

Patterns of Relapse in Patients with Locally Advanced Cervical Cancer after Image Guided Brachytherapy

Fatma Ahmed Abdelfatah^{1*}, Mohamed Soliman Gaber², Ali Mohamed Ali², Mohamed Mahmoud Abdelhakem³

¹Clinical oncology department, faculty of medicine, Luxor university, Egypt.

²Clinical oncology department, faculty of medicine, Sohag university, Egypt.

³Radiation Oncology Department, NCI, Cairo University, Egypt.

*Corresponding Author: Fatma Ahmed Abdelfatah, Email: Fatma.rekabi@med.sohag.edu.eg, Phone: +201002155832

ABSTRACT

Background: In the treatment of locally advanced cervical cancer (LACC), brachytherapy (BT) is a pivotal treatment modality, used in conjunction with external beam radiotherapy (EBRT). However, even with advancements in EBRT and BT techniques, the occurrence of local relapse continues to pose significant challenges.

Objective: This research aimed to examine the recurrence patterns following the administration of concomitant chemoradiotherapy (CCRT) and subsequent enhancement with image-guided brachytherapy (IGBT).

Subjects and methods: The research involved 40 patients diagnosed with locally advanced cervical cancer. These individuals underwent CCRT, subsequently enhanced by IGBT, as part of a phase 2 prospective study.

Results: Among the 40 patients studied, 4 (10%) experienced local recurrence, and among these, 2 also had simultaneous distant relapses. Node recurrence was identified in 2 patients (5%), and 4 patients (10%) had distant failures. Local recurrence within the radiation treatment area was noted in 2 patients (5%), while 2 others experienced recurrence outside the treatment area. Treatments administered included stereotactic body radiotherapy (SBRT) for one patient, salvage surgery for another, and palliative care for the two patients with concurrent distant metastases. The median survival time after recurrence was 12.1 months, with an interquartile range (IQR) of 10 to 14.1 months.

Conclusion: Although the application of IGBT in the treatment of cervical cancer led to commendable local control and disease-free survival rates, the most common failure mode observed was distant relapse.

Keyword: Cervical cancer, Relapse, Image-guided brachytherapy.

INTRODUCTION

Globally, cervical cancer ranks as the second most prevalent cancer among women, posing a significant health risk. The essential cause of cervical cancer has been identified as a continuous infection with high-risk strains of the human papillomavirus (HPV) [1].

Nearly 90% of cases of cervical tumor happen in low- and middle-income nations without systematic screening or HPV immunization initiatives [1].

The development of an all-encompassing approach in order to avoid and manage cervical cancer was expedited by the apparent etiology. When the World Health Organization (WHO) prompted for worldwide cervical cancer eradication in May 2018, over 70 countries as well as worldwide academic bodies complied right away [2].

The standard of care for locally advanced cervical tumor incorporates concurrent chemoradiotherapy succeeded by BT either intracavitary alone or hybrid intracavitary/interstitial brachytherapy. Advances in radiation therapy technology, such as MRI based image guided brachytherapy have led to a decrease in toxicity associated with therapy as well as excellent local control [3].

This study aimed to describe the patterns of relapse after concomitant chemoradiotherapy (CCRT) followed by an image-guided brachytherapy (IGBT) boost.

PATIENTS AND METHODS

Study design and participants: The research was designed as a prospective study carried out at a single institution, spanning from January 2021 to December 2023.

Inclusion criteria: Patients with a pathological diagnosis of adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma of the cervix. To be eligible, individuals had to be diagnosed with cervical cancer stages IB3 to IVA according to the International Federation of Gynecology and Obstetrics (FIGO) standards, be aged 18 or above, and to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

Exclusion criteria: Barred individuals with any other types of cancer (with the exception of cervical carcinoma in situ and basal cell carcinoma of the skin), those with metastasis extending beyond the para-aortic lymph nodes, those who had previously undergone pelvic radiotherapy, and those with contraindications for undergoing magnetic resonance imaging (MRI).

Every participant underwent concomitant chemoradiotherapy, followed by image-guided brachytherapy treatment. The external beam radiotherapy protocol included 25 sessions of pelvic radiotherapy, with each session delivering 1.8 Gy for a cumulative dose of

45 Gy, utilizing either Intensity Modulated Radiotherapy (IMRT) or Volumetric Modulated Arc Therapy (VMAT) approaches, alongside weekly administrations of cisplatin. The image-guided brachytherapy was administered in four sessions, each providing 7 Gy, across a span of two weeks. Following brachytherapy, patients who met the criteria were assessed with a physical examination and pelvic MRI at 12 weeks, followed by check-ups every three months during the initial two years, and semi-annually after that. Further diagnostic tests were conducted as warranted by clinical indications.

