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Locally Advanced Cervical Carcinoma Management

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Abstract

Cervical cancer is a public health burden to Low and Middle Income countries. Whereas strides are being made in the management of malignancies worldwide, resources limited settings are confronted with the paucity of basic awareness, health professionals, diagnosis and management modalities, all contributing to cervical cancer disease late presentation. Among available treatment modalities, the mainstay of treatment for locally advanced cervical cancer remains radiation therapy combined with chemotherapy. Radiation is delivered through external radiation and brachytherapy. The evidence leading to the decision making, the modern management modalities and the general side effects, will be reviewed here.

Keywords: cervical cancer, radiation, brachytherapy

1. Introduction

Cervical cancer represents the second most common malignancy and the third overall cause of cancer mortality in Low and Middle Income Countries (LMICs) [1]. Such countries contribute the majority of the cervical cancer burden worldwide.

The FIGO classification system, endorsed by the American Joint Commission on Cancer 2017, defines locally advanced cervical cancer, as a disease found between stages IB2 to IVA [2]. This subset of diseases is visible on clinical examination and usually predict worse outcome in terms of recurrence and survival rates when compared to early stage disease.

Several studies focusing on the different stages at initial presentation have shown consistently high rates of advanced disease in LMICs (**Table 1**).

Studies	Type	Country	Patients (N)	Stage (rate percentage) at presentation
Chirenje et al. [5]	CS[2]	Zimbabwe	196	Stages IIB - IVA: (80.3%)
Musa et al. [4]	R[1]	Nigeria	65	IA (1.5%) -
				IB (6.1%);
				IIA (20%);
				IIB (35.4%);
				IIIA (9.2%),
				IIIB (24.6%);
				IVA (3.1%)
Mlange et al. [6]	CS[2]	Tanzania	212	IA (1.4%),
				IB (28.2%),
				IIA (6.4%),
				IIB (20.4%),
				IIIA (15.8%),
				IIIB (17.3%),
				IVA (7.4%)
Sharma et al. [3]	R[1]	India	227	IA (3.9%),
				IB (8.7%),
				IIA (6.8%),
				IIB (32.5%),
				IIIA (6.8%),
				IIIB (30.7%),
				IVA (8.7%); IVB (1.9%)

[1]R = retrospective review.
[2]CS = cross-sectional study.

Table 1. Summary of rates of cervical carcinoma disease stage at presentation in LMICs.

Advanced stages present a considerable challenge to achieving adequate treatment. This is compounded by the absence of modern treatment modalities and technologies that are available in high-income countries (HIC).

LMICs face a double burden where patients for different reasons including health system factors presents at hospital with advanced diseases and at the same time there is a pronounced lack of infrastructure to take care of these patients. This leads to an overall poor survival rates.

2. Disease evaluation

Staging with full nodal evaluation remains a crucial aspect of the management of locally advanced cervical carcinoma.

The pattern of spread of cervical cancer follows principles seen in numerous other solid malignancies namely, local extension, lymphatic spread and distant metastasis.

The disease usually spreads directly distally to the vagina, with extension along the parametria, the uterine ligaments (commonly utero-sacral) and the peri-rectal area.

Lymphatic spread occurs by echelon from the pelvic nodes, usually proximally toward the para-aortic nodes, and could substantially lead to left supraclavicular lymph node involvement in rare cases.

There is a high correlation between nodal status and disease outcomes. Contemporary studies have estimated close to 40% of survival at 5-years follow-up if evidence of para-aortic node involvement is established. Risk of nodal metastasis increases approximately by 15% for each stage, from FIGO stage I to III.

A Computed-Tomography (CT) guided biopsy is needed for nodal disease confirmation. For expert centers, an F-18 fluorodeoxyglucose-based positron emission tomography (PET) scan is necessary to establish nodal disease.

The patient needs also to be screened for competing risk factors. Importantly, patients should be evaluated for present or acquired (by local extension, Stage IIIB) kidney disease as the management of locally advanced cervical carcinoma incorporates the use of platinum-based chemotherapy as a radio-sensitizer. Corrections to the management protocols related to the renal disease stage have been suggested and carry promising grounds for further prospective studies.

