

Cervical cancer: what's new?

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SUMMARY

Study conducted at the Mastology Sector, Division of Gynecology, Department of Obstetrics and Gynecology, and the Institute of Cancer of the State of São Paulo, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, SP and the Sector of Mastology and Gynecologic Oncology at Faculdade de Medicina de Ribeirão Preto (HCRP), Ribeirão Preto, SP, Brazil

Article received: 10/20/2015

Accepted for publication: 10/23/2015

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<http://dx.doi.org/10.1590/1806-9282.61.06.536>

Financial support: none

Cervical cancer is the most common gynecological cancer in Brazil. Among women, it is the second most frequent, second only to breast cancer. It is the fourth leading cause of cancer death in the country, with estimated 15,590 new cases (2014) and 5,430 deaths (2013). In order to update information to improve outcomes, reduce morbidity and optimize the treatment of this cancer, this article will address the advancement of knowledge on cervical cancer. The topics covered include the role of surgery in different stages, treatment of locally advanced carcinomas, fertility preservation, the role of the sentinel lymph node technique, indications and techniques of radiotherapy and chemotherapy, and some special situations.

Keywords: cancer, cervix, pelvic exenteration, fertility sparing, sentinel lymph node biopsy, brachytherapy, chemotherapy.

INTRODUCTION

Cervical cancer is the most frequent pelvic cancer among women in Brazil. In the gynecological sphere, it is the second most frequent, immediately after breast cancer. It is the fourth leading cause of cancer death in the country, with estimated 15,590 new cases (2014) and 5,430 deaths (2013).¹

Treatment of cervical cancer is planned depending on the clinical stage of the disease, ranging from surgery alone to a combination of radiation, chemotherapy and surgery in special situations. However, the side effects and morbidity caused by these therapies often deeply affect the quality of life of patients. Another important point is that the staging of cervical cancer is done clinically, including the results of imaging tests, and the initial classification should not be changed depending on surgical findings. The most recent classification of cervical cancer stages by the International Federation of Gynecology and Obstetrics (FIGO) is shown in Table 1.

In order to provide important information to better assist the patients, reducing the morbidity and optimizing the treatment of this malignancy, this article will ad-

dress recent advances of knowledge on cervical cancer. The topics selected include the role of surgery in different stages, fertility preservation, the role of the sentinel lymph node technique, indications and techniques for radiotherapy and chemotherapy, and also some special situations.

THE ROLE OF SURGERY IN THE INITIAL STAGES

Surgery as treatment alone is employed for the initial stages (carcinoma *in situ*, micro-invasive, and invasive stage IB1), but depending on the diameter of the lesion, some centers treat IIA1 cancers surgically. However, this approach is not recommended as initial therapy of IB2 tumors (limited to the cervix and having a diameter above 4 cm).²⁻⁵ For lesions in stage 0 (*in situ* carcinoma), conization with free margins is sufficient.²⁻⁵

In stage IA1 (micro-invasion less than 3 mm), the choice will depend on the patient's desire to preserve fertility, and whether there is lymphovascular invasion. After conization, if the cone margins are free and there is no lymphovascular invasion, clinical monitoring alone is recommended. It is recommended to avoid fragmenta-

TABLE 1 Staging of cervical cancer (Figo 2009*).

Stage	Description
0	<i>In situ</i> carcinoma
I	Carcinoma strictly confined to the cervix (extension to the uterine <i>corpus</i> should be disregarded)
IA	Invasive cancer identified only microscopically. Invasion is limited to measured stromal invasion with a maximum depth of 5mm and no wider than 7mm
IA1	Measured invasion of stroma ≤ 3 mm in depth and ≤ 7 mm width
IA2	Measured invasion of stroma > 3 mm and ≤ 5 mm in depth and ≤ 7 mm width
IB	Clinical lesions confined to the cervix, or preclinical lesions greater than stage IA
IB1	Tumor ≤ 4 cm
IB2	Tumor > 4 cm
IIA	Involvement of up to the upper 2/3 of the vagina
IIA1	Tumor ≤ 4 cm
IIA2	Tumor > 4 cm
IIB	Parametrial tumor involvement
III	The carcinoma has extended onto the pelvic sidewall and involves the lower third of the vagina and/or hydronephrosis and/or non-functioning kidney
IIIA	Involvement of the lower vagina but no extension onto pelvic sidewall
IIIB	Extension onto the pelvic sidewall, or hydronephrosis/non-functioning kidney
IV	The carcinoma has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum (proven by biopsy). Note: bullous edema is not considered stage IV.
IVA	Spread to bladder and/or rectum
IVB	Spread to distant organs

