Stage IB2 and IIB cervical cancer in young patients: Treatment results and management proposal

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Abstract

Introduction: Advanced cervical cancer (CC) remains a major health problem in our country, with an increasing percentage being diagnosed in young women. Objective: The objective of this study is to present an institutional experience with standard treatment in menstruating women with CC at stages IB2 and IIB, with complementary or rescue surgery being added in selected cases, as well as to propose some management alternatives for these patients. Materials and methods: Analysis of the cases of 45-year-old or younger stage IB2-IIB CC patients who received concomitant chemotherapy and radiotherapy with or without further surgery at the Oncology Department of the Hospital General de México. Results: Ninety-eight patients with a mean age of 37.1 years were treated. In 89 patients, there was follow-up data available, of which 63 (70.7%) had an average evolution of 30 months with no evidence of disease: 12/19 (63.1%) were at stage IB2 and 51/70 (72.8%) at stage II (p > 0.05). At stage IB2, only 4/8 adenocarcinomas (50%) had these results versus 8/11 (72.7%) squamous cell carcinomas (p > 0.05). At stage II, the figures were 8/11 for adenocarcinomas (72.7%) and 43/59 for squamous cell carcinomas (72.8%). With further surgery, the results were increased by 10.1%. Failure of established therapeutics was demonstrated in 17 patients (19.3%): 4 cases due to locoregional progression (23.5%) and 13 (76.4%) due to distant dissemination. Conclusions: The results for stage IB2 were inferior to those for stages II, with most failures being related to distant metastasis. To prevent early menopause, exploring the use of neoadjuvant chemotherapy plus radical hysterectomy is recommended in younger patients. (creativecommons.org/licenses/by-nc-nd/4.0/).
INTRODUCTION

Cervical cancer (CC) is a health problem that represents the second malignancy in women worldwide, with more than 500,000 cases annually diagnosed and with more than 260,000 deaths every year. It is the female genital tract most common cancer and the one that causes the highest number of deaths. While at the early stages, outcomes are highly encouraging, those obtained at advanced stages where radiotherapy is used as background treatment are accompanied by treatment failure ranging from 20% to 75%, according to the clinical stage of the disease. Although the advent of platinum-based radiosensitizing chemotherapy for the treatment of advanced stages improved previously obtained results with standard chemotherapy by up to 12%, it has not had the desired impact for these stages, and hence, the efforts made by different authors to increase disease-free interval for these cases and 5-year survival without tumor are only recently obtained in the treatment of this grievous disease to be reckoned with.

In Mexico, CC incidence and mortality figures are only surpassed by those of breast cancer among female cancers, and unfortunately, more than 60% of invasive cancers are diagnosed at advanced stages, which accounts for the nearly 4000 deaths recorded every year in our country. Although the age of disease invasive stages presentation is around 50 years, recent studies show a trend toward presentation at younger ages. At least 15% of cases are estimated to be 40-year-old or younger.

A report deriving from the population that attends the Hospital General de México with 1217 patients showed a mean age of 51.9 years, with predominance for stage I with 353 cases (39%) and stage II with 340 (37%). Of the entire group, 23.7% were menstruating patients of 39 years of age or younger.

The results of CCRT standard treatment in menstruating patients with CC at stages IB2 and IIA2-IIIB of the International Federation of Gynecology and Obstetrics (FIGO) plus complementary or rescue surgery in those showing tumor persistence or risk factors for tumor recurrence or experiencing recurrence are shown in this publication. Some proposals are also made for advanced CC comprehensive management, especially when occurring in younger women, and conclusions are drawn on the subject.

MATERIALS AND METHODS

This was a retrospective, descriptive, observational study of medical records of the Hospital General de México “Dr. Eduardo Liceaga” Oncology Department clinical files during the period encompassed from January 2010 to December 2014, with those from patients with CC at FIGO clinical stages IB2 and IIA2-IIIB, aged 45 years or younger, being selected to be studied. Data were obtained on age, histological varieties (squamous cell carcinoma or adenocarcinoma), established treatment, and results thereof.

The established primary standard therapy was CCRT, using external radiotherapy to the pelvis at 50 Gy doses in 5 weeks with external beam radiation therapy (EBRT) equipment (linear accelerators and less often cobalt 60) plus brachytherapy application at 30 Gy on average at the conclusion of EBRT, for a total of 80 Gy. In addition, concomitant chemotherapy was weekly administered during EBRT, with cisplatin or carboplatin at standard doses for 5 cycles on average.

