadvantages of the main strategies of treatment for women affected by uterine cervical cancer stage ⅠB2-ⅡB.

INTRODUCTION

Uterine cervical cancer is the second most common gynecological malignancy[1]. In developing countries, it is estimated that over 70% of cases are diagnosed at an advanced stage of disease, thus being a major cause of morbidity and mortality[2]. Based on the fact that cervical cancer tends to grow locally involving the cervix and the paracervical structures, the International Federation of Gynecology and Obstetrics (FIGO) staging system is clinical. It is based primarily on pelvic examination to estimate tumor size and local extension toward the vagina, parametria and pelvic sidewalls. Thus, cervical cancer can be divided in three groups: (1) early stage of disease, tumors up to 4 cm without involvement of extracervical structures. (FIGO stage ⅠA- Ⅰb1); (2) locally advanced cervical cancer (LACC), tumors growing locally bigger than 4 cm or with initial involvement of paracervical tissue (FIGO stage ⅠB2-ⅡB); and (3) advanced stage
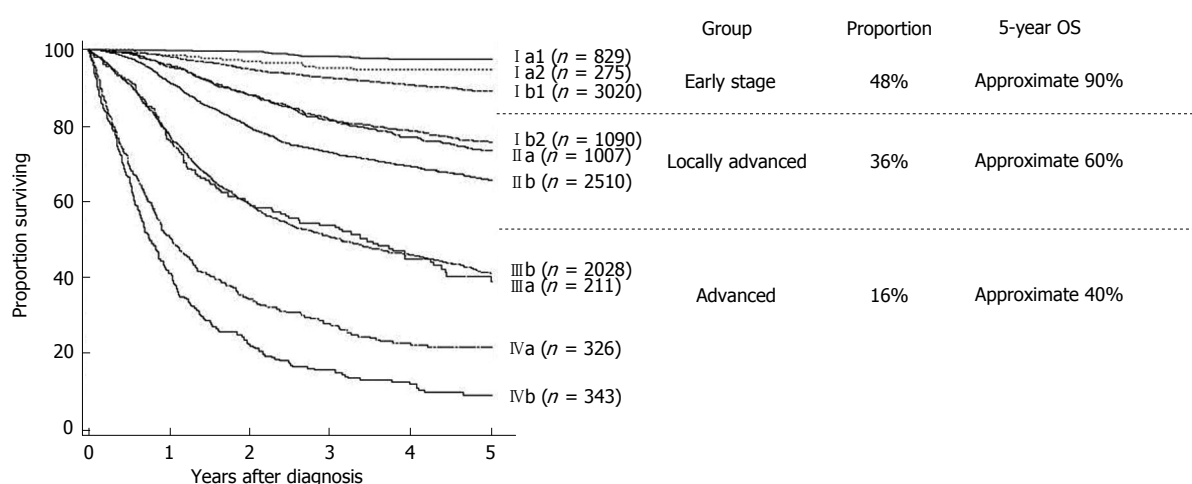
Figure 1 Distribution and 5-year overall survival of women with uterine cervical cancer divided by International Federation of Gynecology and Obstetrics stage disease according with International Federation of Gynecology and Obstetrics annual report[4]. OS: Overall survival.

disease, tumors that largely involve pelvic structures or tumors with distant metastasis (FIGO stage ⅢA-ⅣB).

Despite the fact that radiotherapy and radical surgery (RS) are equally effective for early stage disease[3], the latter strategy is generally accepted as a standard of care with a 5-year overall survival (OS) of 90%[4]. On the other hand, concurrent chemo-radiotherapy is used as first line treatment for patients with advanced stage disease (FIGO stage ⅢA-ⅣB) with a 5-year OS of 40%[4]. (Figure 1) However, there is a group of patients in the middle with locally advanced disease (FIGO stage ⅠB2-ⅡB) with a 5-year OS of 60%[4] for whom there are great controversies regarding the appropriate initial treatment approach. Traditionally, these tumors were treated by radiotherapy alone.