Disease staging provides ground for prognosis, local control and survival prediction in the presence of adequate management modalities. Survival rates vary across studies and are inversely related to stage, with disease control and 5-year overall survival both ranging from 90% for stage IB to only close to 30% for stage IVA, in recent studies.

For aggregate analyses of locally advanced cervical carcinoma management outcome-based studies, newer treatment techniques are providing encouraging survival data.

3. Locally advanced cervical carcinoma management

The standard of care for advanced cervical carcinoma is Radiation Therapy alone (in case of palliation), or in combination with cisplatin-based chemotherapy.

Overall survival is usually a function of disease-free interval rates, highlighting the scarcity of salvage therapy options in case of recurrence.

With limited options for salvage in cases of recurrences, disease-free interval rates directly correlate to Overall Survival and comorbidities of the patients.

Generally, management of cervical carcinoma includes definitive surgery for selected cases, upfront radiation therapy and chemo-radiation. Surgery and radiation therapy amount to the

same effect yet with drastic differences in terms of debilitating toxicities, hence surgery alone is the treatment of choice for initial smaller lesions (<4 cm) with other treatment modalities offered as a salvage in case of recurrence.

4. Primary chemoradiation vs. surgery

As cited above, the widely used treatment scheme for locally advanced cervical carcinoma consists of upfront radiotherapy concurrently with a platinum-based chemotherapy.

Surgery has been proven to not be superior to chemo-radiation, but carries twice a risk of increased toxicity rates.

Adverse features arising post-surgery could be similar to other advanced diseases, including high grade disease, lympho-vascular space invasion (LVSI), positive lymph nodes, prompting the use of multiple modalities of treatment with subsequent considerable toxicities.

The largest comparison study to date by Landoni, compared 343 patients with early disease, contemporarily included in the locally advanced stage (IB - IIA) disease, to undergo an extensive surgery with pelvic lymph node dissection, with a possibility of Radiation Therapy boost in the presence residual disease. This arm was compared with upfront Radiation Therapy. The comparison yielded no differences in survival, but showed considerable difference in toxicity rates [7].

Chemo-radiation has been proven to offer a high survival benefit which is greatly influenced by disease stage. Additionally, concurrent chemo-radiation decreases the recurrence risk.

Radiation consists of external beam radiotherapy session and a stage-variable boosting dose achieved by brachytherapy. Details on patient simulation, field size and dose specification are found below.

5. Combined radiation and chemotherapy regimen

5.1. Chemotherapy regimens

Concurrent radiation with chemotherapy has come to age relatively recently, with cisplatin-based chemotherapy rising at the dawn of the twenty-first century.

Before this era, numerous institutional trials had been published with various chemotherapy regimens selections.

Among previously suggested regimens, hydroxyurea was used in the 1960s, perceived as being a radiosensitizer. Hydroxyurea induces a block on the G1-S phase of the cell cycle, hence enhancing cell kill by radiation; prevention of sub-lethal damage repair has also been proven.

A Gynecological Oncology Group (GOG 56) study confirmed the benefit of added hydroxyurea to radiation therapy, with a higher Progression Free interval, though no significant survival benefit was found [8]. This study was controversial in its setting and the recommendations were not applied widely. Hydroxyurea involves a high risk of myelosuppression, and prospects of considering it as a viable combination therapy to radiation were abandoned overtime.

5-Fluorouracil has also been considered as an alternative chemotherapy regimen for combination therapy. However, the few published studies failed to prove local disease control and survival benefit with an added 5-Fluorouracil regimen [9].

Based on a five-study analysis, cisplatin added to radiation therapy was confirmed to have a superior survival when compared to radiation alone.

A large systematic review of 18 trials combining radiation and chemotherapy for locally advanced cervical carcinoma proved the survival benefit of adding chemotherapy. Platinum based chemotherapy was not seen to be significantly different from non-platinum based chemotherapy (HR: 0.84 vs. 0.76, $p = 0.48$). Platinum-based regimens were also found to have a non-significant increased toxicity trend. However, single agent platinum offered an important alternative with regards to local disease control, adherence to treatment and ease of administration.

