**Case 3: Adjuvant Head and Neck Radiation in a Young Pregnant Woman**

A 32-year-old, pregnant (14 weeks), female patient presented to the emergency room with a 3-month history of a nonhealing, painful ulcer on the right side of the tongue that she initially thought was an accidental bite. She was prescribed antibiotics with recommendations to see oral surgery if no improvement. The patient consulted with oral surgery, and underwent biopsy testing of a 3.5 cm right lateral tongue ulcer. The biopsy test results were consistent with moderately differentiated keratinizing squamous cell carcinoma (p16 negative). A computed tomography scan of the neck revealed a 3.5 \* 1.8 cm enhancing lesion on the right lateral tongue, extending through the full thickness of the tongue without suspicious adenopathy. The patient has a history of smoking (1/4 pack per day for 10 years), but quit 3 years prior.

She underwent a hemiglossectomy and bilateral neck dissection with free-flap reconstruction. Surgical pathology tests revealed 3.5 cm poorly differentiated squamous cell carcinoma with a 13-mm depth of invasion and negative surgical margins (closest margin: 4 mm). Perineural invasion was present without lymphovascular invasion. One ipsilateral, level 2A lymph node (4 mm) was positive without ECE. The patient's carcinoma was staged as pT3, pN1, Mo. She did well after surgery, and was discharged on postoperative day 7. She was 17 weeks pregnant on the discharge date.

**Expert 1: One Treatment but Two Patients**

1. We recommend adjuvant radiation therapy (RT) to the primary site and both sides of the neck. The patient had numerous adverse features that correlate with a significant risk of recurrence and successful salvage of recurrence is unlikely.
2. Intensity-modulated radiation therapy is possible despite increasing the fetal dose compared with 3-dimensional conventional radiation therapy. Fetal shielding, keeping the modulation low, rotation of the collimator (so the multileaf collimator opens along the patient axis), and consideration of flattening-filter-free mode can help mitigate the fetal risk. Final decisions of external beam radiation therapy technique would be made after fetal dose estimations.

Initiating RT 4 weeks after surgery would start treatment at 21 weeks. This is acceptable as the patient is past the most radiosensitive stages of pregnancy. Delaying counters the preferential timing of postoperative RT, and the presumed enhanced safety later in pregnancy is offset by the growth of the fetus closer to the delivered radiation field.

1. Omitting the right neck would not offer meaningful fetal protection.
2. The pregnancy is not a specific contraindication to chemotherapy. The complexity is more that the case described numerous adverse features, but not a positive margin or extranodal extension for which there is consensus for concurrent chemo-RT. There are no data to support aggressive adjuvant chemotherapy in lieu of RT.
3. The patient’s personal priorities may affect the treatment strategy. Although the risk is low to the fetus, there is a remote possibility of effect on growth or cognition and malformation. Additionally, the morbidity of the treatment on the patient may be more difficult to manage during a pregnancy and subsequently with a newborn.

**Expert 2: What to Expect When You’re Expecting: Managing Oral Cavity Cancer in the Setting of a Second Trimester Pregnancy**

It would be standard to recommend postoperative radiation to this young pregnant female with resected locally advanced oral cavity cancer and multiple risk factors including pT3 primary, depth of invasion ≥4 mm, close surgical margins (≤5 mm), perineural invasion, and positive lymph node. The complicating factor is that she is 17 weeks pregnant. Typically, radiation therapy during pregnancy is avoided due to fetal health concerns including miscarriage, fetal death, and radiation-induced malignancies. Given the distance between the target site and pelvis, the primary concern is the peripheral radiation dose, which is comprised of external and internal scatter to the fetus. Radiation during the middle trimester has previously been associated with intellectual delay. Multiple studies have demonstrated peripheral fetal doses of <0.1 Gy with prescription doses of up to 66 Gy, using lead shielding of the pelvis to minimize the dose.

Despite a relatively low fetal radiation dose, we would have a thorough discussion with the patient regarding the risks and benefits of adjuvant photon radiation to 60 Gy to the bilateral neck with lead shielding. We recommend the patient seek a radiation oncologist with experience in treating patients during pregnancy. Overall, we favor 3-dimensional conformal radiotherapy over intensity-modulated radiation therapy due to increased internal scatter associated with the use of collimators in the latter, which would increase radiation dose to the fetus. We would obtain diagnostic noncontrast magnetic resonance imaging for treatment planning and recommend establishing care with a high-risk obstetrician/gynecologist. We would not recommend systemic therapy given health concerns for the fetus and the absence of positive margins or extranodal extension.

**Expert 3: Just Because You Could, Does Not Mean You Should**

Radiation therapy (RT) should be avoided in pregnancy except for select cases where the benefit clearly outweighs the risks. Here, T3 (American Joint Committee on Cancer 8), close margins, and perineural invasion (PNI) are risk factors for a locoregional recurrence (LRR). For similar cases, we would routinely recommend RT to reduce LRR risk. We would treat the primary site and bilateral neck with IMRT to 60 Gy in 30 fractions starting within 6 weeks of surgery. Given no extracapsular extension or positive margins and only a single lymph node metastasis, we would favor no chemotherapy.

From a technical standpoint, fetal dose below the deterministic threshold of 0.1 Gy is possible even without modern techniques. A similar case of a 29-year-old woman with oral tongue squamous cell carcinoma who was 16 weeks pregnant at surgery was reported. She was treated with opposed laterals and electron boost starting 6 weeks after surgery and a healthy baby was delivered 7 weeks after treatment.We would counsel the patient that second trimester pregnancy risks including mental retardation, microcephaly, and carcinogenesis are uncertain, likely small, but not zero. Conversely, assessing the magnitude of benefit of RT is modulated by missing information, namely the number of dissected nodes and the extent of PNI. If the neck dissection was adequate (>18 nodes) and PNI was only a small, single focus, then the LRR risk without RT may be small. Ultimately, we would offer adjuvant RT during pregnancy if desired by the patient.