*Figo Proposals reviewed by the International Gynecologic Cancer Society during the Figo meeting in 2006. International Journal of Gynecology & Obstetrics. 2009;105 (2):103-194.

tion of the specimen and thermal artifacts, which may hinder the histological analysis, and, therefore, in such cases scalpel conization is preferred. If there is no interest in preserving fertility, the recommendation is that the surgery should include plain hysterectomy. Bilateral salpingectomy associated with hysterectomy to prevent ovarian carcinoma is also recommended. However, if there is lymphovascular invasion (very rare situation for this depth of invasion), radical hysterectomy (Class B according to Morrow and Querleau⁶ with resection of the parametrium at the level of ureter) and pelvic lymphadenectomy, or sentinel lymph node technique can be indicated. If the patient wants to preserve fertility, radical trachelectomy can be offered.

As for IA2 and IB1 stages, for patients who do not want to preserve fertility, the best alternative⁷ is radical hysterectomy class C, by Morrow and Querleau, with resection of parametrium at the level of internal iliac artery, which corresponds to the classical Wertheim-Meigs operation, or type III-V Piver-Rutledge, in addition to pelvic lymphadenectomy. For these stages (IA2 and IB1), the sentinel lymph node technique can be proposed to prevent radical lymphadenectomy and risks of associated morbidities (evidence and recommendation 2B for sen-

tinel lymph node). In these stages, if the patient has a clinical contraindication or if she does not accept the surgery, the choice becomes exclusive radiotherapy, using teletherapy supplemented by brachytherapy. Radical surgical procedures can be performed by laparotomy or laparoscopy, including robotic surgery.⁸

Surgery as initial treatment is not indicated for IB2, IIA1 and IIA2 cancers. The probability of positive margins or other indications for radiotherapy or chemotherapy in these stages is very high, around 80%. We know that the addition of adjuvant therapies to surgery (chemoradiation) increases morbidity, worsening the quality of life of the patient.⁹⁻¹¹

An important component of the treatment of cervical carcinoma in the early stages is adding radiation therapy in situations at high risk for local or systemic recurrence. Poor prognostic indicators are obtained from surgical specimens and include the following: positive pelvic lymph nodes, parametrial involvement or positive surgical margin. More recently, another category of prognostic indicators was added to clinical practice and applies to patients without any of the cited criteria. These, considered as minor criteria, are: diameter of the primary tumor associated with lymphovascular invasion, or

deep invasion of the cervical stroma.¹² The presence of any of the major criteria, or a combination of the Sedlis criteria, is an indication for adjuvant pelvic radiotherapy, plus teletherapy associated with brachytherapy in cases of worse prognosis. The addition of chemotherapy concurrent with radiation therapy (cisplatin in weekly doses) for cases with higher risk of recurrence, especially for patients with more than one positive lymph node, showed benefits in terms of overall survival and recurrence-free interval.¹³

TREATMENT OF LOCALLY ADVANCED CERVICAL TUMORS

Tumors at stage IB2, IIA 2, III and IV are included in this category. For all these situations, the recommended treatment since 1999 based on several multicenter randomized trials is the combination of chemotherapy and radiation. The regimen considered standard is IV administration of cisplatin weekly (40 mg/m²) associated with radiotherapy (5 sessions per week for six weeks).¹⁴ For best results, the treatment as outlined above should last between 50 and 55 days. This approach, compared with radiotherapy alone, led to an overall survival benefit of 8%, 9% for local relapse-free interval, and 7% in recurrence-free interval. However, there is increased toxicity and even logistical problems that prevent treatment as required in most of these cases. Adjuvant hysterectomy is a procedure still under debate. The guidelines mention the procedure for situations where the radiation cannot be completed (degree of recommendation 3).¹³ However, response to radiotherapy is worse for adenocarcinomas,^{9,15,16} and a Brazilian study showed high rates of residual tumor in the surgical specimens of patients who underwent surgery 3-4 weeks after completion of treatment with radiotherapy and chemotherapy.¹⁶ When surgery is indicated, salpingo-oophorectomy should be indicated along with hysterectomy^{9,15,16} considering ovarian failure caused by radiotherapy.

