

Neoadjuvant chemotherapy, radical hysterectomy and chemoradiation for stage iva cervical carcinoma

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Summary

Despite the efficacy of chemotherapy and radiotherapy in the management of locally advanced cervical carcinoma, the overall survival rates are relatively inauspicious. We recount a case involving a 56-year-old stage IVA cervical cancer patient who underwent neoadjuvant chemotherapy, a type V radical hysterectomy and adjuvant chemoradiation in April 2006. The patient remained in clinical remission for five years until she developed a metastatic pulmonary nodule in her right middle lobe that originated from the primary cervical cancer. Thereafter, the patient was diagnosed with a right metastatic cardiophrenic nodule that responded favorably to chemotherapy. However, in August 2014, she presented with a metastatic posterior cranial fossa tumor from which she ultimately expired; interestingly, radiologic imaging revealed no evidence of an abdominopelvic recurrence. While a radical hysterectomy is often indicated for advanced cervical cancer patients with residual disease or those who fail chemoradiation, perhaps in select cases (e.g., stage IVA disease), initial treatment with neoadjuvant chemotherapy and surgery followed by chemoradiation may improve patient survival.

Key words: Cervical cancer; Radical hysterectomy; Chemoradiation; Outcomes.

Introduction

There were 13,240 patients in the United States who were diagnosed with cervical cancer in 2018, 4,170 of whom will eventually succumb to their disease [1]. Despite the reasonably favorable cure rates for patients with early-stage disease, the prognosis for stage IVA cervical cancer is inauspicious, with reported 5-year survival rates approaching 16% [2].

Pelvic radiation therapy, single agent or combination platinum-based chemotherapy [3,4] and brachytherapy have eventuated in more beneficial outcomes for locally advanced cervical cancer compared to neoadjuvant therapy and radical hysterectomy. The former regimen is considered the standard treatment for this disease [5] although surgery following neoadjuvant chemoradiation has reportedly further accorded encouraging outcomes in patients with advanced-stage cervical cancer [6-9].

Patients diagnosed with stage IVA cervical cancer have disease involving proximal organs in the pelvis (e.g., the rectum and bladder) [10]. They are characterized as inoperable and despite currently recommended treatment, the long-term clinical outcomes are discouraging [11, 12]. Alternatively, in select patients wherein the tumor is amenable to surgical resection [13, 14], performing an extended radi-

cal hysterectomy for stage IVA disease may be a reasonable consideration. Herein, we describe the long-term history of a stage IVA cervical cancer patient who was initially managed with neoadjuvant chemotherapy, radical hysterectomy and adjuvant chemoradiation.

Case Report

A 56-year-old, nulligravid woman with an unremarkable medical history originally presented to our gynecologic oncology service with metrorrhagia and a hematocrit of 33.7% in April 2006. Following a dilatation and curettage, pathology revealed a grade 3 squamous cell carcinoma. Subsequently, a CT scan of the chest, abdomen and pelvis exhibited a locally confined, 7 cm cervical tumor that infiltrated the superior portion of the vagina (Figure 1). A cystoscopy revealed the presence of bladder invasion; moreover, she was also found to have moderate left hydronephrosis and hydroureter, with decreased left renal perfusion.

The patient completed 3 cycles of paclitaxel (175 mg/m²) and carboplatin (AUC 5) in June 2006, which reduced the tumor size to 4 cm in diameter although there was persistent vaginal involvement. In July 2006, the patient underwent a laparotomy, type V radical hysterectomy [13] with upper vaginectomy, including an en bloc resec-

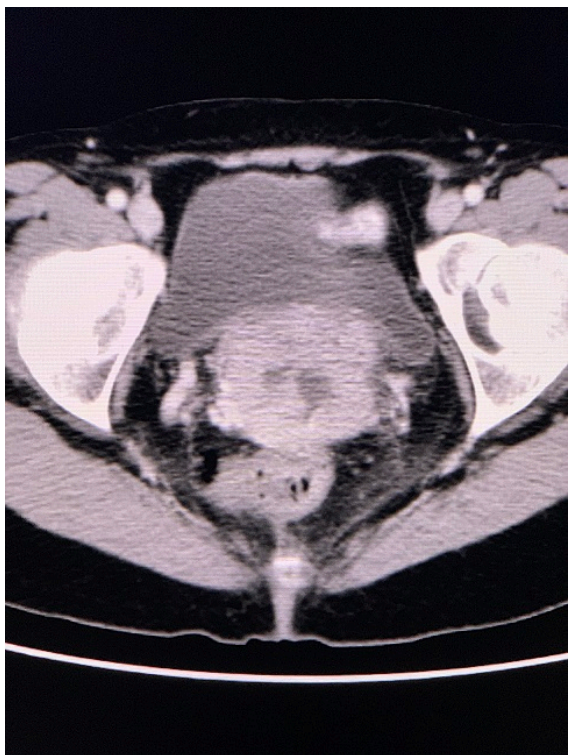


Figure 1. — April 2006 CT scan of the pelvis.



