Chapter 11
Larynx

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11.1 Pearls [1, 2]

- 13,000 annual estimated cases in the USA (~3.4 cases/100,000 people).
- Predominately affects men; median age at diagnosis is 65.
- Etiologies include tobacco, alcohol, betel nut consumption, and deficiencies in vitamins/nutrients (iron, vitamin B12, and vitamin C).
- Common presenting symptoms include hoarseness, dysphagia, odynophagia, chronic cough, and referred otalgia; can be location dependent.
- 90–95% are SCC; can also see verrucous carcinoma, adenocarcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinomas.
- Local anatomy:
  - Divided into three subsites:

    Supraglottis: includes supra- and infrahyoid epiglottis, aryepiglottic folds, arytenoids, ventricles, and false vocal cords.
    Glottis: true vocal cords, infraglottis (free edge of true vocal cord to within 5 mm inferior), and mucosa of the anterior and posterior commissures.
    Subglottis: lower border of glottis to inferior border of cricoid cartilage.

  - Intrinsic muscles of the larynx are innervated by recurrent laryngeal nerve, except for cricothyroid muscle, which is innervated by the superior laryngeal nerve and is solely responsible for producing tension of the vocal cords.

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- Lymph node drainage:
  - Glottis has sparse lymphatic supply, and thus rarely spreads to lymph nodes (T1–2: <5%; T3–4: ~20%). If involved, typically bilateral levels II, III, IV, and VI.
  - Supraglottis has richer lymphatic supply and is thus more common to have nodal metastases at presentation (~50%); drains to bilateral levels II, III, IV, and VI.
  - Subglottis typically drains to levels II, III, IV, VI, and VII.
- Incidence of distant metastases is low (≤10%); common sites include lungs>liver>bone.
- Medical workup:
  - H&P, physical exam requires thorough cervical lymph node assessment.
  - Fiber-optic nasopharyngolaryngoscopy.
  - Biopsy and basic lab work (CBC, metabolic panel, liver function tests, TSH).
  - Dental and baseline speech/swallowing evaluations.
- Imaging workup:
  - CT neck w/wo contrast: look for enhancing mass at level of laryngeal sides (supraglottis), true vocal fold (glottis), or cricoid cartilage (subglottis).
  - CT chest w/wo contrast.
  - Additionally may consider PET/CT: look for primary and nodal metastases with FDG avidity.
- Treatment strategies: radiation therapy alone or surgery for early-stage, T1–2 tumors. Radiation therapy with concurrent chemotherapy or surgical resection for locally advanced T3 tumors. Surgical resection recommended for advanced T4 tumors.

11.2 AJCC Staging (AJCC 8th Ed., 2017)

Primary tumor (T)	
Larynx	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of the base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

Primary tumor (T)	
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: Postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility T1a: Tumor limited to one vocal cord T1b: Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invasion of paraglottic space and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional lymph nodes (N)[a]	
NX	No regional lymph node metastasis can be assessed
N0	No regional lymph node metastasis

Primary tumor (T)	
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension and ENE (−)
N2	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−) or Metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−) or Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node, larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−); or Metastasis in any lymph node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node, larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any lymph node(s) with clinically overt ENE(+)
[a]Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+)	
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
Stage grouping	
0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0 T1-3 N1 M0
IVA	T4a N0-2 M0 T1-3 N2 M0
IVB	T4b, any N, M0 Any T, N3, M0
IVC	Any T, any N, M1

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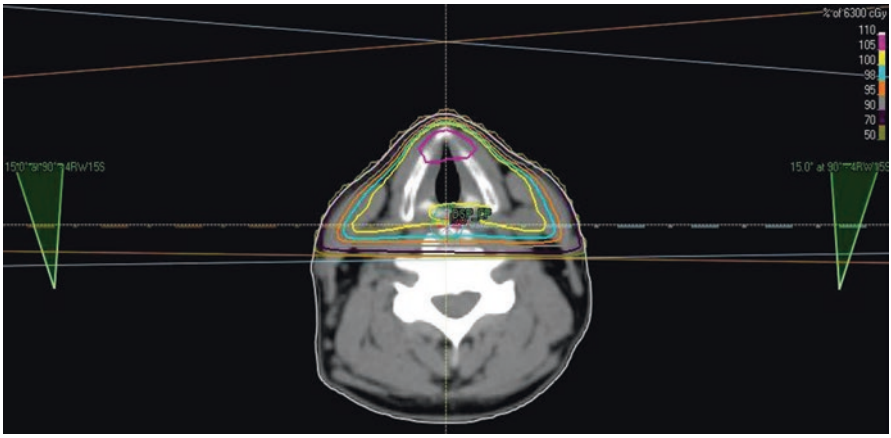
11.3 Patient Selection for Hypofractionation Treatment

- T1–2 tumors of the glottic larynx

11.4 Treatment Planning

Simulation instructions	– Supine, immobilized with head and neck thermoplastic mask – Head/neck hyperextended – Autotraction straps to immobilize and pull shoulders down – Opposed lateral fields typically utilized – 3DCRT plan utilized to minimize normal tissue injury – Daily bolus—Over anterior larynx in thin neck patients and anterior commissure involvement to ensure adequate coverage. 2 cm wide × 5 cm long
Image guidance	– At least weekly portal imaging – Daily clinical verification of light field in the treatment room (palpate thyroid notch = superior field border, cricoid = inferior field border, thyroid alae = posterior field border)
Margins	– T1 tumors: 4 × 4 cm or 5 × 5 cm (preferred) field – T2 tumors: 5 × 5 cm (preferred) or 6 × 6 cm field – Borders: *Superior*: Bottom/mid-thyroid notch (top of notch if there is supraglottic extension) *Inferior*: Bottom of cricoid cartilage (1 cm inferior to cricoid cartilage if subglottic extension) *Posterior*: Anterior edge of vertebral body (split vertebral body if there is posterior commissure involvement) *Anterior*: 2 cm skin flash IMRT (unproven benefit) – CTV = entire larynx (includes anterior/posterior commissures, arytenoids from top of thyroid cartilage to inferior cricoid cartilage) – PTV = CTV + 0–10 mm (wide range in literature)

Light field images showing treatment field.



