Role of chemo-radiotherapy in HPV Negative Oropharyngeal cancers

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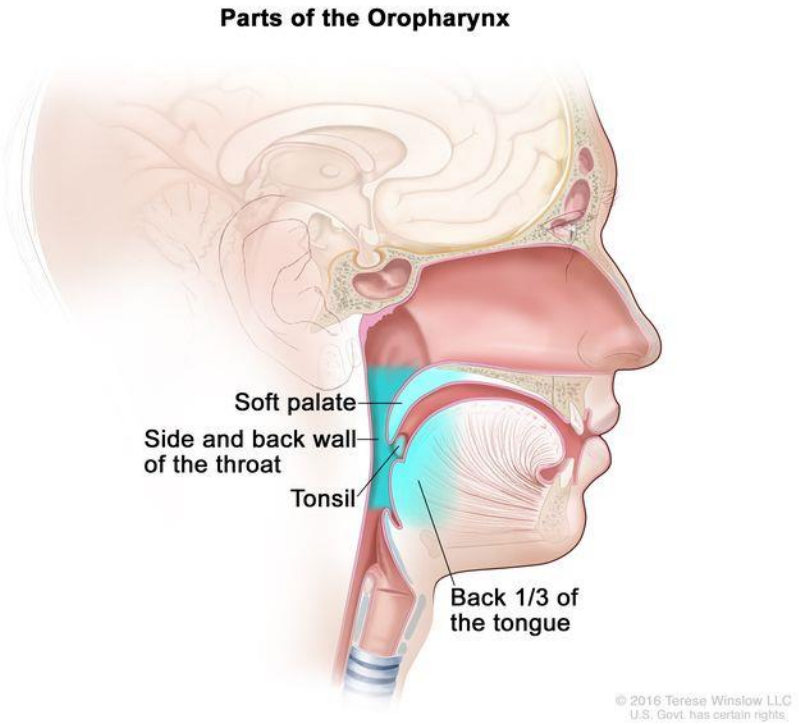
Introduction

* Head & Neck cancer has decreased concomitantly with declining tobacco and smoking rates, oropharynx incidence has significantly increased in recent years. The proportion of OPX caused by HPV has grown from 16% in the early 1980s to nearly 80%, and is expected to exceed Cancer Cervix.

* Expert Rev Anticancer Ther. 2015 Jan; 15(1): 35–49.

* Estimated new cases of oropharyngeal cancer in USA
* New cases: 54,000.
* Deaths: 11,230.
* Oropharyngeal cancer is increasing in incidence, which is attributed to the rise in human papillomavirus (HPV)-associated oropharyngeal cancer; men are more than twice as likely as women to have oropharyngeal cancer and occurs in 5^{th} and 6^{th} decade of life.



* The oropharynx is divided into the following parts:
* Base of the tongue, which includes the pharyngoepiglottic folds and the glossoepiglottic folds.
* Vallecula.
* Tonsillar region, which includes the fossa and the anterior and posterior tonsillar pillars.
* Soft palate, which includes the uvula.
* Posterior and lateral pharyngeal walls.

Retro Pharyngeal Node Involvement

* The incidence of radiographic retropharyngeal node involvement was 10% and was highest for the pharyngeal wall (23%) and lowest for the base of the tongue (6%).
* Retropharyngeal lymph node involvement was associated with inferior 5-year local control and inferior recurrence-free survival, distant metastases–free survival, and overall survival on multivariate analysis.

Risk factors

* Smoking history of more than 10 pack years and tobacco use.
* Heavy alcohol use.
* HPV infection, especially HPV type 16, also known as HPV-16.
* Personal history of head and neck cancer.
* Betel quid chewing.

* Smoking and alcohol consumption after treatment are associated with the development of second primary tumors of the aerodigestive tract. Patients may need counseling to discontinue smoking and alcohol consumption.

* The process of field cancerization may be responsible for the multiple, synchronous, primary SCCs in oropharyngeal cancer and that are associated with a smoking history.
* Originally described in 1953, the concept of field cancerization holds that tumors develop in a multifocal fashion within a field of tissue chronically exposed to carcinogens. Molecular studies that detect genetic alterations in histologically normal tissue from high-risk individuals have provided strong support for the concept of field cancerization.

Symptoms

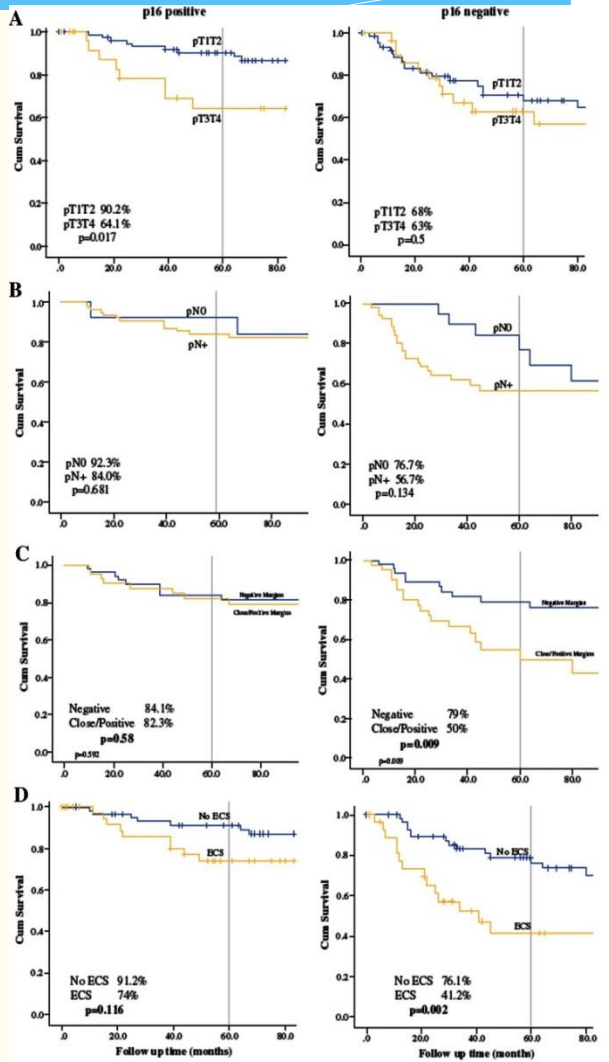
* A sore throat that does not go away.
* Trouble swallowing.
* Trouble opening the mouth fully.
* Trouble moving the tongue.
* Weight loss for no known reason.
* Ear pain.
* A lump in the back of the mouth, throat, or neck.
* A white patch on the tongue or lining of the mouth that does not go away.
* Coughing up blood.

