

Review Article

Prognostic significance of the Central Tumor Size (CTS) in Cervical Cancer (CC) stages IIb and IIIb: What should we do with the FIGO staging system and therapeutic strategies?

Alejandro Soderini*, Alejandro Aragona, Agustin Quintaie, Horacio Moschen and Martín Mendez

Chair of Gynecologic Oncology, University of Buenos Aires, Oncologic Hospital of Buenos Aires, Marie Curie, Argentina

Abstract

Cervical cancer constitutes an issue in public health, becoming the leading cause of death by cancer in women between 20-40 years of age in Latin America. In Argentina 5000 new cases are diagnosed each year, where more than 56% are in advanced stages. The aim of the present current opinion or critical review article is to remark the importance of the prognostic significance of the Central Tumor Size in stages IIB and IIIB cervical cancer, as well as to propose a new FIGO Staging System for Cervical cancer and trying to find out a role for the different therapeutic strategies for those cases.

Introduction

Cervix cancer (CC) has been historically associated with poverty and low social and cultural levels, and is currently the type of neoplasm which most accurately reflects the inequality of the health care system. At present, the high risk of CC has also reached the middle class due to changes in social and sexual behavior, persistent cultural barriers and the concern about the spread of the human papilloma virus (HPV) [1].

Regardless of the social class, CC clearly reflects the failure of public health interventions due to State inaction in terms of control policies for a sexually transmitted disease which is preventable and, in theory, eradicable. Unfortunately, the likelihood of eradication is remote given the current setting in our region [2].

Cervix cancer is rather uncommon in Europe, but still represents a public health issue. The estimated number of new cases of cervical cancer in Europe in 2018 was 61,000 including 25,800 deaths [3].

Survival at 5 years for European women diagnosed with cervix cancer in 2000-2007 was 62%, ranging between 57%

in Eastern Europe and 67% in Northern Europe. Survival was particularly low (< 55%) in Bulgaria, Latvia and Poland, and higher in Norway (71%). The remarkable geographical difference in cervix cancer rates evidences differences in the detection tools available and the prevalence of the human papilloma virus (HPV) infection.

In Argentina, about 4,000 new cases of cervical cancer are diagnosed each year, and about 1,800 women die from the disease; 82% of the deaths occur in women over the age of 40 [4].

Based on these statistics, it can be stated that one woman dies from cervix cancer every 4 hours in Argentina. Patients in the high risk tumor group (bulky tumors, parametrium involvement, young women) have a worst outcome already at the time of diagnosis.

The role of tumor size in stages Ib and IIa is well known; however, the prognostic value of tumor size in advanced stages might not seem so clear when considering treatment since the gold standard is related to a poor outcome in overall and specific survival and quality of life [2].

More Information

*Address for Correspondence:

Alejandro Soderini, MD, PhD, University of Buenos Aires, Oncologic Hospital of Buenos Aires, Marie Curie, Argentina,
Tel: +5491157420830;
Email: Alejandro.soderini@yahoo.com.ar;
alejandrosoderini@gmail.com

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ORCID: orcid.org/0000-0001-7481-1445

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Keywords: Cervical cancer; Central tumor size; FIGO staging system; Neoadjuvant chemotherapy; Oncological treatments





The aim of the present current opinion or critical review article is to remark the importance of the prognostic significance of the Central Tumor Size in stages IIB and IIIB cervical cancer, as well as to propose a modification of the FIGO Staging System for Cervical cancer trying to find out the most accurate therapeutic possibilities.

Tumor size in cervix cancer is important from the time it becomes microinvasive. We used to consider microinvasive carcinomas on the one hand, and truly invasive carcinomas of the cervix (stages Ib) when the tumor was larger than microinvasive tumors.

As size increased, so did the risk for node metastasis, relapse, lower survival rates and failure of the traditional treatment options, surgery and radiotherapy.

Considering this setting, in 1994 FIGO divided microinvasion into stages Ia 1 and 2, and Ib1, for tumors measuring less than 4 cm [5].

In the mid-80s, as survival rates stagnated and treatment options for large tumors confined to the cervix failed, a notable fact in the treatment field occurred: the introduction of chemotherapy for the primary management of this disease.

Chemotherapy was introduced as neoadjuvancy, that is before the main treatment, either surgery or radiotherapy. The aim was to reduce or eliminate the tumor, optimize standard therapy and manage distant metastasis [6-8].

The knowledge obtained about tumor biology, the improvement of treatment modalities and statistical analyses have shown a 90% cure rate in the initial stages of the disease with surgery alone, when the tumor was under 2 cm. Less radical or conservative surgical approaches might be performed (Piver II, radical trachelectomy) [9-11], with similar results as those obtained with radical surgery.

Neoadjuvant chemotherapy proved to be beneficial in stage Ib1 for it reduced the recurrence rate so that conservative surgeries, including chemoconization followed by simple trachelectomy [6,9,17], or vaginal [8] or abdominal [9] radical trachelectomy might be performed.

This conservative strategy was especially indicated in women with tumors over 2 and under 4 cm, with oncological safety and an significant success rate related to fertility sparing [16,18].