Figure 2. — October 2011 CT scan of the chest.

tion involving the base of the bladder and distal portion of a double left ureter, double left ureteral neocystotomy with placement of two left ureteral stents, intentional ante-

rior cystostomy with placement of a right ureteral stent, and bilateral pelvic and para-aortic lymphadenectomy. There were no significant intraoperative complications and estimated blood loss was 400 mL.

There was gross tumor residuum measuring $4.5 \times 3.0 \times 1.0$ cm involving the bladder mucosa; the surgical margins and resected nodes were negative. In consideration of the bladder involvement, final pathology revealed a poorly differentiated, squamous cell, stage IVA cervical carcinoma.

In September 2006, the patient commenced with 3 cycles of weekly cisplatin (30 mg/m^2) chemotherapy, 50.4 Gy of pelvic radiotherapy and 14 Gy to the bladder, to which the disease responded favorably. In October 2009, the patient experienced chronic pain and was admitted to the Operating Room, whereupon she underwent a laparoscopic lysis of adhesions; there was neither evidence of a bowel obstruction nor tumor recurrence.

The patient remained disease free until October 2011, wherein a CT scan of the chest revealed a pulmonary nodule in her right middle lobe (Figure 2). A CT-guided biopsy of the lung lesion confirmed squamous cell carcinoma. In December 2011, the patient underwent a right middle lobe lobectomy. Pathology from the lesion corroborated invasive squamous cell carcinoma, consistent with her cervical primary. The patient subsequently underwent surveillance.

In December 2012, a right cardiophrenic mass was identified via a core biopsy, which revealed moderately differentiated squamous cell carcinoma and focal necrosis; there was no evidence of recurrent abdominal or pelvic cancer. The patient was administered 6 cycles of paclitaxel (175 mg/m^2) and carboplatin (AUC 6) in January 2013, followed by 6 cycles of paclitaxel (135 mg/m^2) maintenance chemotherapy. In December 2013, the chemotherapy was changed to bevacizumab (10 mg/kg) every 3 weeks, of which she received 6 cycles. However, in August 2014, the patient was diagnosed with a large, posterior cranial fossa tumor (Figures 3a and 3b) and underwent a craniotomy; pathology revealed metastatic, poorly differentiated squamous cell carcinoma. The imaging findings were negative for an abdominopelvic recurrence. The patient remained in clinical remission for eight years following her initial diagnosis but ultimately, she died from the neurologic disease in October 2014.

Discussions

Since locally advanced cervical cancer is potentially difficult to manage, clinicians have endeavored to maximize disease control and improve patient survival. Unfortunately, the relapse rates, especially for FIGO stage IVA cervical cancer, following chemoradiation are high, and patient 5-year overall survival rates are discouraging [2].

Recently, clinical management for advanced cervical cancer has also included targeted therapy, intensity-modulated radiotherapy, dose-dense chemotherapy and minimally invasive surgery [15-17]. However, despite the advances in chemotherapy and radiotherapy, random-

