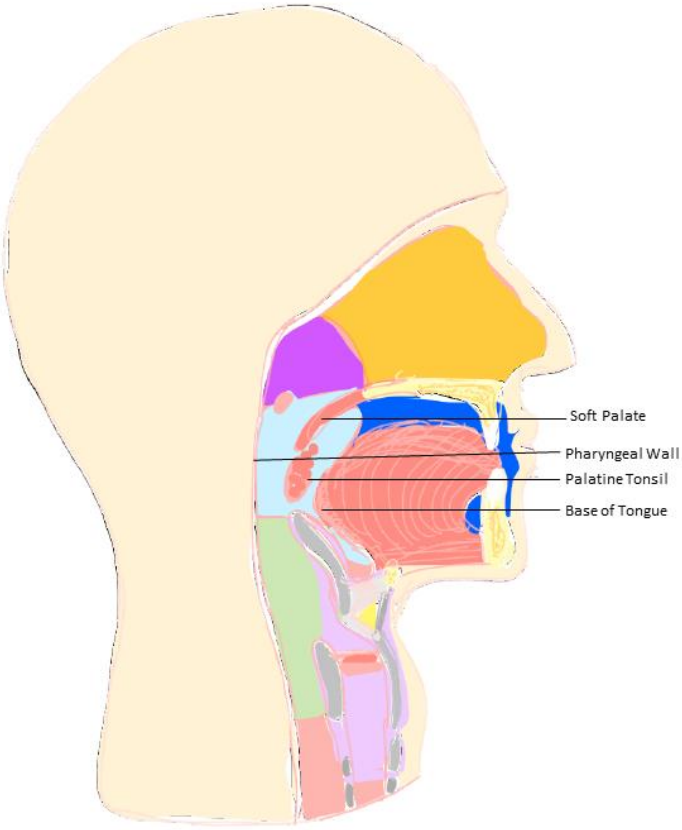
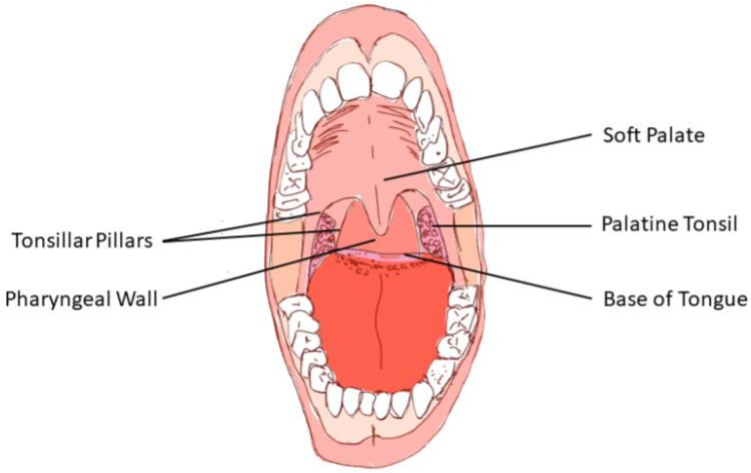
Oropharynx

a. Anatomy
    i. The oropharynx is an area in the back of your mouth and upper throat. This begins from the soft palate, the very back of the tongue, and the tonsils and extends to the back of the throat. From top to bottom, this area extends from the level of the soft palate to the root of the epiglottis (the lid that covers the voice box upon swallowing to help direct food into the esophagus or swallow tube). Within the oropharynx there are two sets of tonsil tissue. The palatine tonsils are located on the side of the throat and more commonly referred to as tonsils and are most commonly removed surgically after multiple infections. The second set of tonsils, lingual tonsils, are positioned at the very back of the tongue, also known as the tongue base.
    ii. The oropharynx plays a very important role in normal swallowing. The oropharynx functions to direct and push food down to the esophagus in a coordinated effort. First the soft palate moves up and backward to touch the back of the throat, preventing food and liquid from traveling into the nasal passage. The tongue base moves back and downward, driving food down toward the esophagus. At the same time, the epiglottis turns down to cover the entrance to the voice box, protecting food from entering the “windpipe” (trachea) and lungs.
    iii. Squamous cells make up the lining, also known as the mucosa, of the oropharynx. That is why squamous cell carcinoma is the most common type of oropharynx cancer. Lymphomas and tumors arising from saliva producing glands can also occur in this location.