In the case of tumors over 4 cm confined to the cervix, FIGO Ib2 stage, more than 1000 publications have reported the benefits of neoadjuvant chemotherapy followed by radical surgery. The most important publications were by Sardi [8], Benedetti-Panicci [19], Kim [20], Lai [21] and the MRC meta-analysis [22], after which FIGO in 2003, suggested neoadjuvant chemotherapy followed by surgery as an alternative to concurrent chemotherapy [12,13,23,24].

However, the study of tumor size was still remarkable, mainly after complete response to chemotherapy in the cervix or when the residual tumor was under 2 cm. This enables consolidation with chemotherapy [10,11]. A recent publication suggests dividing stage Ib into tumors under 2 cm, from 2 to 4 cm and over 4 cm.

However, in this paper no reference is made to the importance of tumor size in stages IIb and IIIb [25]. Sardi, et al. in 1998 [26], were the first to state the importance of tumor size in stage IIb, and so divided tumors into those over 5 cm and under 5 cm, showing that larger tumors had a less favorable outcome, even when the best results were obtained with chemotherapy followed by surgery.

In that report, and later Kim, et al. in 2006 [20-27], stated that neoadjuvant chemotherapy was an "in vivo" marker of tumor response, so chemoresistant tumors would also be radioresistant, and radical extended surgery, when possible, was a valid option. No doubt, in these stages we still face a challenge.

Based on our investigation, we underline that overall survival and disease free survival decrease when the central tumor is over 6 cm, and even more when they are over 8 cm, regardless of the treatment option [2]. McConmark in 2013 [28] published encouraging results using neoadjuvant chemotherapy followed by concurrent chemoradiation in locally advanced disease with central bulky tumors [28], as well as other authors [29,30], arrived to similar conclusions, also considering the quality of life of these patients [31]. At this time, it is important to remember that was proven no difference between neoadjuvant chemotherapy vs. chemoradiation [32,33].

Considering our previous published results [2,34], it might be necessary to subdivide these stages according to the size of the central tumor, as follows: under 6 cm, from 6 to 8 cm and over 8 cm. so as to design and individualize the best treatment strategy for each particular patient. So, we suggest that stages IIb and IIIb should be divided into II/IIIb 1, 2 and 3, respectively. But, which may be the best treatment option in these cases? We still do not know, but we believe that both chemotherapy and the new molecular target therapies, radiotherapy and even surgery, might play a role when choosing the best treatment option. It must not be forgotten chemoresponders tumors will also be radioresponders [26], so, the combination chemotherapy followed by chemoradiation could be a good alternative to choice.

For central tumors under 4 cm, standard chemoradiation might still being the standard treatment, for 4-6 cm tumors, neoadjuvant chemotherapy followed by chemoradiation might be beneficial; but when the tumor is over 6 cm more than one treatment should be administered, either simultaneously or sequentially, to achieve disease control. But, what must



we think and what must we do in stages IIIc1 or 2 of the new classification of cervical cancer? Particullary, nothing different. Despite the lymphnodes involment, the central tumor size must continious being taken into account as it is an independent prognostic factor as was published [2,34]. As all we know, chemotherapy is also active over the metastatic nodes and using neoadjuvant chemotherapy, the number of positive lymphnodes and the diameter of the central tumor size, will decrease [35]. So, again, the strategy proposed by McConmarck and others is absolutely valid. In table 1, we can see the changes we are proposing to the FIGO STAGNG SYSTEM in cervical cancer.

Table 1: FIGO staging sistem proposal.

FIGO Stage	< 6 cm.	6 cm. -8 cm. > 8 cm
IIb	1	2 3
IIIb	1	2 3

Giving pass to new waves, advances in molecular biology will be useful to determine which patients might respond to neoadjuvant chemotherapy, and so, careful patient selection will be essential [36].

Conclusion

Tumor size is still an independent prognostic factor.

When the central tumor is over 6 cm in stages IIb and IIIb, survival and disease-free survival drop dramatically as was published [34].

Consequently, there is a need to subdivide at least these stages for tumors over 6 cm and under 6 cm in order to carefully select patients and target therapies accordingly.

In spite of the above, no woman is supposed to die of cervix cancer for treatment options are available in the early stages of the disease.

Authors work

Alejandro Soderini, MD., PhD, Author and Writer, Associate Professor of Gynecology, Chairman of the Gynecol Oncol. Fellowship. University of Buenos Aires. Oncologic Hospital of Buenos Aires Marie Curie.

Alejandro Aragona, MD, Co-writer, Assistant Professor of Gynecology. Gynecol Oncol. Fellowship. University of Buenos Aires. Oncologic Hospital of Buenos Aires Marie Curie.

Agustin Quintaie, MD, Gynecol. Oncol. Fellow. University of Buenos Aires. Oncologic Hospital of Buenos Aires Marie Curie.

Horacio Moschen, MD, Gynecologist Oncologist. Oncologic Hospital of Buenos Aires Marie Curie.

Martín Mendez, MD, Gynecologist Oncologist. Oncologic Hospital of Buenos Aires Marie Curie.

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