The limited results of chemoradiation for locally advanced tumors, especially related to small impact on reducing recurrences at a distance, led to the search for new strategies and the application of additional cycles of chemotherapy after completion of the initial treatment.¹⁷ The most studied drugs are cisplatin, combined or not with gemcitabine,¹⁸⁻²² and paclitaxel combined with carboplatin. Despite promising results, with improved survival and disease-free interval, there is substantial increase in toxicity with additional cycles of chemotherapy. Currently, two international phase 3 studies are in progress. The drugs studied are carboplatin and paclitaxel in four cycles after chemoradiotherapy (ANZGOG 0902/ GOG

0274/NCT01414608 and Radiation Therapy Oncology Group [RTOG] 0724/NCT00980954).²² Another alternative for the treatment of locally advanced lesions is neoadjuvant chemotherapy followed by surgery in cases with good response. Although not recommended as a standard therapy, this approach is employed in about 25% of patients with locally advanced tumors. Although not indicated in the guidelines as an alternative²³ non-randomized studies and meta-analyses²⁴ show that this treatment gives better results than radiotherapy alone.²⁵ The meta-analyses show a reduction of up to 35% in the risk of death, and gain of 15% in survival after 5 years, compared to the use of radiotherapy alone.^{14,17} It is also observed reversal of intermediate and high risk indicators, such as parametrial invasion, depth of cervical invasion and tumor diameter.²³ The only randomized study comparing this treatment alternative with chemo-sensitization is in patient follow-up phase (EORTC55994/NCT00039338) and its results will be presented in 2018.

FERTILITY PRESERVATION

To preserve fertility, conservative surgery (with preservation of uterine body) and ovarian transposition are discussed.

In patients without children and with initial tumors of the cervix, radical trachelectomy is an alternative employed for some time. This surgery involves removing the cervix, along with parametria, proximal third of the vagina and pelvic lymph nodes. The abdominal approach allows better dissection of the parametria but the vaginal route can be used by trained teams. For lymphadenectomy, laparoscopy is the preferred option. Trachelectomy is considered a safe procedure if the following selection criteria are used: usual histology (squamous cell carcinoma or adenocarcinoma, but not neuroendocrine tumors), tumor size less than 2 cm (confirmed on physical examination and MRI of the pelvis), no disease beyond the cervix (confirmed by CT, MRI or PET-CT), tumor-free pelvic lymph nodes, and surgical specimen with free margins.²⁶⁻²⁸ However, we know that the removal of parametria and proximal third of the vagina affects the future obstetric condition of the patient, with higher frequency of miscarriages and premature births. Thus, in view of the low probability of parametrial involvement in patients with stage IA2 and IB1 (tumor measuring up to 2 cm), conization to obtain clear margins associated with pelvic lymphadenectomy has been studied without parametrectomy and colpectomy in these situations.^{3,4} Another approach to IB1 tumors is the use of neoadjuvant chemotherapy prior to trachelectomy.²⁹

For patients with cancer at more advanced stages or for those not eligible for conservative treatment, one option is ovarian transposition, with the purpose of maintaining hormonal function and ovarian reserve. Surgery consists of releasing the tube and ovary from the pelvic infundibulum, attaching them above the edge of the pelvis, which is the cranial limit for pelvic radiotherapy fields. It is suggested placing clips on the new topography of the annexes, in order to identify these structures later on imaging studies. Keep in mind the risk of ovarian metastasis from cervical carcinoma, which is 0.6% for squamous cell carcinomas and 6% for adenocarcinomas, requiring careful evaluation during surgery and removal of suspicious attachments. The success rate is quite variable, and often there is anticipation of menopause in cases treated with transposition.³⁰

Some of this variation is due to concurrent or adjuvant chemotherapy, which implies a high chance of ovarian failure induced by the chemo in patients older than 35 years.³¹⁻³³ Other approaches to preserve fertility include advanced procedures such as ovulation induction and oocyte retrieval, *in vitro* fertilization and embryo freezing, and preservation of ovarian tissue for reimplantation.