This study centers on patients who underwent secondary treatment interventions following a recurrence of their condition. Our research delved into the initial occurrence of recurrence, the therapeutic approaches employed post-relapse, and the clinical outcomes up to the final follow-up or the patient's demise. We categorized recurrence patterns into four types: "local" (limited to the cervix, uterus, and surrounding tissues), "nodal" (restricted to the pelvic and para-aortic lymph nodes), "distant" (signifying widespread systemic failure), and "combined" (encompassing both pelvic and distant recurrences).

The duration of survival after a recurrence was determined from the time the recurrence was identified until the last follow-up or the patient's death.

Ethical considerations: This research received approval from Faculty of Medicine Research Ethics Committee, Sohag University. Written informed consents were obtained from all participants for themselves before they were included in the study. The consent document clearly stated their willingness to be part of the research and for their data to be published, with a firm assurance of maintaining their anonymity and privacy. The conduct of this study adhered to the ethical guidelines set forth by the World Medical Association's Declaration of Helsinki for human research.

Statistical analysis

The statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21 (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied to evaluate the patterns of relapse and the treatment responses. Survival rates post-relapse were calculated using the Kaplan-Meier estimator, with the log-rank test determining the significance of the differences observed.

RESULTS

During a median observation period of 27 months, out of 40 patients with locally advanced cervical cancer undergoing concomitant chemoradiotherapy (CCRT)

followed by image-guided brachytherapy, 9 patients (22.5%) encountered a recurrence. Histological proof of the recurrence was established in 3 patients, whereas in the other 6, conducting a biopsy was not possible. In these cases, the recurrence was identified through MRI or PET/CT imaging. The clinical manifestations observed at the time of recurrence included symptoms such as lower abdominal or pelvic discomfort (n=1), vaginal bleeding (n=1), and cough or shortness of breath (n=2).

Patterns of relapse:

The patterns of relapse, as depicted in Figure (1) showed that local relapse occurred in 4 patients (10%), with 2 experiencing synchronous distant failure. Nodal relapse was observed in 2 patients (5%), and 4 patients (10%) experienced distant failure without local failure. Local relapse within the radiotherapy field occurred in 2 patients (5%), and outside the field in another 2 (5%). Systemic metastases were identified in the lungs (3 patients, 7.5%), liver (1 patient, 2.5%), and bones (1 patient, 2.5%), with one patient (2.5%) having metastases in both the lung and liver. The FIGO stages of patients at the time of relapse were as follows: IB3 (2.5%), IIA (2.5%), IIB (7.5%), IIIB (2.5%), IIIC (5%), and IVB (2.5%).

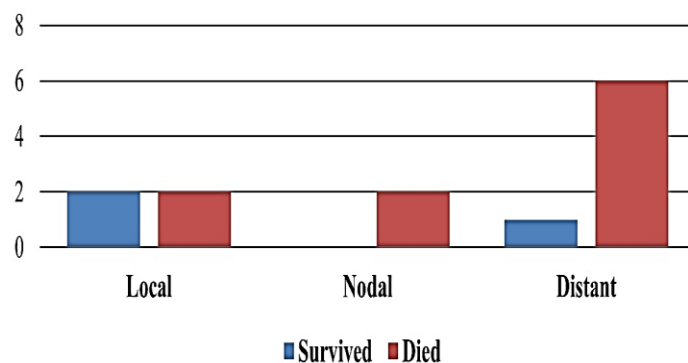


Figure (1): Pattern of relapse

Post-relapse treatment:

The treatment approach following the diagnosis of relapse was determined by various factors, including medical comorbidities, performance status, previous treatments, and the pattern and burden of relapse. Fifteen percent of the patients, totaling six, were administered chemotherapy for palliative care, while one individual received treatment via stereotactic body radiotherapy. Additionally, salvage hysterectomy was the chosen treatment for two patients, representing 5% of the group. Following relapse, the median duration of survival was recorded at 12.1 months (Figure 2).