b. Risk Factors

i. Historically oropharyngeal cancer was mostly associated with tobacco and alcohol consumption, more recently the most common risk factor is the Human Papilloma Virus (HPV), a virus which also causes cervical cancer.
    1. HPV associated oropharyngeal SCC has been rising, especially among younger age groups
    2. HPV can be associated with oral sexual behaviors
        a. Risk increases with > 11 vaginal sex partners and 6 oral sex partners
    3. HPV cancer may also be related to marijuana use
    4. Poor dental hygiene may be associated with non-HPV associated oropharyngeal cancer

c. Symptoms
    i. It is common for patients with HPV associated oropharyngeal cancer to present with a painless neck mass
    ii. Symptoms of oropharynx cancer:
        1. Neck mass
        2. Sore throat
        3. Voice or speech changes
        4. Ear pain
        5. Spitting out blood
        6. Difficulty or pain with swallowing

d. Diagnosis
    i. Once a suspicious growth, ulcer or lesion is identified within the oropharynx (tongue base, soft palate, tonsil) a biopsy of the suspected area will be required to confirm the diagnosis of an oropharyngeal mucosal malignancy. Due to the location of the cancer, a biopsy at your doctor's office using both topical and local anesthesia may be difficult. To effectively biopsy and evaluate the extent of the oropharyngeal cancer, you may require biopsy under general anesthesia in the operating room. Prior to scheduling your biopsy under general anesthesia, a complete head and neck exam including possible in-office fiberoptic camera exam may be performed.
    ii. Patients presenting with a neck, mass may undergo a needle biopsy in the office with or without radiologic image or ultrasound guidance.
    iii. Biopsies are often tested for HPV or p16 to determine if the cancer is related to the Human Papillomavirus.
    iv. Your doctor may also order a variety of medical imaging:
        1. Computerized tomogram imaging (CT scan)
        2. Magnetic resonance imaging (MRI)
        3. Positron emission tomography (PET)
        4. Dental imaging (cone beam scan or Panorex).

    These images will help to further delineate the extent and spread of the cancer. The CT scan and dental imaging will help to identify disease within the jaw bone

(mandible or maxilla) and condition of the teeth. Intravenous contrast enhanced CT scan and MRI can identify soft tissue structures within tongue, tonsil, palate, throat or neck that may have disease. PET imaging is a special technology that identifies a glucose (sugar) molecule being absorbed by the cancer cells and help determine whether the cancer has spread to other parts of the body. Alternatively, CT scan imaging of the chest may be performed to visualize any spread of disease to the lungs.

v. In some patients, the primary oropharynx cancer site may be undetectable on examination. Your doctor may recommend removal of the tonsils and superficial surface of the tongue base under general anesthesia to identify the tumor where it started.

e. Staging
    i. The American Joint Committee on Cancer (AJCC) has created a staging system (TNM staging that groups cancers into stages based on their anatomic extent. The staging helps to determine the optimal treatment for a specific cancer, and provides information about expected survival rates.
    ii. The staging system includes information about the extent of the original or local tumor (T classification or primary tumor extent), spread to lymph nodes (N-classification or nodal metastases), and spread to distant parts of the body (M classification or distant metastases). Combinations of T, N and M-classifications produce an overall stage. There are four stages (Stage 1-4) reported with increasing disease burden and potentially worse prognosis as the AJCC stage number increases.
    iii. Human papillomavirus (HPV) causes most oropharyngeal mucosal cancers. Identification of this virus within the biopsy specimen and/or following surgical tumor removal is essential for accurate staging and prognosis.
    iv. New AJCC staging guidelines (8^{th} edition) has a different staging system for oropharynx cancers caused by HPV and those not caused by HPV. In general terms, patients with HPV-positive tumors of the oropharynx have a better long-term survival and less aggressive disease than HPV-negative oropharynx cancers, even if the cancer has already spread to lymph nodes.
    v. Lymph nodes are small oval shaped structures found within the fat of the neck that harbor specialized immune cells that filter and fight infection and disease. Cancer cells from the mouth detach from the cancer and can become trapped and grow within the individual nodes.
    vi. For HPV negative cancers, the number of abnormal lymph nodes and their size is important. Sometimes, the cancer in a lymph node grows out of the lymph node, a property known as extranodal extension (ENE). A special subclassification for the lymph nodes is designed to report on the involvement cancer (number of nodes involved with cancer and size in centimeters within the lymph nodes of the neck, as well as ENE.
    vii. The staging system includes different criteria for HPV positive and HPV negative cancers, even though both types originate in the squamous cells in the mucosal lining of the oropharynx. For HPV positive cancers, the spread of cancer to lymph