Plan design showing isodose lines.

11.5 Common Dose/Fractionation Schemes

Dose/Fx	Number of fx	Total dose	Notes
2.25 Gy	28	63 Gy	T1 tumors; treat daily [3–6]
2.25 Gy	29	65.25 Gy	T2 tumors; treat daily [3, 5, 6]

11.6 Normal Tissue Tolerances

- The main relevant dose constraint is to ensure that overall plan is not too hot (goal of 105% of the prescription with a max of 110%) to minimize the risk for laryngeal edema and necrosis.
- Several studies have reported increased risk of carotid artery-related adverse events after radiation therapy.
  - We interpret the studies on cerebrovascular disease to show that the risk of moderate and severe carotid complications from neck radiotherapy is so low that very few patients will end up with a better clinical outcome as a result of changing the radiotherapy (e.g., using carotid-sparing IMRT).
  - There is no specific study associating dose volume data with clinical outcomes of carotid artery stenosis/stroke.

11.7 Patient Management

(a) No premedications required.

- Tobacco cessation important—smoking during treatment increases acute toxicities and decreases local control.

(b) Toxicity

- Acute:
  - Skin/soft tissue (dermatitis, mucositis, dysphagia, laryngeal edema)

    Emollients (aquaphor, calendula): Remove 4 h prior to RT treatment.
    Baking soda/salt rinses up to 12×/day.
    Oral solutions (first BLM, magic mouthwash): Use TID prior to meals.
    Pain medication (fentanyl patch 25–100 mcg q72 h, oxycodone 5–20 mg q4–6 h).

  - Late:

    Skin/soft tissue (fibrosis, laryngeal edema, fistula) (<10%)
    Hypothyroidism (20–30%)
    Osteoradionecrosis (ORN) (<5%)
    Carotid blowout (1.7%)

    ****For above late complications, recommend referral to appropriate specialty for management (ENT, surgery, PCP, etc.).*

11.8 Follow-Up

- H&P, fiber-optic nasopharyngoscopy every 3 months for first 2 years, q6 months years 3–5, then annually.
- Chest CT w/o contrast, TSH q6–12 months.

11.9 Relevant Literature

Study	Patients	Treatment	Median f/u	Outcomes
Randomized controlled trials				
Moon (2014) [3]	*n* = 156, T1–2 N0 glottic SCC RT alone conventional vs. hypofractionation	1) 2 Gy × 33–35 fx 2) 2.25 Gy × 28–30 fx Opposed laterals	67 months	**2.25Gy/fx**: 94% 5-year LC 88% 5-year LPFS **2Gy/fx**: 89% 5-year LC 77% 5-year LPFS Toxicity: No difference between arms

Study	Patients	Treatment	Median f/u	Outcomes
Yamazaki (2006) [4]	*n* = 180, T1 glottic SCC RT alone conventional vs. hypofractionation	1) 2 Gy × 30–33 fx 2) 2.25 Gy × 25–28 fx	64 months	**2.25Gy/fx**: 92% 5-year LC 100% 5-year CSS **2Gy/fx**: 77% 5-year LC 97% 5-year CSS Toxicity: No difference between arms
Retrospective studies				
Chera (2010) [5]	*n* = 585, T1/2 N0 glottic SCC Retrospective RT alone, hypofractionated	2.25 Gy × 28–29 fx (T2 lesions offered 1.2 Gy/fx BID) Opposed laterals	144 months	**Local control**: 93% 10 years (T1a) 91% 10 years (T1b) 80% 10 years (T2a) 67% 10 years (T2b) **Overall survival**: 62% 10 years (T1a) 57% 10 years (T1b) 51% 10 years (T2a) 49% 10 years (T2b) Toxicity: 10 pts. with G4/5; one fatal RT-induced carotid artery angiosarcoma
Gowda (2003) [7]	*n* = 200, T1 N0 glottic SCC Retrospective RT alone, hypofractionated	3.12 or 3.28 Gy × 16 fx Opposed laterals	72 months	93% 5-year LC 80% 5-year OS Toxicity: No severe acute toxicity; 1 pt. with severe late toxicity (continued to smoke following tx)
Le (1997) [6]	*n* = 398, T1–2 glottic SCC RT alone, opposed laterals	Total dose: T1 63Gy, T2 65Gy Fx sizes: <1.8 Gy 1.8–1.99 Gy 2–2.24 Gy ≥2.25 Gy	116 months	**T1 tumors** ≥ 2.25Gy/fx: 94% 5-year LC <1.8Gy/fx: 79% 5-year LC **T2 tumors** ≥ 2.25 Gy/fx: 100% 5-year LC <1.8Gy/fx: 44% 5-year LC

11.10 Summary

Hypofractionation has been shown to improve LC versus standard fractionation schedules with low rates of severe complications. Currently there is no data on the use of stereotactic ablative doses.

11.11 UNC Experience

Our standard is to treat with 5 × 5 cm opposed lateral fields with daily clinical verification of the light field by the physician. Our interpretation of the published literature on the potential increase in carotid artery-related adverse events is that the risk, if any, is small. We do not treat with carotid-sparing EBRT.

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