At treatment completion, the patients were assessed by the treating radio-oncologist physician, who referred patients with suspected tumor persistence or progression, as well as those with risk for tumor recurrence due to highly bulky tumors and unfavorable histopathology (adenocarcinoma), and those that for some reason did not complete the brachytherapy established dose.

These patients were considered for complementary surgery to be performed between 6 and 10 weeks after treatment completion with a mean of 8 weeks, with the procedures consisting in class II radical hysterectomy without pelvic lymphadenectomy or class III radical hysterectomy with lymphadenectomy at the surgeon’s judgment.

Patients with tumor persistence diagnosed during the first 5 months following treatment conclusion or with tumor recurrence occurring after this period were assessed for rescue surgery consisting in pelvic exenteration or class III radical hysterectomy after a tumor activity, positive biopsy was obtained and tumor restriction to the pelvis was demonstrated by computed axial tomography and/or positron-emission tomography.

Patients with tumor progression who were not eligible for rescue surgery were assessed to receive palliative chemotherapy with platinum-based regimens.

The obtained results underwent statistical analysis with the Chi-square test and Fisher’s exact test when one of the cells had an expected value lower than 5, with 95% confidence intervals. The statistical package Info 6.04 was used. Confidence values lower than 95% were considered non-statistically significant (NS).

RESULTS

Clinicopathological aspects

During the analyzed period, 400 patients with advanced CC completed their treatment, of which 98 (24.5%) were at stages IB2, IIA2, and IIB, 23 (27.3%) at stage IB2, 5 (5.1%) at stage IIA2, and 70 (71.4%) at stage IIB. The average age of the group was 37.1 years; 80.6% had squamous cell carcinomas and 19.3% adenocarcinomas (Table 1).

Results of the concomitant treatment with radiotherapy and chemotherapy

Seventy-two patients (73.4%) completed their treatment without clinical or imaging evidence of tumor activity, whereas 26 (26.5%) showed tumor persistence, progression, or recurrence. Nine patients (9.1%) who completed their treatment without tumor activity were lost to follow-up during...
of the 1st month after treatment conclusion and were not considered for final results.

Final results assessment included 89 patients, of which 63 who received primary treatment (70.7%) spent from 12 to 62 months, with an average of 30, with no evidence of tumor activity. This number included 12 of 19 patients at stage IB2 (63.1%) and 51 of 70 (72.8%) at stages IIA-B (Table 2). In addition, 12 of 19 (63.1%) had adenocarcinomas and 51 of 70 (72.8%) had squamous cell carcinomas (p = 0.5265; NS) (Tables 3 and 4).

Disease-free follow-up for the referred period by clinical stage according to histological type was as follows: For stage IB2, 4 out of 8 patients (50.0%) had adenocarcinomas and 8 out of 11 (72.7%) had squamous cell carcinomas (p = 0.3765; NS); for stages IIA2-B, 8 out of 11 (72.7%) had adenocarcinomas, and 43 out of 59 (72.8%) had squamous cell carcinomas (p = 0.7819; NS) (Tables 3 and 4).

Complementary and rescue surgery

Two patients with incomplete brachtherapy, 9 with tumor persistence, and one with recurrence were considered for surgical exploration after tumors limited to the pelvis susceptible to be extirpated became evident by clinical and/or imaging examination. Two cases with tumor persistence (16.6%) were unresectable since laparotomy revealed the presence of para-aortic metastases (one patient at stage IB2 with clear-cell adenocarcinoma and one with stage IIB squamous cell carcinoma).

Five class II hysterectomies without lymphadenectomy, 3 class III radical hysterectomies, and 2 pelvic exenterations (one anterior and one total) were carried out (Table 5). In 4 of the 10 patients with resection (40.0%), 3 with class II hysterectomy, and 1 with anterior pelvic exenteration; pathology final reports showed no residual tumor. Included reports are both patients with incomplete brachtherapy treated with class II hysterectomy, one with class II hysterectomy with cervical residual and one of the 2 patients with exenteration. The patient who underwent anterior exenteration had the previous report of squamous cell carcinoma tumor recurrence and the specimen reported chronic granulomatous disease.

Only in one of the 10 operated patients was their treatment failure. It was a stage IIB adenocarcinoma with tumor persistence at the cervix that was treated with class III radical hysterectomy, the specimen of which showed tumor residual at the cervix with extension to the uterine isthmus without any other adverse prognostic risk factors. The patient developed new tumor recurrence 7-month post-surgery and was lost to follow-up.

