**Case 13: Radiation Therapy for Cure or Palliation: Case of the Immunosuppressed Patient with Multiple Primary Cancers and Liver Transplant**

A 66-year-old man with a history of esophageal cancer was found to have a suspicious erythematous lesion on the palatine arch during endoscopy surveillance.  
Two years prior, the patient received a diagnosis of low-risk prostate cancer managed by active surveillance. Simultaneously, cT3N0M0 lower thoracic esophageal squamous cell carcinoma was found in this patient. Surgery was not an option based on his previous liver transplant. The patient was treated with external beam radiation therapy to 50 Gy in 25 fractions. Chemotherapy was omitted as a result of his comorbidities; however, the patient remained with an Eastern Cooperative Oncology Group performance status of 0 throughout the treatment. Unfortunately, 6 months after radiation therapy, biopsies confirmed local recurrence at the site of initial tumor. The decision was made to defer salvage brachytherapy because the patient had no local symptoms.

The patient’s medical history is significant for portal hypertension, esophageal varices, orthotopic liver transplantation for liver cirrhosis and pT4pN0 hepatocellular carcinoma, autoimmune thrombocytopenia, splenomegaly, and left kidney agenesis. He is taking 2 anti-rejection medications, and his liver graft function is stable.  
At the most recent presentation, computed tomography confirmed a right-sided, palate-confined mucosal and submucosal lesion measuring 1.5 cm with no neck lymphadenopathy (Fig. 1). Biopsy confirmed basaloid squamous cell carcinoma.

Fig. 1: (a) Contrast-enhanced computed tomography of head and neck demonstrating 1.5-cm large soft palate (fourth) primary tumor with no neck lymphadenopathy in a patient with hepatocellular carcinoma and localized prostate and locally recurrent esophageal cancer treated with curative external beam radiation therapy—axial plane. (b) Soft palate primary tumor (coronal plane).

**Expert 1: Short and Simple Palliative Radiation Therapy**

1. What would be the approach to the oropharyngeal cancer?

* Biopsy (check p16). Ensure this is not a metastasis from another cancer, such as hepatocellular carcinoma.
* Consult with multidisciplinary team. Estimate prognosis from each condition. Which is the most immediate threat to survival and to his quality of life? What can each discipline do to optimize the patient’s situation?
* Discuss the available options and goals of therapies, including uncertainties. What are the patient’s main priorities?

Assuming a primary head and neck squamous cell cancer:

- Palliative radiation therapy (RT) is recommended because growth of the cancer will worsen quality of life.

- A short RT fractionation is suggested given likely poor survival/palliative goals—for example, 0 to 7-21 (24 Gy in 3 fractions).

- Neither chemotherapy nor surgery are options given comorbidities.

2. What would be the approach to the recurrent esophageal cancer?

* Given an incurable presentation, the goal is palliation of symptoms.
* If the patient is asymptomatic, provide supportive care.
* If bleeding is present, use single brachytherapy insertion or external beam RT (6 Gy, single fraction).
* If dysphagia or odynophagia are present, options include:

- High-dose-rate brachytherapy, 10 Gy in 1 fraction or 12 Gy in 2 fractions.

- Stent (preferred for a short life expectancy, such as <2 months).

- External beam RT, 20 Gy in 8 fractions.

3. Are there any special considerations given the multiple primary cancers and the setting of immunosuppression?

* Immunotherapy and conventional chemotherapy would be poorly tolerated.
* Tolerance of RT can be less, so constraining volumes in keeping with palliative goals is key. Focus on gross disease without prophylactic nodal irradiation.
* Seek proactive involvement of the palliative care team and psychosocial oncology.
* Consider genetic counseling/testing.

**Expert 2: A Hard Case to Swallow: Multiple Primary Cancers with Multiple Possible Answers in the Setting of Solid Organ Transplantation**

Multiple primary cancers = multiple possible answers.

The patient’s poor prognosis may obscure the fact that his quality of life is largely preserved, and a vigorous, if realistic, palliative regimen is indicated. His ongoing immunosuppression requires no modification of radiation therapy recommendations. The oropharyngeal cancer and the recurrent esophageal cancer represent different challenges and should be addressed separately.

The patient’s esophageal cancer has recurred 2 years after treatment with RT alone, a presentation for which 5-year survival is near zero. We advise continued observation and would consider the palliative Radiation Therapy Oncology Group 8502 regimen (“QUAD SHOT”)2 when symptoms occur. This is a short-course radiation therapy protocol consisting of cycles of 3.7 Gy fractions twice daily for 2 consecutive days that can be repeated every 4 weeks for up to 3 cycles in the absence of toxicity or disease progression. We have found that the opportunity given by this regimen for frequent midtreatment reassessments is a particular advantage for patients whose good performance status does not belie their vulnerability to decline.