SENTINEL LYMPH NODE ROLE IN THE TREATMENT OF CERVICAL CANCER

The rationale for the use of sentinel lymph node (SLN) technique, such as in the case of breast carcinomas, is that this is the first lymph node that receives drainage from the tumor. Thus, if it is disease-free, the other nodes will also be. And the patient is spared complete lymph node dissection, associated with high morbidity. The main study on the use of this technique to treat cervical carcinomas is the SENTICOL trial, which showed high sensitivity for detection of sentinel lymph node (92%), high negative predictive value (98.2%), and no false-negative cases when there was bilateral identification of sentinel lymph nodes.³⁴ Other studies have shown similar results.³⁵⁻³⁷

However, the following criteria must be met: the technique is indicated for tumors in stages IA2, IB1 and IIA1 (tumor up to 4 cm), except for cases in which there is reduced sensibility using the method, such as in tumors sized more than 2 cm; absence of lymph node involvement (on imaging and intraoperative); bilateral identification of the sentinel lymph node (at least one node in each hemi-pelvis). The accuracy of the method is improved by lymph nodal "ultra-staging" (serial sections of the sentinel lymph node).^{36,37} Nevertheless, it cannot be performed during surgery, and, if the nodes are positive, a second operation is needed. The SENTICOL II trial is cur-

rently in progress with removal of the sentinel lymph node alone, without lymphadenectomy, in cases of negative SLN. It will, therefore, be possible to verify whether this procedure can be regarded as the gold standard.

ADVANCES IN RADIOTHERAPY FOR CERVICAL CANCER

With regard to radiotherapy, the novelty is the planning of external radiation therapy (teletherapy) and brachytherapy guided by magnetic resonance imaging (MRI). For study of the cervix and pelvis, as a whole, MRI showed image resolution better than computed tomography (CT), with better definition of anatomical planes. Thus, a better definition of the fields would be possible, minimizing side effects and improving tolerability to treatment with lower toxicity in bone marrow, bladder and rectum. The existing studies that adopt historical controls for comparison show improved local control and survival, especially in the treatment of advanced tumors (stage IIIB).³⁸⁻⁴² But there are no prospective studies confirming these results. Moreover, the application of these radiotherapy techniques almost quadruples the time spent with each patient, making it difficult to use in most public services, where there are patients awaiting radiotherapy for a considerable time.

ADVANCES IN SYSTEMIC TREATMENT OF RECURRENT CERVICAL CANCER

With respect to chemotherapy, we now present some advances in the treatment of patients with metastatic disease and the role of antiangiogenic and immunogenic therapies. For the treatment of recurrent cervical cancer, various approaches can be employed depending on the previous treatment, and where the recurrence was detected. Thus, radiation may be an option if it has not been used before, and surgeries such as rescue hysterectomy may be the choice in cases previously treated with radio and chemotherapy. Another alternative rarely used is anterior, posterior or total pelvic exenteration. Most cases, however, have been treated with chemotherapy. Several prospective studies have shown that the schemes based on the use of cisplatin⁴³ have no significant impact on survival. The use of carboplatin leads to reduction of toxicity but has no better results in terms of survival.

A substantial gain in survival was observed in a prospective phase 3 study (GOG 240). In this study, patients received one of two chemotherapy regimens, with or without bevacizumab as angiogenesis inhibitor (total of 4 arms). The drug is a monoclonal antibody directed to vascular endothelial growth factor (VEGF). In the popula-

tion included in the study, 75% had received prior treatment with cisplatin for recurrent disease. The use of bevacizumab led to improved overall response, progression-free time and survival.⁴⁴⁻⁴⁶

There was benefit for patients with recurrent disease in previously irradiated areas. Adverse effects included neutropenia, hypertension (grade 3), gastrointestinal fistula, and thromboembolism. However, the use of targeted therapy allowed an improvement in overall survival compared to chemotherapy alone. Other agents with anti angiogenic activity that proved useful in the treatment of other malignancies are being investigated for cervical cancer, such as sunitinib, pazopanib, lapatinib and cediranib.⁴⁴

The goal of immune therapy in cervical cancer is to modify the patient's immune response leading to the elimination of cancer cells. One approach explores the relationship of this malignancy with the human papilloma virus (HPV). An Indian study of a vaccine with HPV-induced E7 protein, together with attenuated bacterium (*Listeria monocytogenes*) as a vector, in over 100 women with refractory or recurrent cervical cancer⁴⁷ showed promising results. After six months, 63% of patients were alive and 12 patients had partial or complete response.⁴⁷ Another approach is the induction of regulatory cytotoxic T lymphocyte-associated molecule 4 (CTLA-4), which is important for activation of cellular immune response. Monoclonal antibody ipilimumab blocks CTLA-4 and promotes antitumor immunity, generating effective immune response against the tumor. This drug is in a phase 1 study (GOG 9929/NCT01711515).²⁰ Last, another possibility being studied for cervical cancer is that of the inhibitory receptor 1 of cell death (PD-1). When attached to its ligand PD-L1, which is found on tumor cells and leads to blockage of effective antitumor immune response, antibodies to both proteins may restore effective immune response.²⁰

SPECIAL SITUATIONS

In this topic, we will discuss the treatment of patients with involvement of para-aortic lymph nodes, the role of para-aortic lymphadenectomy, and surgical indication in local recurrences (pelvic).