In 1999, based on the results of five large randomized controlled trials, the National Cancer Institute of United States launched an alert recommending concurrent chemoradiation for treating women with LACC becoming the standard of care[5]. Nevertheless, other treatment modalities with similar efficacy were developed in other regions such as Europe, Japan, South Korea, and Latin America. These include: platinum-based neoadjuvant chemotherapy (NACT) followed by radical hysterectomy[6-8]; chemoradiotherapy followed by adjuvant chemotherapy[9] or followed by RS[10]. Therefore, the treatment of women with LACC seems to be multidisciplinary and the standard of treatment seems to be far from being elucidated. Thus, this article describes the different options of treatment, with their advantages and disadvantages, for women with uterine cervical cancer IFGO stage ⅠB2-ⅡB.

CONCURRENT CHEMORADIATION

Radiotherapy has been the standard of care for treating women affected by LACC for the past 100 years. In 1999, after publication of five randomized controlled trials (RCT)[11-15], the National Cancer Institute issued an alert recommending that "concomitant (cisplatin-based) chemoradiotherapy be considered instead of radiotherapy alone

in women with cervical cancer". This led to a change in the treatment of many women with cervical cancer[5]. Latter on, a meta-analysis evaluated 15 RCTs comparing chemoradiotherapy *vs* radiotherapy alone in 3452 women with cervical cancer FIGO stage ⅠB2-Ⅳ[16]. Eleven trials used platinum-based chemoradiotherapy, either as a single agent (eight trials) or in combination regimens (three trials). Three trials used nonplatinum regimenes comprising of fluorouracil, mitomycin, or a combination of the two. Each of the trials aimed to prescribe external-beam radiation at a dose to a tumor of between 40 and 61.2 Gy, and 14 trials used brachytherapy. The total planned duration of radiation treatment (external-beam plus brachytherapy) was from 40 to 70 d across all trials. The median follow-up for surviving patients across all 15 trials was 5.2 years. The study noted a 6% improvement in 5-year survival with chemoradiotherapy in comparison with radiotherapy alone (HR = 0.81, $P < 0.001$). However, a great majority of the trials evaluated in this meta-analysis included patients with cervical cancer FIGO stage ⅠB2 to ⅣB and, as Figure 1 shows, there is a great disparity regarding OS between them.

It is interesting to note that only one study compared chemoradiation *vs* radiation alone in patients with cervical cancer FIGO stage ⅠB bulky[11]. This study included 374 patients with FIGO stage ⅠB2 excluding high-risk patients with evidence of radiologic enlarged lymph nodes. Women were allocated to receive radiotherapy alone or radiotherapy plus weekly cisplatin intravenously at a dose of 40 mg/m². They observed a risk of progression of the disease and death of 0.51 (95% confidence interval, 0.34 to 0.75) and 0.54 (95% confidence interval, 0.34 to 0.86), respectively. The rates of both progression-free survival ($P < 0.001$) and OS ($P = 0.008$) were significantly higher in the combined-therapy group at four years. With this treatment modality, 80% of patients did not relapsed and 85% were alive at four year after initial treatment.

Current recommendations state that the total paracervical tumor dose (sum of external-beam radiotherapy and brachytherapy) be between 85 and 90 Gy, that total pelvic

sidewall dose be between 55 and 65 Gy, and that overall treatment time not exceed 8 wk[17]. The greater majority of trials comparing radiotherapy *vs* chemoradiation were conducted in United Stated and Canada, under strict criteria of treatment administration and in well-equipped institutions. In this sense, radiotherapy is administered by using conventional equipment in the majority of women with cervical cancer and mainly in developing countries where this disease is more frequent[18]. Nevertheless, by integrating computed tomographic imaging into the radiotherapy planning process, allow the dose of the radiation to match or conform to the outline of the target. The recently introduced intensity-modulated radiotherapy (IMRT) is an extension of this principle. The aim is to produce a highly shaped high-dose volume that maximizes normal tissue sparing with the goals of decreasing toxicity and possibly increasing tumor dose. Thus, the dose distribution with IMRT fits more precisely to the target volume, reducing the dose to the rectum, the central bladder and bowel. Several clinical studies have demonstrated a reduction in the mean volume received on the bladder, the rectum, and the bowel[19], decreasing bowel adverse events and lymphedema[20]. A pilot study compared 58 women with cervical cancer treated with radiotherapy (*n* = 35 in four-field box group, *n* = 33 in IMRT group) reporting similar local control of the disease with less toxicity in IMRT group[21]. Other authors recently confirmed the same results[22]. Thus, the availability of modern equipment of radiotherapy such as IMRT can help to reduce treatment's morbidity. Radiation therapy, in addition, should be taken with caution if an ideal schedule of care is not possible for some patients.