nodes does not have the same negative effect on survival. HPV-related cancers that spread to lymph nodes may still represent early-stage disease. In contrast, HPV-negative cancers that have spread to lymph nodes are considered at least Stage 3.

Primary Tumor Stage: HPV-related Oropharynx	
Stage	Description
T0	No primary tumor identified
T1	Tumor 2 cm or smaller
T2	Tumor larger than 2 cm but not larger than 4 cm
T3	Tumor larger than 4 cm; **or**, Tumor extends to lingual surface of the epiglottis
T4a	Tumor invades larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible or beyond

Regional Nodal Stage: HPV-related Oropharynx	
Clinical Stage	Description
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph node, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	One or more lymph node larger than 6 cm

Regional Nodal Stage: HPV-related Oropharynx	
Pathologic Stage	Description
pNX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

AJCC Prognostic Stage Groups: HPV-related Oropharynx	
Clinical Stage	Description
I	T0-2, N0-1, and M0
II	T0-2, N2, M0; **or**, N3, N0-2, M0
III	T0-4, N3, M0; **or**, T4, N0-3, M0
IV	Any T, any N, M1

AJCC Prognostic Stage Groups: HPV-related Oropharynx	
Pathologic Stage	Description
I	T0-3, N0-1, M0
II	T0-2, N2, M0; **or**, T3-4, N0-1, M0

III	T3-4, N2, M0
IV	Any T, any N, M1

Primary Tumor Stage: HPV-negative Oropharynx	
Stage	Description
Tx	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or smaller
T2	Tumor larger than 2 cm but not larger than 4 cm
T3	Tumor larger than 4 cm; **or**, Tumor extends to lingual surface of the epiglottis
T4a	Tumor invades larynx, extrinsic muscles of tongue, medial pterygoid, hard palate, or mandible
T4b	Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery

Regional Nodal Stage: HPV-negative Oropharynx	
Stage	Description
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral node, 3 cm or smaller and ENE (-)
N2a	Metastasis in a single ipsilateral node 3 cm or less and ENE (+); **or**, A single ipsilateral node larger than 3 cm but not larger than 6 cm and ENE (-)
N2b	Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm and ENE (-)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm and ENE (-)
N3a	Metastasis in a lymph node larger than 6 cm and ENE (-)
N3b	Metastasis in a single ipsilateral node larger than 3 cm and ENE (+); **or**, Multiple ipsilateral, contralateral or bilateral nodes, any with ENE (+); **or**, A single contralateral node any size and ENE (+)

AJCC Prognostic Stage Groups: HPV-negative Oropharynx	
Stage	Description
0	TisN0M0
I	T1N0M0
II	T2N0M0
III	T3N0M0, T1-3N1M0
IVA	T4aN0-1M0, T1-4aN2M0
IVB	Any T, N3, M0; **or**, T4b, any N, M0
IVC	Any T, any N, and M1