**Expert 4: Maximal Cancer Control, Minimal Risk to Fetus**

Given that the patient is 17 weeks pregnant, her management requires a multidisciplinary approach involving the radiation oncologist, medical oncologist, obstetrician, and oral surgeon to ensure the best possible outcome for both the mother and the fetus.

Our recommendation would be as follows:

* Adjuvant therapy: As the patient has a high-risk tumor (pT3, pN1, and presence of perineural invasion), adjuvant therapy should be considered. The choice of adjuvant therapy (chemotherapy or radiation) would depend on the evaluation of potential risks to the fetus and the mother.
* Radiation therapy: Radiation therapy can be a suitable adjuvant treatment option for this patient. However, given the patient's pregnancy, additional precautions should be taken to minimize radiation exposure to the fetus. Intensity-modulated radiation therapy (IMRT) or volumetric modulated arc therapy (VMAT) can be used to target the tumor bed and the ipsilateral neck with higher precision and lower radiation doses to surrounding tissues. The treatment can be planned during the second trimester (when the patient is beyond 17 weeks pregnant) when the fetus is less sensitive to radiation.
* Chemotherapy: The use of chemotherapy in pregnant patients is generally avoided, especially during the first trimester due to potential teratogenic effects on the fetus. However, certain chemotherapy agents like cisplatin have been used during the second and third trimesters in some cases with close monitoring. The decision to use chemotherapy as part of adjuvant treatment should be made after thorough discussion with the patient and a careful evaluation of the potential risks and benefits.
* Close monitoring: The patient should be closely monitored by the obstetrician during and after the radiation therapy. A fetal ultrasound should be performed before initiating treatment and at regular intervals throughout the therapy to ensure the health of the fetus.

The therapeutic approach recommended above aims to maximize the chances of controlling the patient's cancer while minimizing the risks to the fetus. It is important to have a detailed discussion with the patient about the benefits and potential risks of the proposed treatment plan and obtain her informed consent. Additionally, the patient should be counseled on the importance of regular follow-up and surveillance for early detection of potential recurrences or metastasis.

**Expert 5: Reconsidering How It Begins**

The optimal management of oral tongue cancer in a young patient is often challenging. The management of a concurrent pregnancy is even more fraught, requiring measured discussions of the risks and benefits of different treatment approaches. In this case, the patient presented with an oral tongue cancer at 14 weeks of gestation and was taken to surgery. The questions posed in this case occurred after that decision had already been made.

We imagine that a multidisciplinary evaluation was conducted at the time of presentation. Optimal care would have included a well-rounded discussion of the options for the pregnancy from a qualified maternal-fetal medicine specialist in addition to the more traditional oncologic discussion of the potential roles of chemotherapy, radiation, and surgery for the cancer. At 14 weeks of gestation, the patient is early in the second trimester of pregnancy. Facing a life-threatening cancer diagnosis, with treatment options potentially limited by the fetus and fetal health, termination of thepregnancy should have been a medically appropriate, proposed option. In the current political climate within the US, this conversation may now be limited by individual state laws. However, with a commitment to the best outcome for this patient with a new cancer diagnosis, pregnancy termination undoubtedly should have been sensitively explored at the initial presentation. If the patient had chosen to terminate the pregnancy, then the treatment would have proceeded along a standard pathway, likely with surgery and adjuvant radiation as indicated by pathology.

If the patient had chosen not to terminate the pregnancy, then discussion of the optimal multidisciplinary management of oral cavity cancers in the setting of pregnancywould have been appropriate. Although surgery with adjuvant radiation is the standard treatment in a patient who is not pregnant, this situation could warrant other approaches. For instance, there are several studies of induction chemotherapy before surgery for oral cavity cancers, and numerous chemotherapy agents, including platinum derivatives and taxanes, have been established as safe in the second and third trimesters of pregnancy. Three cycles of induction chemotherapy could have been used, followed by surgery, delivery at the earliest safe time per maternal-fetal medicine, and then radiation therapy in the postpartum patient.

At this point, with the pathologic diagnosis of pT3N1 oral tongue squamous cell carcinoma with perineural invasion in a patient now at 17 weeks of gestation, the options for radiation therapy become more risky and dire, for both the patient and the fetus. We would not recommend radiation therapy at this time. Fundamentally, optimal postoperative radiation in 2022 (with intensity modulated radiation therapy, treatment to the primary and bilateral neck) could put the fetus at risk for harm. However, compromising that with use of older techniques or limited fields could result in less effective treatment and put the patient at risk for severe toxic effects or recurrence. In this setting, we would carefully consult with the maternal-fetal medicine specialist to plan for the earliest safe delivery of the fetus, followed by almost immediate start of adjuvant radiation. In this current interval between resection and radiation, we would also strongly consider adjuvant chemotherapy. Although adjuvant chemotherapy given before adjuvant radiation does not have a proven survival benefit in nonpregnant patients with oral cavity cancers, it does not pose a survival detriment. In this case, we would offer systemic treatment known to be active in oral cavity squamous cell carcinoma and with acceptable safety for the patient and fetus, such as cisplatin and docetaxel, to control microscopic disease and minimize the risk of interval recurrence owing to radiation delay.

Ultimately, the cancer is only one aspect of this woman's care. The options for pregnancy management, including termination,early delivery, and deployment of all multimodality options, are crucial conversations to have with the patient and a maternal-fetal medicine provider. We would explore all options for cancer management to delay the radiation therapy until after resolution of the pregnancy state.