In this sense, it has been demonstrated that a prolonged treatment time, beyond 50 to 56 d, is associated with a 1% loss of local control for every additional day of treatment with radiotherapy[23]. In addition brachytherapy, as an integral part of radiation treatment for cervical cancer, is critical for obtaining a cure. Unfortunately, 5% to 10% of patients are unable to receive brachytherapy[24] because of technical difficulties with the insertion of the devises (*e.g.*, stenotic cervix).

NACT FOLLOWED BY RS

Cervical cancer was traditionally interpreted as chemoresistant cancer. Since 1983, where the first study reporting a response to combined systemic therapy was reported[25], chemotherapy was evaluated in patients with cervical carcinoma. Thus, in regions such as Europe, Asia or Latin America, NACT followed by radical hysterectomy has been suggested for treating patients with LACC. The main objective of NACT is, to reduce the volume of the tumor, to achieve radical operability; and to reduce the number of patients who finally require adjuvant radiation treatment[8]. This strategy is based on the strong surgical tradition in some centers; and the lack of accessibility of patients to the radiotherapy centers in some countries. To this regard, one Italian multicenter RCT compared NACT followed by RS *vs* radiotherapy alone in patients

with LACC[26]. The authors found that only 23% of patients allocated to radiotherapy arm received the adequate treatment in terms of total dose and/or time of delivery of radiotherapy[26].

The efficacy of NACT for treating LACC has been largely tested by several authors over the last 30 years[7,8,27]. An Italian multicenter RCT compared 441 women with LACC FIGO stage I B2-Ⅲ who randomly received radiotherapy alone or NACT followed by RS. The 5-year survival in patients FIGO stage I B2 to Ⅱ B showed significantly longer progression-free survival (59.7%, 95%CI: 51.3%-68.1% *vs* 46.7%, 95%CI: 38.1%-55.3%, *P* < 0.02) and OS (64.7%, 95%CI: 56.5%-72.9% *vs* 46.4%, 95%CI: 37.2%-55.6%, *P* < 0.005) for patients in NACT + RS arm[26]. Additionally, RS might play an important role in patients with stable disease after 3 courses of NACT. One study[28] evaluated 32 patients with cervical carcinoma FIGO stage I B2-Ⅱ A with stable disease after receiving 3 cycles of cisplatin and 5-fluorouracil-based NACT. The 5-year OS in patients who received RS after NACT was 76.4%, while those patients who received NACT followed by adjuvant radiation treatment experienced a 5-year OS of 37.5%, *P* = 0.01.

A meta-analysis[16] compared the results of five studies evaluating NACT followed by RS *vs* radical radiotherapy. A total of 872 women were included, mostly with FIGO stage I B-Ⅱ A tumors. The number of curses of NACT ranged between two and seven cycles of cisplatin based, chemotherapy before radical hysterectomy. Together these trials gave a highly significant (HR = 0.65, 95%CI: 0.53-0.80, *P* < 0.0004) 35% reduction in the relative risk of death, with NACT. These results translate into a 14% absolute improvement in 5-year survival and this effect did not seem to vary according to age, stage, histology, grade or performance status. Local, distant and overall disease-free survival (DFS) was similar between groups.