Historically, the GOG 120 compared different chemo-radiation regimens, combined with a brachytherapy boost. The arms had a cisplatin alone, a hydroxyurea alone and a cisplatin/5-Fluorouracil/Hydroxyurea components. The arms containing cisplatin had improved survival and disease down-staging was achieved. Subsequent studies removed hydroxyurea and compared upfront radiation therapy with concurrent cisplatin (with or without 5-Fluorouracil) with radiation therapy, which established the standard of care of adding chemotherapy to radiation therapy, as it was shown to increase survival and decrease recurrence risks.

The rationale behind adding cisplatin to radiation is that it acts as a radiosensitizer, by preventing the Non-Homologous End Joining pathway, which is paramount in the Double Strand Breaks repair. Double Strand Breaks in DNA are induced by high energy radiation therapy.

Cisplatin is given on a weekly basis, a few hours before radiation therapy, and care needs to be taken for its administration. As a nephrotoxic agent, adequate hydration is to be ensured, before and after cisplatin infusion. Together with knowing prior the renal status of the patient, dosing can be altered to prevent toxicity. Carboplatin has been shown to provide a suitable alternative to cisplatin for patients who are not candidates to cisplatin infusion (**Table 2**).

Gemcitabine could also be a choice when cisplatin is contraindicated. However, in the absence of level I evidence, and with the increased toxicity risk associated with Gemcitabine, carboplatin remains the preferred choice in case of intolerance to cisplatin, and deranged renal function tests.

5.2. Radiation therapy

Radiation Therapy is provided by both External Beam Radiation (EBRT) and brachytherapy (BT) to increase local control.

Cisplatin - dosage and premedications	Details
Prior to Treatment Work-up	Complete Blood Count - with a low Absolute Neutrophil Count, consider adding Filgrastim (if available) prior to chemotherapy infusion
	Renal Function Tests - use the Glomerular Filtration Rate to determine fitness of the patient to receive cisplatin
	Serum Electrolytes (K$^+$, Na$^+$)
Dosage	40 mg/m^2 IV weekly
Pre-medications	Hydration – 2 l Normal Saline (0.9%) over 2 hours prior and after a cisplatin infusion
	Ondansetron 16 mg IV and Dexamethasone 16 mg IV, both mixed with 100 ml of Normal Saline (0.9%)

Table 2. Summary—cisplatin treatment planning and dosage.

Total doses above 45 Gy are preferred as they are proven to offer a survival advantage.

Radiation therapy is offered to post-operative patients confirmed to have adverse features (mainly Lympho-Vascular Space Invasion, positive pelvic nodes, involved parametria and positive surgical margins), with stages IA2, IB. It is also the definitive treatment, with concurrent chemotherapy for stage IIB- IVA.

The typical dose given by EBRT varies between 45 and 50 Gy depending on the stage and prior treatment. For patients treated with a prior hysterectomy, lower doses (typically below 45 Gy) are preferred to avoid radiation induced bowel toxicity; higher doses are safe to be delivered on an intact uterus and cervix.

Current RTOG and GOG protocols suggest total doses for cervical carcinoma treated with definitive radiation therapy to be around 80–90 Gy to a point defined within the paracervical triangle, namely the point A.

The point A has been varied over the years, and is defined as being at 2 cm above the external cervical os and 2 cm lateral to uterus midline. This corresponds to the paracervical triangle, where the uterine vessels cross the ureter, medial to the broad ligament.

Given the proximity of the cervix to the major pelvic organs and the femoral heads, the external beam radiation doses are limited to an overall dose of 50 Gy. Institutional practices vary, some preferring doses below 45 Gy before proceeding to brachytherapy, with options of lowering the field size to boost to gross residual and nodal disease to doses up to 50 Gy.