The two most important prognostic factors in cervical cancer, in addition to staging, are tumor size and lymph node involvement. Among the patients with locally advanced tumors (IIB or higher), 15-30% have para-aortic lymph node involvement. Imaging studies CT, MRI or positron emission computed tomography (PET-CT) have high rates of false negatives.⁴⁸⁻⁵⁰ PET-CT has better accuracy, but fails in about 10-20% of cases (false negatives in

para-aortic region). The objective of investigating lymph nodes in this region would be to select cases for treatment with para-aortic field. However, studies in which routine para-aortic lymphadenectomy was performed in locally advanced tumors showed worse prognosis of patients, even with more aggressive adjuvant treatment, such as extending the radiotherapy field to the para-aortic region. Benefit with increased survival to justify a para-aortic lymphadenectomy was observed in patients with negative PET-CT results, and with microscopic disease found only in pathological examination of the para-aortic lymph nodes.⁵¹⁻⁵³ Apparently, patients with the disease in para-aortic lymph nodes represent a group in which even radiotherapy applied directly to these lymph nodes associated with chemotherapy, or chemotherapy alone, is not able to improve prognosis.

Pelvic recurrence is a failure event that compromises the survival and quality of life of patients. In such cases, surgical treatment of choice is pelvic exenteration, a procedure that is re-assessed whenever progress is achieved in the areas of surgery, supportive therapy and imaging evaluation. This surgery may be divided into anterior, posterior or total. Anterior exenteration comprises the removal of the recurrent tumor in addition to the bladder compartment. Posterior exenteration refers to the removal of the rectum in addition to the tumor. Last, total exenteration includes the removal of both the bladder and rectum. Another more recent classification divides surgery into categories (supralevator, infralevator, and infralevator with vulvectomy) that are chosen based on the extent of the recurring disease.^{54,55} Due to high rates of complications and mortality associated with this surgery, it should be reserved for much selected cases. It is especially suitable for pelvic recurrence after chemoradiation and when the surgeon anticipates the possibility of obtaining surgical margin, a prerequisite for cure.

Selection criteria include centered relapse with negative lymph nodes and no visceral metastases.^{54,55} As preoperative assessment, all the candidates for pelvic exenteration should undergo PET-CT to rule out distant disease. PET-CT is the imaging study with greater accuracy to detect cervical cancer recurrences.⁵⁶⁻⁵⁸ As the occurrence of positive lymph nodes is one of the most frequent reasons to quit exenteration during surgery, prior assessment of pelvic and para-aortic lymph nodes by laparoscopy may be an alternative.

Successful exenteration depends on the following preoperative prognostic factors: tumor size, time from initial treatment to recurrence (disease-free survival) and tumor histology. Tumor size greater than 5 cm, recur-

rence after less than two years of initial treatment, and histological type of squamous cell carcinoma (SCC) are associated with poor prognosis.^{54,55} Regarding postoperative prognostic factors, worst outcome is found in the presence of positive meso-rectal lymph nodes, positive lymphovascular invasion, and margins compromised by tumor, with survival after two years around 10%.^{54,55}

RESUMO

Câncer de colo do útero: o que há de novo?

O câncer de colo uterino é o câncer ginecológico mais frequente em nosso meio. Entre as mulheres, é o segundo mais frequente, atrás apenas do câncer de mama. É a quarta causa de morte por câncer no Brasil, com estimativa de 15.590 casos novos (2014) e com 5.430 mortes (2013). No intuito de atualizar informações para a melhora do prognóstico, redução da morbidade e otimização do tratamento dessa neoplasia, serão abordados neste artigo os avanços nos conhecimentos sobre o câncer cervical. Entre os temas apresentados, estão o papel da cirurgia nos diferentes estádios, o tratamento dos carcinomas localmente avançados, a preservação da fertilidade, o papel da técnica do linfonodo sentinela, indicações e técnicas da radio e quimioterapia, além de situações especiais.

Palavras-chave: câncer, colo do útero, exenteração pélvica, preservação da fertilidade, biópsia de linfonodo sentinela, braquiterapia, quimioterapia.

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