f. Treatment
    i. Typically, patients have a team that includes a head and neck surgeon, medical oncologist, radiation oncologist, nurse practitioner or physician assistant (APP), and speech language pathologist (SLP) who will determine treatment options at your initial visit.
    ii. Squamous cell carcinoma of the oropharynx is effectively treated with surgical and non-surgical options. Patients with a significant history of smoking, regardless of HPV-status are most commonly treated with radiation therapy combined with chemotherapy (typically cisplatin) administered concurrently (during the same 6-week-long interval). Patients with HPV-driven squamous cell carcinoma are staged differently due to higher survival rates. As such, many patients with HPV-driven oropharynx cancer are actively being treated with lower doses of radiation therapy combined with chemotherapy and/or immunotherapy (currently only in the setting of clinical trials), to try and reduce the side effects of high dose radiation while maintaining high cure rates. For this reason, treatment options vary and may continue to change as information from clinical trials becomes available.
    iii. *The current standard of care for non-surgical therapy is radiation to 70 Gy combined with cisplatin.* Depending on the tumor stage and extent, patients may be eligible for treatment with radiation alone, without chemotherapy.
    iv. Some patients with oropharynx cancers may be candidates for surgical removal of their cancers. Transoral surgery (i.e. surgery through the mouth) is a surgical approach to tumor removal in a less invasive manner than traditional surgery, resulting in a quicker recovery and fewer complications. Transoral surgery is performed with a microscope or a robotic device to enhance the ability to see in a small space. TransOral Robotic Surgery (TORS) specifically refers to using a robot during surgery. It uses a computer system to guide the surgical tools which is controlled by a trained surgeon. Using a robotic system to guide the tools allows for more precise movements and allows the surgeon to be able to operate in small spaces with 3-D visual magnification. TORS is FDA approved for removing smaller tonsil and tongue base cancers (i.e. classified as T1 or T2 tumors). The overwhelming majority of surgically treated patients also require surgery to remove the lymph nodes in the neck that may contain cancer or are at risk for harboring cancer. Approximately 70-90% of patients who undergo surgery will require postoperative radiotherapy, and 25-50% will require chemotherapy. Transoral surgery is typically performed for the following reasons:
        - To reduce the dose of radiation treatment received to the neck and throat
        - To prevent the need for extra treatments such as chemotherapy

The survival and swallowing of patients who undergo initial surgery followed by radiation appears to be favorable, but head to head comparisons have not been performed. Long term effects of different treatment approaches have also not been well described but are active areas of investigation.

g. Survival
    i. Initial cancers stage is the most important factor to affect survival for oropharynx cancer patients. A higher stage suggests a more advanced cancer and a lower survival. We also know, for the oropharynx, cancers that are related to the human papilloma virus (HPV) tend to do better than similar cancers not caused by this virus. In general, the overall 5-year survival associated with oropharynx cancer as reported by the American Cancer Society is 67% not considering a patient's age, smoking or alcohol history, or HPV status. Early cancers have a reported 5-year survival of 84% which decreases to 66% if the lymph nodes are involved and to 39% if distant organs are involved.
    ii. In addition to considering survival, it is important to discuss the impact that the cancer and cancer treatment can have on a person's overall function and lifestyle. For patients who undergo surgery for oropharyngeal cancers, changes in appearance may be minimal, though there can be external scars related to the removal of neck lymph nodes. For more advanced cancers, surgery may involve complex reconstruction which may have other associated scars which your surgeon can discuss in more detail. Surgery can also impact your swallowing which is discussed below.
    iii. For those patients who require non-surgical treatment such as radiation with or without chemotherapy, the treatment can have other effects. Short term side effects, that occur during and immediately after treatment, include mucositis, rashes, nausea and vomiting, weight loss, pain including pain with eating or swallowing, and muscle aches. Mucositis refers to sores that can occur inside the region receiving radiation treatment and can include the mouth and throat. This can make swallowing painful. Your doctors may prescribe medications to help numb the throat in the area to make the sores more tolerable. The sores typically resolve after completing treatment. Patients who are getting radiation to the face and neck can develop a red rash with peeling and dry skin in the areas receiving radiation. This can be worsened by certain types of chemotherapy. Often moisturizers and skin emollients are prescribed to help manage the skin. Nausea and vomiting are seen more often in patients also receiving chemotherapy and your doctors may prescribe specific medications to help manage these symptoms. These symptoms may make it difficult to get adequate nutrition, and weight loss is common. Some patients require a stomach tube to maintain their weight and support their nutrition.
    iv. Long term side effects can include taste dysfunction, dry mouth, trouble swallowing, neck and facial swelling (or lymphedema), hearing loss and nerve pain or neuropathy. For many patients their taste is altered during and

immediately following radiation treatment and recovers to some degree in the months following treatment. Taste changes can include a lack of taste or food tasting too sweet or too salty or burning.

v. Many patients suffer from dry mouth or xerostomia following radiation therapy as the saliva glands are particularly sensitive to radiation. This can lead to thickened saliva in the mouth and generally a dry mouth feel. This may be permanent. Many patients are accompanied by a water bottle, and take sips frequently. Additionally, certain over the counter saliva substitutes can help keep the mouth moist. Sugar free gum can also help improve saliva production.

