Survival in unresectable sinonasal undifferentiated carcinoma treated with concurrent intra-arterial cisplatin and radiation

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Abstract
We report the successful use of RADPLAT to treat a patient with an unresectable T4N0 sinonasal undifferentiated carcinoma. This patient received 4 cycles of weekly intra-arterial cisplatin together with thiosulfate infusion with concurrent radiation therapy. Radiation therapy was given in 28 daily fractions to 54 Gy using intensity-modulated radiation therapy followed by a hypofractionated stereotactic boost of 3 fractions to 13 Gy to a total dose of 67 Gy in 31 fractions to the nasal sinus and bilateral neck. Intra-arterial cisplatin was administered using a bilateral approach due to the midline site of this tumor. Within days of the first intra-arterial cisplatin, there was an obvious decrease in tumor size. She has been followed with magnetic resonance imaging and positron emission tomography, and remains disease-free 47 mo post-treatment. Centers with expertise in intra-arterial chemotherapy could consider the RADPLAT approach for patients with unresectable sinonasal undifferentiated carcinoma.

Key words: Sinonasal undifferentiated carcinoma; Radiation; Intra-arterial cisplatin; Survival; RADPLAT

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Core tip: Our patient with unresectable sinonasal undifferentiated carcinoma has enjoyed nearly 4 years disease-free survival after concurrent intra-arterial cisplatin and radiation.

INTRODUCTION
Sinonasal undifferentiated carcinoma (SNUC) is a
Figure 1  T1 magnetic resonance imaging of sinonasal undifferentiated carcinoma neoplasm prior to treatment. A: Axial T1 magnetic resonance imaging (MRI) and B: Sagittal T1 MRI show an avidly enhancing mass centered in the left ethmoid air cells with extension into the left frontal sinus with adjacent retained fluid and maxillary sinus with erosion of the medial orbital walls bilaterally, left greater than right. The majority of the ethmoid air cells are replaced by the neoplasm. Extension through the cribriform plate is noted with involvement of the left olfactory lobe, predominantly along the gyrus rectus. There is extensive surrounding edema in the left frontal lobe, extending back to the frontal horn of the left lateral ventricle.

Figure 2  Right and left external carotid artery angiography injections. A: Right and B: Left external carotid angiographic injections demonstrate the tumor blush (arrows) at the first chemo treatment.

A 60-year-old woman presented with nasal congestion and a prominence on the left side of her nose. Computed tomography (CT) revealed a tumor arising from the ethmoid sinus extending through the cribiform plate and into the anterior cranial fossa without metastasis to the chest and neck. Magnetic resonance imaging (MRI) of the face showed edema in the left frontal lobe, interpreted as suspicious for brain invasion (Figure 1). Biopsy revealed large pleomorphic tumor cells with a high nuclear to cytoplasm ratio, prominent nucleoli and focal areas of necrosis. Immunohistochemistry was positive for pancytokeratin and CD56 and weakly positive for chromogranin. She was diagnosed with a T4N0 SNUC. Since the tumor was deemed unresectable due to brain involvement, the RADPLAT protocol was chosen in hopes of maximizing her chance for local control. She received concurrent 4 cycles of weekly intra-arterial (IA) cisplatin at 150 mg/m², administered as a divided dose through left and rightsided feeding arteries for this midline tumor (Figure 2). With the IA cisplatin, she received intravenous (IV) thiosulfate bolus followed by thiosulfate infusion. Radiation therapy was given in 28 daily fractions to 54 Gy using intensity-modulated radiation therapy (IMRT) followed by a hypofractionated stereotactic boost of 3 fractions to 13 Gy to a total dose of 67 Gy in 31 fractions to the nasal sinus and bilateral neck. The biologically effective dose for the radiation treatment is equivalent to 82 Gy² and 117 Gy².

**Response to RADPLAT**

After the first administration of intra-arterial cisplatin, there was an obvious and rapid decrease in tumor size, suggesting response to the chemotherapy. There was marked tumor size reduction after the final cycle of chemotherapy (Figure 3). She tolerated treatment well, with no toxicity from chemotherapy and expected acute sequelae including grade 2 mucositis, grade 2 dermatitis, and grade 1 conjunctivitis. Collagenase and polysporin powder with Xeroform.
was used to treat radiation conjunctivitis. Positron emission tomography (PET)/CT four months post-treatment showed persistent soft tissue density in the anterior ethmoid sinuses, without fluorodeoxyglucose (FDG) uptake (Figure 4). Thirty months post treatment, MRI revealed no evidence of recurrent disease and a decrease in the previously noted inflammatory changes in the sinuses (Figure 5). The patient continues to be disease-free 47 mo post-treatment.