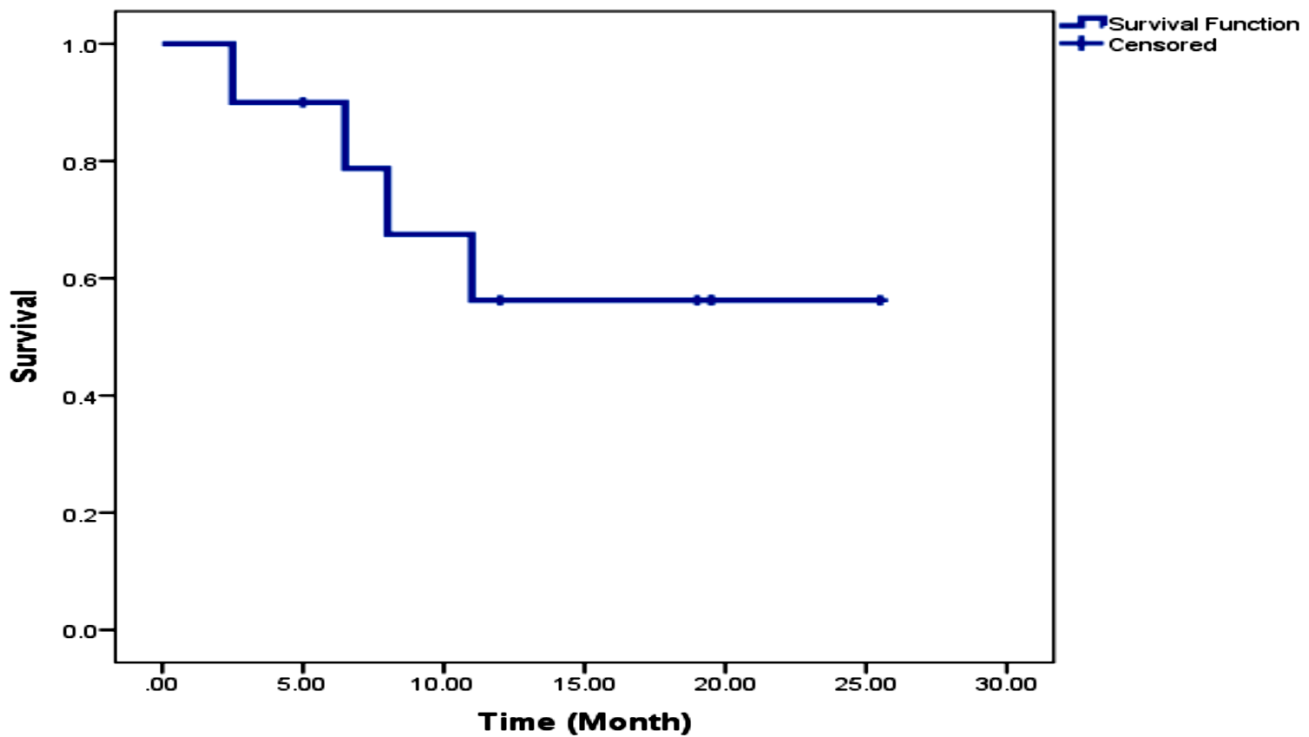


Figure (5): Survival after relapse.

DISCUSSION

In this research, we noted outstanding efficacy in local disease management, with a 90% control rate at three years for patients suffering from locally advanced cervical cancer, following the combined treatment of chemoradiotherapy and image-guided brachytherapy. This outcome aligns well with findings from earlier studies [4]. Specifically, the RetroEMBRACE and EMBRACE I studies documented a similar overall local control success rate of 91% at the three-year mark [5, 6], highlighting the critical role of MRI-guided brachytherapy in treatment success.

The specifics regarding the location of local recurrence after undergoing image-guided brachytherapy have been less explored in previous research. **Ribeiro and colleagues** [7] have documented a remarkably high local control rate of 96% at the 36-month milestone. In our study, local failure was primarily parametrial, and half of the failures were associated with nodal or systemic failure. This result aligns with that of **Mignot et al.** [8] who reported a local relapse rate of 10.8% (28 out of 259), with more than half of these patients developing synchronous nodal and systemic relapse.

Despite the dose escalation facilitated by MRI-guided brachytherapy, our study observed local relapse in 4 patients, only 2 of them were treated with salvage hysterectomy for isolated local recurrence, proving surgery effective without major perioperative complications. Furthermore, our analysis of the site of relapse for each patient revealed that the lungs were the

most common site of extrapelvic involvement. This result agrees with previous series, highlighting the importance of including this site in follow-up imaging [9].

Most patients who relapsed were not eligible for any curative treatment and received only palliative chemotherapy, which was comparable to historical series [10].

Our protocol was in strict compliance with existing global guidelines for post-treatment follow-up, which advocate for a pelvic MRI and physical examination three months subsequent to the completion of brachytherapy. This is to be followed by quarterly physical examinations and bi-annual imaging of the pelvis through MRI, along with abdominal CT scans [11, 12]. The detection of all cases of recurrence occurred during these standard follow-up appointments, with only three patients exhibiting symptoms at the time their recurrence was identified. This observation points to a relatively minor role of routine imaging, such as CT scans and MRIs, in influencing survival outcomes for patients without symptoms, thereby highlighting the necessity for future studies focused on the cost-effectiveness of various monitoring approaches to evaluate their comparative benefits.

In our study, the median survival post-recurrence was 12.1 months, favorably comparing with previous series [13-16].

Earlier studies employing 3D brachytherapy have shown disappointing survival rates following recurrence, whether the failure was local or loco-regional, with the

median survival post-recurrence being just 8 months [17, 18].

The constraints of our research were primarily the limited number of participants and the brief duration of follow-up.

CONCLUSION

In summary, for locally advanced cervical cancer managed with simultaneous chemoradiotherapy and subsequent image-guided brachytherapy, distant metastasis emerged as the predominant site of recurrence.

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- **Conflict of Interest:** Nil.

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