In the remaining 9 cases, a follow-up was achieved of between 13 and 61 months post-surgery, with a mean of 30 months without evidence of disease. This included 4 of 4 patients at stage IB2 and 5 of 6 at stage IIB (Table 2), and by histological lineage, 2 of 3 adenocarcinomas and 7 of 7 squamous cell carcinomas (Tables 3 and 4).

When the primary CCRT treatment results had further surgery results added, the overall figure with no evidence of disease, which initially was 70.7%, was observed to rise to 80.8%, which represented a 10.1% increase (p = 0.437; NS). For stage IB2, the figure increased from 63.1% to 84.2% (p = 0.2690; NS); for stage II, from 72.8% to 80.0% (p = 0.5451; NS); for adenocarcinoma, from 63.1% to 73.6% (p > 0.05), for squamous cell carcinoma, from 72.8% to 82.6% (p = 0.3255; NS) (Tables 3-4).

Treatment failure

In 17 of the 89 patients (19.1%) with follow-up data available, failure of the established treatment was demonstrated.
Table 3. Treatment results: Adenocarcinoma

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Radiotherapy plus chemotherapy</th>
<th>Subsequent surgery**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>(a) 4/8 (50.0)</td>
<td>1/1 (100)</td>
<td>(c) 5/8 (62.5)</td>
</tr>
<tr>
<td>Stage IIA-IIIB</td>
<td>(b) 8/11 (72.7)</td>
<td>1/2 (50.0)</td>
<td>(d) 9/11 (81.8)</td>
</tr>
<tr>
<td>Total</td>
<td>(e) 12/19 (63.1)</td>
<td>2/3 (66.6.0)</td>
<td>(f) 14/19 (73.6)</td>
</tr>
</tbody>
</table>

*30 months on average. **In patients with tumor persistence or recurrence. Statistical significance: (a) versus (b): p = 0.376; (c) versus (d): p = 0.1909; (e) versus (f): p > 0.05.

Table 4. Treatment results: Squamous cell carcinoma

<table>
<thead>
<tr>
<th>Clinical stage</th>
<th>Radiotherapy plus chemotherapy</th>
<th>Subsequent surgery**</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Stage IB2</td>
<td>(a) 8/11 (72.7)</td>
<td>3/3 (100)</td>
<td>(c) 11/11 (100)</td>
</tr>
<tr>
<td>Stage IIA-IIIB</td>
<td>(b) 43/59 (72.8)</td>
<td>4/4 (100)</td>
<td>(d) 47/59 (79.6)</td>
</tr>
<tr>
<td>Total</td>
<td>(e) 51/70 (72.8)</td>
<td>7/7 (100)</td>
<td>(f) 58/70 (82.8)</td>
</tr>
</tbody>
</table>

*30 months on average. **In patients with tumor persistence or recurrence. Statistical significance: (a) versus (b): p = 0.7819; (c) versus (d): p = 0.1909; (e) versus (f): p = 0.3255.

Table 5. Performed surgical interventions

<table>
<thead>
<tr>
<th>Surgery</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>Class II hysterectomy</td>
<td>5 (41.6)</td>
</tr>
<tr>
<td>Class III hysterectomy</td>
<td>3 (25.0)</td>
</tr>
<tr>
<td>Pelvic exenteration</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Laparotomy and biopsy</td>
<td>2 (16.6)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (99.8)</td>
</tr>
</tbody>
</table>

devoted. These patients were part of the group with tumor persistence, progression, and recurrence (17/26: 65.3%). This figure includes 6 of 13 patients (46.1%) with tumor persistence who showed progression, 5 of them with para-aortic metastases, and the patient with tumor persistence treated with radical hysterectomy that developed tumor recurrence and was lost to follow-up without further treatment. It also includes 11 of 12 with tumor recurrence (91.6%), 4 of 7 with adenocarcinoma (57.1%), and 13 of 18 with squamous cell carcinoma (72.2%) (Table 6), and by clinical stage, 1 of 4 (25.0%) at clinical stage IB2 and 5 of 9 (55.5%) at clinical stage IIB.

Tumor recurrence

Twelve patients developed tumor recurrence, which occurred between 7 and 28 months post-primary treatment, with a mean of 16 months. Eleven patients died with tumor activity, and only in one case, disease-free control was obtained; it was a patient with stage IIB squamous cell carcinoma who developed tumor recurrence 10-month post-primary treatment and underwent total pelvic exenteration. She had 24-month disease-free post-surgery control. Three patients developed locoregional progression and died without further treatment, and 8 had distant disease, 5 of them with locoregional activity. Distant metastases location for the entire group is shown in Table 7.