vi. In addition to affecting saliva, radiation treatment can also affect swallowing. The radiation therapy can stiffen the swallowing muscles making it harder to get the food to go down. Patients report feeling persistent "phlegm". Surgery can also worsen swallowing by altering normal anatomy, causing scar tissue and changes in sensation or feeling in the back of your throat. Swallow therapists (known as speech-language pathologists) can help patients strengthen and coordinate their swallowing muscles to improve their swallowing.

vii. Certain chemotherapy drugs can lead to hearing loss or ringing in the ears. Your doctor may check your hearing before and after treatment. The effect to your hearing is usually related to a nerve related damage which may not recover. If the effect is significant, a hearing aid may need to be considered to help treat the hearing loss. Both radiation and chemotherapy can lead to long term nerve and muscle pains. The likelihood of this occurring is related to the amount of chemotherapy and radiation you receive. Some effects lessen the further out from treatment you are.

viii. References:

American Cancer Society. Cancer Facts & Figures 2020. Atlanta: American Cancer Society; 2020.

h. Surveillance/Survivorship

i. Surveillance: As with any cancer, there is a risk that oropharynx cancer will come back ('recur') after treatment. 'Surveillance' means that your doctor(s) will monitor you after treatment with a combination of physical examination and imaging studies in order to detect recurrent disease early. Protocol details will vary from institution to institution. Patients will be followed for at least 5 years. Once cleared by the treating physician, patients may transition into a cancer surveillance/survivorship clinic, often run by an advanced practice provider (APP) that is well trained in head and neck cancer surveillance.

1. Physical examination: Your doctor(s) will examine you according to the following schedule:
    a. Year One: every 1-3 months
    b. Year Two: every 2-6 months
    c. Years Three through 5: every 4-8 months
    d. After 5 years: every 12 months or as needed

2. Imaging: The timing and type of imaging you have will be based on your doctor's judgment.
    a. Baseline imaging within 6 months of completing treatment may be considered.
    b. Imaging may include CT scans, PET/CT scans, MRI, or sometimes ultrasound.
    c. Additional imaging will be based on your symptoms, exam, and your doctor's judgment.
    d. It is important to let your doctor know if you feel a new persistent pain or neck mass.

ii. Survivorship: Oropharynx cancer and its treatment can affect many areas of your health and quality of life. 'Survivorship' refers to caring for your health and well-being from the moment you receive your diagnosis, and for the rest of your life. Depending what your treatment involves, important parts of survivorship for oropharynx cancer may include:
    1. Speech and swallowing evaluation and therapy: This is typically with a Speech-Language Pathologist, or SLP, with expertise in speech and swallowing for head and neck cancer patients.
        a. Swallowing: Safe swallowing is important for your health and quality of life. Poor swallowing function, called 'dysphagia', can lead to health problems such as pneumonia or malnutrition, and may lead to the need for a feeding tube. You may also be referred to a dietician for guidance on how to get adequate nutrition to maintain your health.
        b. Esophageal stricture: Some patients develop a narrowing of your esophagus, called an 'esophageal stricture'. This can be diagnosed with a swallowing test. Some patients benefit from having their esophagus stretched.
        c. Speech: Rehabilitation of your speaking is important for your communication and quality of life.
    2. Oral and dental health: Oropharynx and its treatment can have a major impact on your teeth, taste, saliva and jaw bone health.
        a. Dental cleaning and care: Oropharynx cancer patients should establish care early after diagnosis, ideally before treatment, with a dentist who has experience in head and neck cancer. Some dental work may be necessary prior to treatment. In the long term, patients should have routine cleaning and examination. Routine fluoride treatments may be recommended.
        b. Radiation and dental health: Radiation can be detrimental to your dental health. Without the protective enzymes in you saliva that protect your teeth and gums from harmful bacteria, your teeth become susceptible to severe dental caries leading to jaw infections. It is especially important for patients who undergo

radiation to have regular dental care and excellent dental hygiene.

c. Dry mouth: Dry mouth, or 'xerostomia', is common after radiation therapy and can have a significant negative impact on quality of life. There is no cure for xerostomia. If you have xerostomia, you can decrease the symptoms by staying hydrated, using salivary substitutes, and maintaining excellent dental hygiene.
d. Osteoradionecrosis (ORN): Patients who undergo radiation are at risk for breakdown of the jaw bone, or osteoradionecrosis (ORN). This may cause ulcers, exposed bone, pain, and chronic infection. ORN is diagnosed with history, examination and imaging. Treatment may involve medications, hyperbaric oxygen treatments, or in advanced cases, bone removal and reconstruction.
e. Trismus: Surgery and radiation can cause difficulty opening your mouth, called trismus. This can interfere with dental care and with eating. Ask your doctor about ways to improve your mouth opening.