The patient’s oropharyngeal tumor, left untreated, can lead to difficulty in speaking, eating, and breathing, which could be prevented and even cured with 6 weeks of unilateral RT alone. For patients unable or unwilling to undergo daily treatment, we prefer stereotactic body radiation therapy to gross disease. Gogineni et al3 report results for stereotactic body radiation therapy in this setting similar to our experience: 1-year local control and overall survival were 73% and 64%, respectively, and toxicity was low (3% acute grade 3, no grade 4+).

**Expert 3: Less Is More: Lower Doses for Intermediate-Term Oropharyngeal Control**

Management of the localized oropharyngeal cancer should be based on the expected prognosis of the locally recurrent esophageal cancer.

Radiation therapy without chemotherapy for cT3N0 esophageal cancer is palliative, based on 0% survival at 3 years in Radiation Therapy Oncology Group 8501. Reirradiation can be considered in select cases, and nivolumab can be used after definitive trimodality therapy or after chemotherapy for recurrent disease. However, local recurrence only 6 months after radiation therapy without the options of chemotherapy (presumably a poor candidate given omission upfront) or immunotherapy (due to prior liver transplantation) portends a poor overall prognosis.

Although resection of the cT1N0 soft palate tumor is feasible, it could lead to velopalatal insufficiency or other complications with speech and swallowing, as well as significant

periprocedural risks of morbidity in the context of immunosuppression. Therefore, we would prefer accelerated hypofractionated radiation therapy alone. A definitive approach could include 66 Gy in 30 fractions per Radiation Therapy Oncology Group 0022, but for this patient we would favor 50 to 60 Gy in 20 fractions (split midcourse for 2-4 weeks). Another option is 30 Gy in 10 fractions while reserving another 30 Gy in 10 fractions as salvage therapy should an oropharyngeal recurrence become more problematic than the esophageal cancer. Especially if the tumor was p16-positive, it may be reasonable to consider this lower-dose regimen to the primary alone (omitting elective lymph nodes to spare toxicity), because a locoregional recurrence could be salvageable.

It is also critical to discuss with transplant hepatology whether the dose of immunosuppressive medication can be decreased.

ChatGPT’s initial recommendation

**Expert 4: A Multidisciplinary Approach for Complex Medical History and Immunosuppression**

In the context of this patient's unique medical history and the challenges associated with immunosuppression, a multidisciplinary consultation is essential for determining the most appropriate therapeutic approach for both the oropharyngeal cancer and the locally recurrent esophageal cancer.

* Multidisciplinary consultation:

a. Collaborate with various specialists to carefully evaluate the patient's condition and develop a tailored treatment plan.

b. Consider the patient's quality of life, prognosis, and preferences when determining the most appropriate therapeutic approach.

* Favored therapeutic approach:

a. For the oropharyngeal cancer, consider palliative radiation therapy to minimize toxicity and prevent decline in the patient's quality of life.

b. For the recurrent esophageal cancer, focus on managing symptoms and preserving the patient's quality of life through palliative radiation therapy.

Our recommendation seeks to address the challenges presented by the patient's complex medical history and immunosuppression while prioritizing their quality of life. By utilizing a multidisciplinary approach, the goal is to develop a comprehensive and tailored treatment plan that best meets the patient's needs.

ChatGPT’s revised recommendation after seeing other human experts’ recommendations

**Expert 5: A Tailored Approach for Complex Medical History and Immunosuppression**

Management of the localized oropharyngeal cancer and the locally recurrent esophageal cancer should be based on the patient's unique medical history and the challenges associated with immunosuppression. A multidisciplinary consultation is essential for determining the best course of action.

1. For the oropharyngeal cancer:
   1. Utilize unilateral RT alone or stereotactic body radiation therapy to minimize toxicity and prevent decline in the patient's quality of life.
   2. Consider accelerated hypofractionated radiation therapy alone, with the possibility of a lower-dose regimen depending on the patient's prognosis and preferences.
2. For the recurrent esophageal cancer:
   1. Continue observation with the possibility of using the palliative Radiation Therapy Oncology Group 8502 regimen when symptoms occur.
3. Consult transplant hepatology to discuss the possibility of adjusting the patient's immunosuppressive medication.

This tailored approach aims to address the challenges presented by the patient's complex medical history and immunosuppression while prioritizing their quality of life.