Six of the 17 patients with treatment failure (35.2%) received palliative chemotherapy with platinum-based schemes, without treatment influencing on subsequent evolution.

DISCUSSION

The treatment of CC advanced stages, which are predominant in developing countries, remains an enormous challenge for institutions in charge of the management of this disease.13,7,12

Although the advent of chemotherapy came to globally improve the results obtained with radiotherapy as the treatment of choice,4,6,18 the eventual inaccessibility in developing countries to modern radiotherapy equipments and to drugs whose combination is being shown to improve the results reported with the use of CCRT4,19,20 are factors that contribute for CC to continue representing an important cause of death for women in countries such as ours.12,13,15,16

The authors’ institution is a reference center for the population without social security, and only 30% of CC patients live in Mexico City; 60% of invasive cancers are diagnosed at advanced stages of the disease, without taking into account those that have already been treated outside the institution. Four-hundred eighteen patients out of 908 (46%) treated under the catastrophic expenses program of the Federal Government Ministry of Health were at FIGO stages IB2 and II15, in which tumor persistence or recurrence between 15% and 23% has been reported with
standard treatment, as well as 5-year disease-free survival of 75.7% and 65.8%, respectively\(^{7,9,10}\). We selected for the study menstruating patients at stages IB2-IIB conventionally treated with CCRT owing to concerns deriving from reports that show that at least 15% of CC cases occur in younger women\(^9\) and to the desire to obtain information on treatment results in these patients, considering that 23.7% of patients with CC attending the authors’ institution are 39 years old or younger\(^{15}\).

In this series, 98 patients were part of a group of 400 who required standard CCRT treatment and that, having been classified at stages IB2-IIB, were 45 years old or younger, with a mean of 37.1 years. With this therapy, tumor-free follow-up of 12-62 months, with a mean of 30 months, was achieved in 63 of 89 patients (70.7%).

For stage IB2, the figures were 12/19 (63.1%), including 4/8 adenocarcinomas (50%) and 8/11 squamous cell carcinomas (72.7%). For stage II, 51 of 70 (72.8%): 8/11 adenocarcinomas (72.7%) and 43/59 squamous cell carcinomas (72.8%). The figures referred for stage IB2 are lower than the value reported in the references (75.6%)\(^{1,4,6}\), inspite of follow-up not being at 5 years. Of note, only half of the patients in this study with a diagnosis of adenocarcinoma evolved with no evidence of disease for the referred period, a situation that should be, especially, taken into account to be corroborated or not in the future, once a larger number of patients with stage IB2 diagnoses is available, although adenocarcinoma accounts only for 11% of CC cases in our institution\(^{15}\).

Twenty-six patients in the present series evolved with tumor persistence or recurrence, and 12 of them (46.1%) were candidates to complementary surgery with suspected or confirmed tumor persistence or to rescue surgery for tumor recurrence, with tumor-free follow-up figures being able to be increased by means of these treatments from 63.1% to 84.2% for stage IB2 (p = 0.2690; NS) and from 72.8% to 80.0% for stages II (p = 0.5451; NS).

The value of rescue surgery for patients in whom CCRT has failed is well documented\(^{1,4,6}\), with some authors highlighting the usefulness of practising non-exenterative complementary surgeries in patients with suspected or confirmed central tumor persistence\(^{7,9,10}\), and others, the convenience to consolidate CCRT conventional therapy with additional chemotherapy cycles\(^{7,11}\).

In this series, 10 of 12 patients with suspected tumor residue, persistence, or recurrence underwent complementary or rescue surgical procedures and treatment failure was observed only in one case with one patient with tumor persistence treated with class III radical hysterectomy developing tumor recurrence and being lost to follow-up in these conditions. Two pelvic exenterations were performed with disease control. The performed surgeries allowed for previously obtained results with CCRT to be improved by 10.1% (p = 0.437; NS). These results are consistent with those referred in the literature with similar therapeutics\(^{4,7,9,10}\).

Although in 4 of the 10 referred cases (40%) surgical specimens showing the absence of tumor residue was interpreted as a pathologic complete response to CCRT, the need or the convenience to carry out the referred surgical interventions was preoperatively documented. In some series, where a similar management approach has been used, pathologic complete responses of up to 60-67.4% have been reported\(^{10}\).