The optimal drug and schedule is also to be determined. During the last three decades, several institutional experiences (with disparity on the drugs combinations and schedules), few phase Ⅱ trials[29] and RCT have been reported[30,31]. Despite some differences in design and results between trials, the reported response rate achieved a range between 70% and 100%[32]. The main tested drugs include cisplatin, taxanes, irinotecan, vinorelbine, and gemcitabine. The combined regimen, however, have been also investigated with encouraging results[30,31]. In 2005, the first RCT comparing different schemes of NACT was published[30]. An Italian Multicenter study compared 219 patients with LACC FIGO stage I B2-Ⅳ who received ifosfamide 5 g/m^2 during 24 h plus cisplatin 75 mg/m^2, plus paclitaxel 175 mg/m^2 (TIP scheme) or ifosfamide 5 g/m^2 during 24 h plus cisplatin 75 mg/m^2 every 3 wk for three courses (SNAP-01). The authors observed grade 3 to 4 neutropenia, anemia, and thrombocytopenia to be more frequent with TIP; and a higher optimal pathologic response rate, defined as residual disease < 3 mm of stromal invasion, with TIP (48% *vs* 23%; OR = 3.22; 95%CI: 1.69-5.88; *P* < 0.0003). In the median follow-up of 43.4

Table 1 Institutional capabilities, advantages and disadvantages of the main strategies of treatment for treating locally advanced cervical cancer International Federation of Gynecology and Obstetrics stage I B2-IIB

	Institutional capabilities	Advantages	Disadvantages
CT-RT	Well radiotherapy equipment (ideally, intensity-modulated radiotherapy IMRT) Availability of schedule for radiotherapy	Well-documented oncologic benefit over radiotherapy alone Standardized treatment	Limited benefit in case of delay of treatment for toxicity or difficult access to radiation treatment (schedule, few equipment, *etc.*) Possible permanent local toxicity of radiotherapy, mainly in young and sexually active women
NACT + RS	Welltrained surgeons Institutional support for complex surgical procedure (Intensive care units, Urologists, Internist, *etc.*)	Reduce the tumor size Control of metastasis Select chemosensitive patients (prognostic factor) Allow to spare RT for relapsed disease or chemorefractory patients	Delay local treatment such as RT or RS selection of resistant cells clones chemotherapy-induced immunosuppression Negative lymph nodes at RS Cumulative toxicity of multimodal treatment, mainly in case of adding postoperative RT
Chemoradiation + adjuvant chemotherapy	Similar to CT-RT strategy	Possible but not welldocumented benefit yet (limited trials)	Similar to chemoradiation cumulative toxicity of multimodal treatment

NACT: Neoadjuvant chemotherapy; RS: Radical surgery; IMRT: Intensity-modulated radiotherapy; CT-RT: Chemoradiation.

mo there were no significant differences in terms of OS between both groups of treatment[30]. A subsequent Italian Multicenter study (SNAP-02) investigated 154 patients who were randomized to receive TIP as it was previously studied or paclitaxel 175 mg/m^2 + cisplatin 75 mg/m^2 for three cycles, followed by RS. Grades 3-4 leukopenia (6%/53%) and neutropenia (26%/76%) were significantly more frequent with TIP. The overall optimal response showed a significant benefit by using TIP OR = 2.3 (95%CI: 1.1-4.7, P = 0.027). No significant differences in survival were noted between groups[31].

The possible limitation of this strategy is the fact that over 30% of patients will require adjuvant radiotherapy after surgery due to pathologic risk factors on the specimen[33]. Thus, patients could have the adverse effect of a RS plus radical pelvic/abdominal radiotherapy (Table 1).

The question of whether NACT or chemoradiation is a more efficacious treatment for patients with LACC (FIGO stage I B2-IIB) remains to be answered. The current RCT being conducted by the European Organization for Research in Cancer Therapy (EORTC) compares these two treatment modalities in patients with LACC (EORTC-55994, NCT00193739) and is expected to reveal important information for determining the most effective treatment protocol.

ADJUVANT CHEMOTHERAPY AFTER INITIAL TREATMENT

Chemotherapy could be given after initial treatment in patients with a higher risk of systemic relapse. Peters *et al*[13] evaluated 268 patients who were randomly treated with surgery plus radiotherapy or surgery plus chemoradiation plus adjuvant chemotherapy based on four cycles of 5 fluorouracil every 3 wk in patients with early stage disease (FIGO stage I A2-IIA). Progression-free and OS was significantly improved in patients receiving chemotherapy. The hazard ratios for progression-free survival and OS in the radiation only arm *vs* the chemoradiation

arm were 2.01 (P < 0.003) and 1.96 (P < 0.007), respectively. This advantage was more pronounced in patients that received three or four cycles of adjuvant chemotherapy. In addition, a recent analysis of more mature data[34] showed maximal benefit for patients with spread to two or more lymph nodes after postoperative radiotherapy and adjuvant chemotherapy compared with patients receiving postoperative radiotherapy alone (5-year survival 55% *vs* 75%). However, the effect was minimal in low-risk patients, such as only one metastatic lymph node or a tumor size of 2 cm or less in diameter[34].