**DISCUSSION**

This case report presents long survival in a patient with an inoperable SNUC treated with concurrent intra-arterial cisplatin and radiation therapy.

Similar to our case, 84% to 92% of patients with SNUC present with T4 disease\(^4\) to \(^9\). In many cases, the cancer can extend beyond the nasal and paranasal sinuses to involve the orbit and/or brain\(^5\).

Currently there is no standard of care available for SNUC. Unresectable SNUC is generally treated with radiation or concurrent chemoradiation. Because the interventional radiologists and treating oncologists were familiar with RADPLAT, we opted to utilize this protocol in hopes of maximizing local control. In 213 patients with stage III-IV head and neck squamous cell cancer (SCC) treated with RADPLAT, Robbins et al\(^10\) reported a 5 year overall survival of 38.8% and locoregional control of 74.3%\(^10\). Similarly, Rabbani et al\(^11\) reported locoregional control in 78% and four year overall survival in 57% in a study of 35 patients with stage III head and neck cancer. Homma et al\(^12\) evaluated the efficacy of RADPLAT for untreated advanced cancers (T3, T4a, and T4b) of the nasal and paranasal sinuses in 47 patients. During the median follow-up period of 4.6 years, the 5-year local progression-free survival rate was 78.4% for all patients\(^12\). Furthermore, the 5-year overall survival rate was 69.3% for all patients\(^12\).
This study indicates that the RADPLAT protocol can not only effectively treat SCC of the head and neck, but also provide locoregional control and long-term survival in cancers specific to the paranasal and nasal sinuses.

The RADPLAT protocol involves intra-arterial infusion of cisplatin with intra-venous systemic neutralization using thiosulfate. The rapid infusion of cisplatin enables high doses of the drug to directly reach the tumor bed while the thiosulfate infusion prevents the systemic toxicity of large doses of cisplatin\textsuperscript{18,11}. The cytotoxic effects of cisplatin are potentiated by radiation\textsuperscript{13}. This effect was first demonstrated in murine models of tumors\textsuperscript{14}. Studies have found that tumor resistance to cisplatin can occur within 2-4 cycles\textsuperscript{15,16}. However, resistance can be overcome by increasing doses of cisplatin as demonstrated by \textit{in vitro} and \textit{in vivo} studies\textsuperscript{17,18}. Elevated doses are not well-tolerated in patients because they can lead to undesirable side-effects such as neurotoxicity, nephrotoxicity, mucositis, and other systemic effects\textsuperscript{19}. To circumvent the high-dose toxicity of the cisplatin, the intra-arterial infusion of cisplatin with concomitant thiosulfate enables high doses of cisplatin to reach the tumor bed without systemic toxicity. With the RADPLAT protocol, it is possible to deliver doses 10 times higher than can be delivered intravenously\textsuperscript{17,18}.

Many studies highlight the importance of surgery in improving survival in patients with SNUC\textsuperscript{2,6,20,21}. In our case, brain involvement of the patient’s SNUC made her a poor candidate for surgery, so she was treated with radical chemoradiotherapy to the primary site and bilateral neck. Elective neck irradiation for node negative SNUC is important for regional control\textsuperscript{3,20}. Chemoradiation has previously been shown to be a viable treatment option for advanced SNUC. In one study, the 2-year progression-free survival and overall survival were 43% and 64%, respectively, with three cycles of platinum and 5-fluorouracil followed by radiation with two cycles of concurrent platinum, suggesting that induction chemotherapy followed by concurrent chemoradiation is effective\textsuperscript{22}. This study found that among patients with SNUC treated to 50-60 Gy, all 4 patients treated with at least 60 Gy were alive without local progression at last follow-up\textsuperscript{22}. Another study found that all patients that achieved cause-specific survival when treated with doses greater than 62.5 Gy\textsuperscript{23}. Thus, doses of at least 60-70 Gy to the primary site are recommended, if feasible.

In conclusion, our patient was effectively treated with RADPLAT with minimal toxicity and lasting disease control for nearly 4 years. Centers with expertise in intra-arterial chemotherapy could consider this modality for patients with unresectable SNUC.

**REFERENCES**