Addition of brachytherapy has shown high rates of cancer-specific and overall survival benefits when compared to external beam radiation therapy alone. The objective of brachytherapy addition is to reach the desired total dose of 80–90 Gy to the disease site while minimizing toxicity to organs at risk.

5.3. External beam radiation techniques

The distal most part of the disease needs to be marked with radiopaque gold seeds for disease localization prior to treatment imaging. In the absence of gold seeds, radiopaque materials

such as lead or steel-made wires can be used for disease localization. The same needs to be applied to the vagina and anus areas.

For a 4-field (antero-posterior, postero-anterior and lateral fields) treatment, the simulation is done in the supine position and CT or Fluoroscopic images taken. Patients are positioned with arms on the chest, knees and lower legs immobilized. Anterior and lateral tattoos are marked and aligned with lasers for lateral rotation prevention. Obese patients may benefit from prone belly boards, to avoid small bowel inclusion in the radiation volume.

Intra-venous contrast CT scans are taken to help highlight the pelvic vessels used as reference to delineate the pelvic nodes.

For centers using two-dimensional planning and fluoroscopic imaging, the same marking has to be done, with fluorescent markers, and tattoos where applicable.

The borders are:

- Superior: Lumbar spine level 4/5

- Lateral: 1.5–2 cm away from the pelvic brim

- Anterior: 1 cm anterior to pubic symphysis

- Posterior: Entire Sacrum to be included

- Inferior: Below the ischial tuberosity or the inferior obturator foramen if bony landmarks are used

For advanced disease involving the lower vagina (stage IIIA), include at least a margin of 3 cm away from the distal most part of the disease.

Extensive Radiation Therapy has been suggested in the presence of para-aortic lymph nodes, with the superior-most border being T12/L1, with kidney blocks [10].

Stage IIIA is associated with inguinal nodes, and the field needs to include the vaginal introitus as the inferior border; with a common iliac nodes disease presence, the superior border is to be raised up to L3/4.

Dosing should be up to 50 Gy delivered in 25 equal fractions, daily. This is usually given within 5 days a week for 5 weeks, allowing a 2-day rest between weeks of treatment.

Dose limiting organs are mainly the bladder, rectum, femoral heads, and with a lower instance, the small bowel and ovaries.

5.4. Brachytherapy

As per the American Brachytherapy Society guidelines, brachytherapy for cervical cancer needs to be applied for a disease not exceeding a size of 5 cm.

The preferred brachytherapy technique is the High Dose Rate Brachytherapy, delivering above 12 Gy/hour.

The point of interest for brachytherapy delivery is defined in the contemporary method as per the Manchester point A - 2 cm superior to the external cervical os and 2 cm lateral to the central uterine canal. The objective is to deliver a cumulative dose of 80–90 Gy.

Due to nodal disease associated with locally advanced cervical cancer, a Manchester point B is defined at 3 cm lateral to point A. With this system, bladder, vaginal and rectal points are also defined. Care needs to be taken to minimize the radiation dose to the bladder and rectum by anteriorly and posteriorly packing through the vagina and around the brachytherapy applicators.

Brachytherapy delivery is provided once weekly over a time interval of 3–6 weeks. Total radiotherapy treatment (EBRT and BT) should be completed within a time period of 7–8 weeks.

6. Complications

Acute complications commonly include local features, consisting with dry and moist skin desquamation, vaginitis, cystitis, and proctitis. Management of these complications varies between anti-inflammatory medications and anti-microbial drugs given for prophylaxis.

Brachytherapy side effects are mainly due to neighboring organ toxicity and include vaginitis, cystitis and uterine perforation.

Late complications include vaginal stenosis, recto-vaginal and vesico-vaginal fistula and intestinal perforation.

7. Conclusions

With increasing rates of advanced cervical cancer disease in Low and Middle Income countries, adherence to evidence-based literature for treatment is key. Radiation therapy combined with chemotherapy are the mainstay of management for locally advanced cervical carcinoma. The treatment should ideally not exceed eight (8) weeks after the baseline work-up and disease evaluation to maximize disease control.

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