Adjuvant chemotherapy was also investigated after NACT followed by RS. In 1998, Sananes *et al*[35] evaluated the efficacy of adding 3 curses every three weeks of cis-platinum 50 mg/m^2, methotrexate 30 mg/m^2, and cyclophosphamide 500 mg/m^2 in 56 women with LACC FIGO stage I B-IIIB after NACT followed by RS. After a median follow-up of 75 mo the authors noted an OS for stage I B of 88%, Stage IIB 78%, and 50% for IIIB. Angioli *et al*[36] reported a case series of 246 women affected by a LACC FIGO stage I B2-IIB who had undergone NACT followed by RS and postoperative adjuvant chemotherapy based on 4 cycles of Cisplatin 100 mg/m^2 and Paclitaxel 175 mg/m^2. The study showed a 5-year OS and DFS are 77% and 61%, respectively.

In summary, adding chemotherapy after initial treatment for treating women with LACC requires further investigation. Despite the fact that this strategy should be used under clinical trials, it seems reasonable its indication in high-risk patients, such as node metastasis and lymphovascular space involvement.

AORTIC LYMPH NODE TREATMENT

Lymph node involvement and tumor size are the most important prognostic factors in women with LACC[37,38]. Based on the results of positron emission tomography-computed tomography (PET-CT), over 20% of patients with LACC have aortic node metastasis, and 93% of them have concomitant pelvic node involvement[39]. De-

termination of nodal involvement before treatment has been suggested as an important factor for disease control and for obtaining better oncologic outcomes[40]. Surgical staging has been demonstrated to be the best option for establishing the status of aortic node in women with LACC. A prospective study on 60 women with LACC without evidence of aortic involvement on CT scan underwent PET-CT and aortic surgical staging. A total of three out of 26 patients (21%) with negative pelvic and aortic node on PET-CT had histological positive aortic nodes (false negative rate). In addition, 6 (22%) patients with positive pelvic but negative aortic nodes on PET-CT had positive aortic node at final histology report[41]. Other similar study on 125 patients performed by Leblanc *et al*[42] found similar results. Standard treatment for patients with aortic nodal involvement is based on the extension of radiation field to the aortic area up to the level of the renal veins. As it was previously mentioned, that using IMRT the intestinal toxicity can be reduce without effect on survival[43].

Despite the fact that aortic lymph node dissection can be performed by laparoscopy or robotic surgery, arguments against lymphadenectomy include increased morbidity, delay in starting first line treatment and the questionable advantages on the patients' OS[40]. To this regard, the oncological outcomes of aortic lymph node dissection have been evaluated in several studies with controversial results. A sub-analysis of three gynecologic oncology group (GOG) studies (GOG 85, GOG 120, and GOG 165) analyzed the impact of surgical staging (n = 555) or radiographic determination (CT or magnetic resonance imaging) (n = 130) on survival in women with LACC after chemoradiation treatment[44]. Despite the fact that the multivariate analysis demonstrated a positive benefits of surgical staging on progression free survival and OS, the study had some limitations. Inclusion criteria for this sub-analysis were heterogeneous and the population was unbalanced not only in the sample size, but also regarding the pre-surgical nodal evaluation[40]. The effect on survival of aortic node dissection in women with LACC and negative aortic nodes on PET-CT is currently being investigated in two phase Ⅲ RCT. (NCT01049100 and NCT01365156).

CONCLUSION

During the last years, several strategies of treatment have been evaluated for treating LACC FIGO stage Ⅰ B2- Ⅱ B. After reviewing the literature, there is clear evidence that chemoradiotherapy is better that radiotherapy alone but there is no evidence for using chemoradiotherapy in lieu of NACT followed RS as standard of care. Until definitive trials currently ongoing are published, the strategy of treatment should be individualized after adequate patient counseling and based on specific institution capability.

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