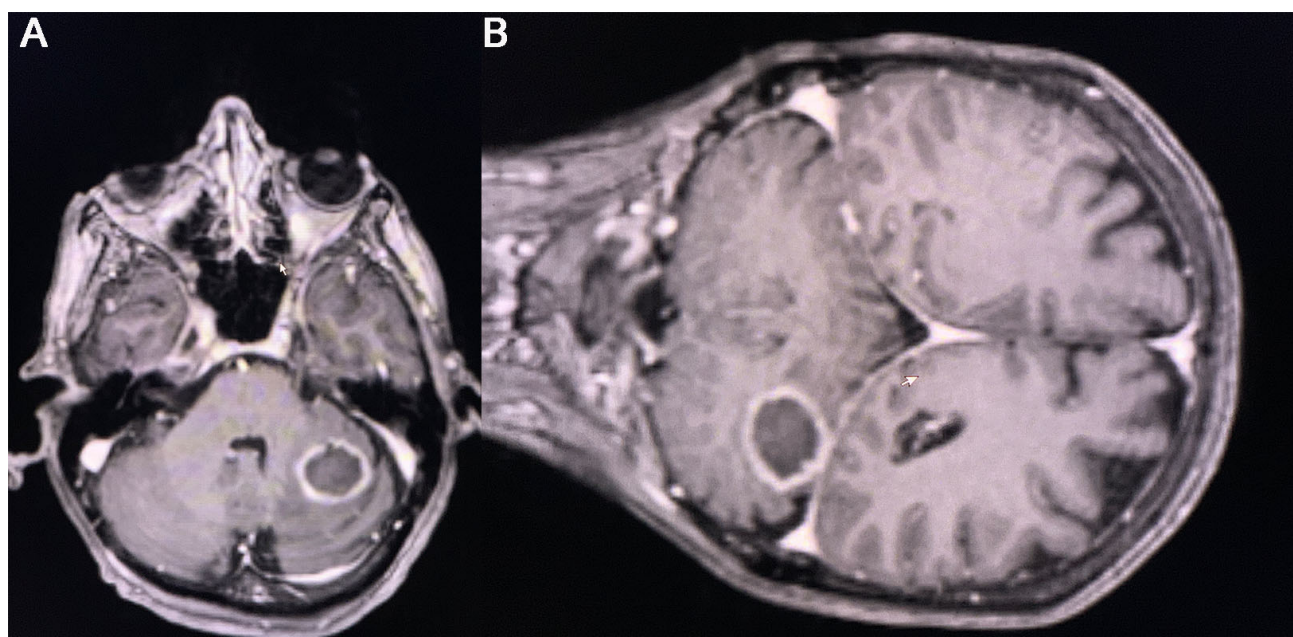


Figure 3. — August 2014 MRI axial (Figure 3A) and coronal (Figure 3B) T1-weighted scan displaying the posterior cranial fossa lesion.

ized trials have not demonstrated their superiority over surgery and chemotherapy [18]; thus, if indicated, the role of surgery for stage IVA cervical carcinoma should be considered a viable option in patients for whom the tumor is amenable to surgical resection [13, 14].

In the present case study, we recount the long-term history of a stage IVA cervical cancer patient who presented with a large, 7 cm cervical tumor that included bladder invasion. Following neoadjuvant chemotherapy, an extended radical hysterectomy and chemoradiation, the patient's disease remained in clinical remission for over 5 years. Since the initial results described in locally advanced cervical cancer trials [19], the utility of a radical hysterectomy has been impugned, primarily because of unimproved patient survival rates and the elevated incidence of post-operative bowel and bladder morbidity [20]. Instead, a radical hysterectomy is often reserved for those patients who have residual disease or fail chemoradiation, although this procedure does not appear to improve survival outcomes [14, 21]; one study indicated that there was only a 3% survival benefit from a radical hysterectomy for patients with relapsed III–IVA disease [14].

In this case study, the stage IVA cervical cancer patient was managed with carboplatin, paclitaxel and bevacizumab to address her disease recurrence although we recognize that paclitaxel and cisplatin are the standard of care [22] although we recognize that paclitaxel and cisplatin are the standard of care [23]. We also treated the patient with paclitaxel maintenance therapy to further prolong the response [24]. Nevertheless, there is cumulative toxicity inherent in chemoradiation, namely bowel necrosis, myelosuppression and neurotoxicity [25], the latter of which was potentially mitigated by the reduced dose of paclitaxel [26].

Prior studies employing neoadjuvant chemotherapy and radical hysterectomy have documented 5-year OS rates of 90.8%, 72.6%, and 52.5% for FIGO stage IB2–IIA, IIB, and III, respectively [27]; since current 5-year survival rates for stage IVA cervical carcinoma are nearly 16% [2], perhaps neoadjuvant chemotherapy and radical hysterectomy should be further evaluated in the management of this disease.

When considering stage IVA cervical cancer, surgically addressing rectal involvement is theoretically easier than bladder invasion. Specifically, posterior stage IVA patients can be treated with a primary posterior exenteration and low rectal reanastomosis, on which we previously reported with a stage IIIB cervical carcinoma patient who remained in clinical remission for eight years [28]. However, a pelvic exenteration is associated with high morbidity and mortality rates [29].

We acknowledge that the inclusion of a radical hysterectomy in first line treatment of locally advanced cervical carcinoma is not considered standard of care. We also recognize that the patient's beneficial outcome may have been attributed to chemoradiation alone (*i.e.*, the surgery's impact on survival may have been inconsequential) or a favorable tumor biology. Nevertheless, surgery after neoadjuvant therapy for advanced cervical cancer potentially results in acceptable morbidity and facilitates a pathological response, which may also improve disease free survival [6, 7].

Despite the NCCN guidelines for managing locally advanced cervical carcinoma, one may conjecture that initially resecting aggressive cervical carcinoma lesions wherein the prognosis is very unfavorable (*e.g.*, stage IVA disease) potentially confers improved patient outcomes.

Additional study incorporating the impact of an extended radical hysterectomy into standard therapy for highly selected stage IIB, IIIB and IVA cancers on survival is warranted.

Author contributions

JM and MAR contributed significantly to the study's initiation, development and manuscript revision. BG substantially contributed to the study's development and manuscript revision. HE conducted the review of the patient's pathologic diagnosis and treatment history and also substantially contributed to the study's development and manuscript revision. MCR was instrumental in reviewing the patient's charts, conducting the radiologic evaluation and revising the manuscript. RB reviewed the patient's chart, analyzed the chemotherapy treatment lines and corresponding outcomes, and significantly assisted with the manuscript development and revision.

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Ethics approval and consent to participate

The authors received verbal consent to publish this case report. Additionally, the case report was prepared in accordance with HIPAA requirements and privacy regulations.

Conflict of Interest

All authors deny any conflict of interest associated with this manuscript.

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