3. Thyroid function testing: If you have had radiation therapy, you have an increased risk of low thyroid function, or 'hypothyroidism'. Symptoms of hypothyroidism may include fatigue, weight gain, constipation and depression. Your thyroid function should be tested every 6-12 months to determine whether you need treatment with thyroid hormone supplementation.
4. Tobacco use:
    a. Most head and neck cancers are associated with tobacco use, especially smoking cigarettes.
    b. Continued tobacco use after treatment is associated with worse survival and higher risk of other cancers, among many other negative health effects.
    c. Quitting tobacco will improve your overall health and chances of survival from head and neck cancer.
    d. If you still use tobacco after head and neck cancer treatment, we strongly encourage you to consider quitting. Your doctor can help you find resources, including medications and counseling programs, that have been proven to help.
5. Lymphedema: Lymphedema is swelling of the soft tissue that is common for patients who have had surgery and/or radiation. Specialized Physical Therapy called Lymphedema Therapy, including massage, compression garments, exercises and skin care, is available and can significantly improve lymphedema.
6. Shoulder dysfunction: Many head and neck cancer survivors have shoulder dysfunction, including decreased range of motion, weakness and stiffness as a result of surgery and/or radiation. Physical therapy is

very helpful in improving shoulder function. If you have problems with your shoulder, ask your doctor about a referral to a physical therapist.

7. Obstructive sleep apnea: Survivors of head and neck cancer treatment are at risk for obstructive sleep apnea (OSA) because of changes to the upper airway anatomy. Symptoms may include daytime sleepiness, snoring, gasping or choking during sleep, daytime headaches, and irritability. OSA is diagnosed with a sleep study, and there are several options for treatment. Discuss your risk of OSA with your doctor..
8. Carotid artery stenosis evaluation: Radiation therapy to the neck increases the risk of carotid artery narrowing (stenosis) later in life. Carotid artery stenosis increases the risk of stroke. If you have had radiation to your neck, ask your doctor about an ultrasound or carotid Doppler to look for carotid artery stenosis.
9. Mental and sexual health: Head and neck cancer and its treatment can result in cognitive dysfunction, anxiety, depression, body image concerns, and changes in sexual function and desire. If you suffer from any of these, you are not alone. Ask your doctor about meeting with a mental health professional to determine whether counseling and/or medication may be helpful for you.
10. Hearing evaluation: Head and neck cancer treatments, especially with certain chemotherapy drugs, can cause hearing loss. If you have decreased hearing, you should have a hearing test to evaluate your hearing and determine whether you may benefit from hearing augmentation, such as with a hearing aid.

i. Questions for your doctor
    i. Before/during treatment:
        1. Is my tumor caused by HPV? How does this affect my prognosis?
        2. What types of treatment are recommended (such as surgery, radiation, and/or chemotherapy)?
        3. Are there any other treatment options that I should learn about, such as clinical trials?
        4. Should I see a dentist before treatment begins?
        5. How long will treatment take? How long will it take to fully recover after treatment?
        6. What are the risks and side effects of each part of treatment? Which side effects are temporary, and which might be permanent?
        7. Will I need a feeding tube or a breathing tube (tracheostomy)? Will they be temporary or permanent?
        8. What will my swallowing, speech and breathing be like after treatment?
        9. Will I have any other functional problems after treatment?
        10. Will I be able to keep doing my job after I've recovered?
    ii. After treatment:
        1. Should I have any imaging studies?

2. When should my next follow-up appointment be, and with whom?
3. Should I have my thyroid function tested?
4. Should I be referred to a speech and language pathologist (SLP), and or to a physical or occupational therapist?
5. Am I receiving appropriate dental care?
6. Should I have a sleep study?
7. Do I need a carotid artery ultrasound?
8. Should I have a hearing test?