Failure of the established therapy was demonstrated in 17 patients of 89 where follow-up data were available (19.1%), including 6 of 13 patients with tumor persistence who showed progression (46.1%) and 11 of 12 with tumor recurrence (91.6%) who had the same behavior. Four patients had uncontrollable locoregional tumor activity, and 13 developed the distant disease. Only 6 of the 17 patients (35.2%) received further oncologic treatment without objective results. The fact that 13 of the 17 treatment failures (76.4%) were due to distant dissemination should make us reflect on the convenience of consolidating our CCRT treatments, with additional cycles of platinum-based chemotherapy, as some authors are recommending, as well as to administer 3-4 chemotherapy cycles before surgical exploration in patients who will undergo rescue surgery\(^{7,17,11,20}\).

One problem that occurs at the authors’ institution is CC occurrence in younger patients, since 23.7% of the population attending the department with this diagnosis is 39-year old or younger\(^{15}\), and a considerable proportion of these patients receive radiotherapy as basic therapeutic measure.

Standard treatment with CCRT in menstruating patients suppresses ovarian function in a sudden form, which results

<table>
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<tr>
<th>Table 6. Treatment failure</th>
<th>Histopathology</th>
<th>Total</th>
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<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>Squamous cell carcinoma</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Tumor persistence</td>
<td>2/4 (50.0)</td>
<td>4/9 (44.4)</td>
</tr>
<tr>
<td>Tumor recurrence</td>
<td>2/3 (66.6)</td>
<td>9/9 (100)</td>
</tr>
<tr>
<td>Total*</td>
<td>(a) 4/7 (57.1)</td>
<td>(b) 13/18 (72.2)</td>
</tr>
</tbody>
</table>

*a(a) versus (b): p = 0.6395.

<table>
<thead>
<tr>
<th>Table 7. Distant metastasis in 13 patients</th>
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<tbody>
<tr>
<td>Site</td>
</tr>
<tr>
<td>Paraaortic</td>
</tr>
<tr>
<td>Lung</td>
</tr>
<tr>
<td>Mediastinum</td>
</tr>
<tr>
<td>Skeleton</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Supraclavicular lymph nodes</td>
</tr>
</tbody>
</table>

*a5 patients with metastasis to 2 sites.*
in premature menopause, vasomotor symptoms, loss of bone mineral density, tendency to overweight and to develop metabolic syndrome, diabetes mellitus, high blood pressure, and coronary disease; therefore, in these patients, the trial of management approaches that tend to preserve ovarian function is warranted.

Although ovarian lifting away from radiation fields constitutes a logical solution for these patients, other options should be considered in countries like ours, where the radiation treatment demand often surpasses the offer of equipments available in our institutions. One of these options is the use of neoadjuvant chemotherapy with platinum-based schemes, just as recommended in some European clinics, and especially in Asian countries.

Neoadjuvant chemotherapy is intended to decrease tumor volume, to make originally inoperable neoplasms operable, and to eradicate or biologically alter micrometastases. Responses to platinum-based schemes are referred to range from 70% to 100%.

CONCLUSIONS

- In our series, patient mean age was 37.1 years, 23.4% were classified at stage IB2, and 19.3% of the entire group had adenocarcinomas.
- Sixty-three of 89 patients (70.7%) with post-CCRT follow-up spent a mean of 30 months without evidence of disease, including 63.1% of patients at stage IB2 and 72.8% at stages II, as well as 63.1% with adenocarcinoma and 72.8% with squamous cell carcinoma.
- With the referred treatment, evolution was less favorable for stage IB2 adenocarcinomas, since only 4 of 8 patients (50%) with this diagnosis had tumor activity-free follow-up versus 8 of 11 (72.7%) with squamous cell carcinoma.
- The results were similar for both histological types at stage II: 8 of 11 (72.7%) for adenocarcinomas and 43 out of 59 (72.8%) for squamous cell carcinomas.
- With complementary or salvage surgery, follow-up global figures without evidence of disease were increased by 10.1%.
- Established treatment failure was observed in 17 cases (19.3%): 4 due to non-controllable locoregional progression (23.5%) and 13 (76.4%) due to distant dissemination.
- Although surgery improved the results obtained with CCRT by 10.1%, consolidating conventional treatment with chemotherapy schemes should be considered in the future to decrease local recurrence and distant metastasis figures.
- It is convenient to try different treatment approaches in menstruating patients at stages IB2-IIb to avoid premature menopause. Neoadjuvant chemotherapy with platinum-based schemes plus radical hysterectomy offers a field worthwhile to explore.

DECLARATION OF INTEREST

The authors declare not having any conflicts of interest.

REFERENCES