Prognostic factors

* HPV status.
* Smoking history (pack-year smoking history of 10 or more years).
* Tumor stage and nodal status.

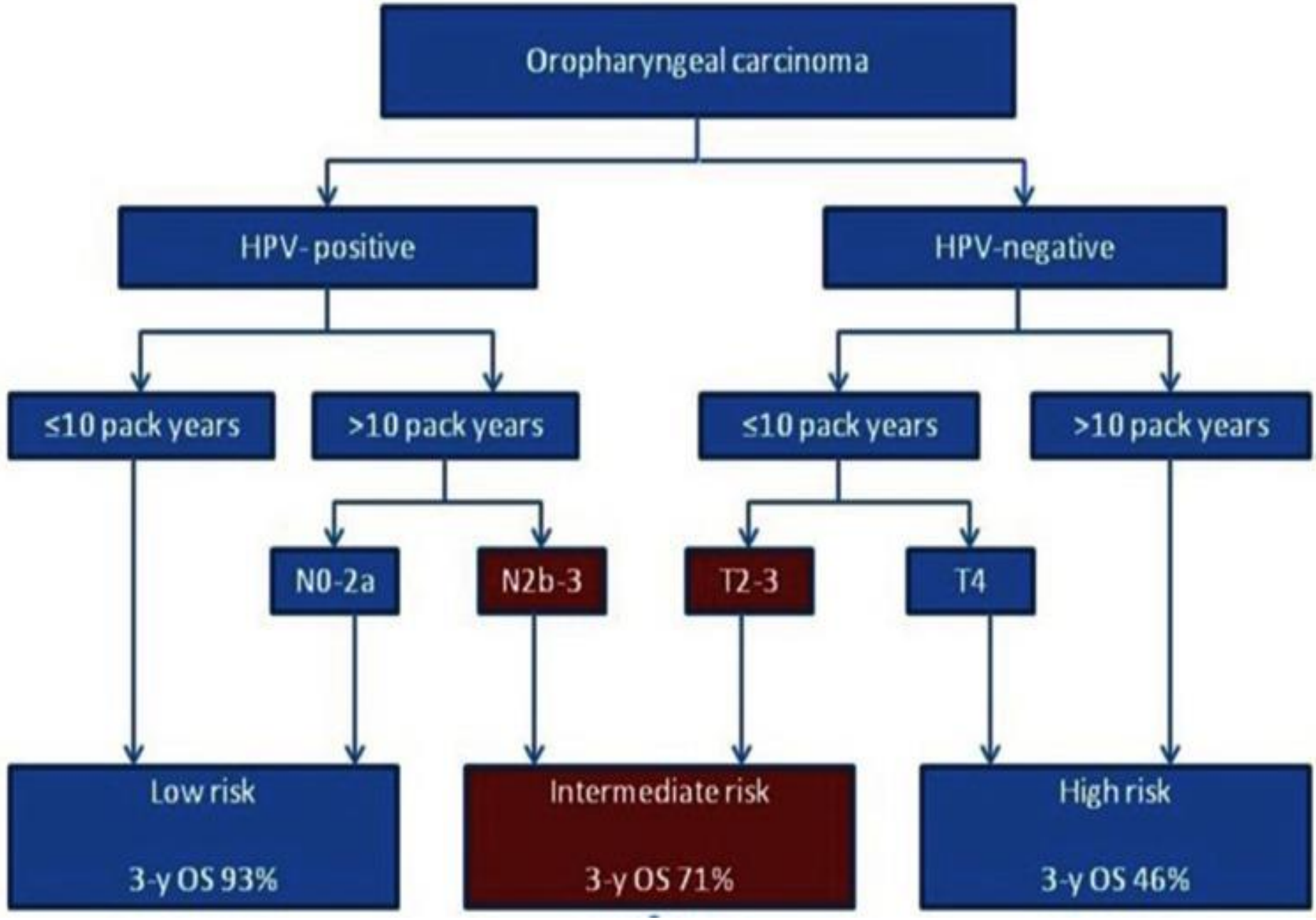
Multivariate analysis showing factors predictive of OS, DSS, and RFS in p16-negative patients that received initial management with surgery at Memorial Sloan-Kettering Cancer

Predictive factor	Outcome	HPV negative Hazard ratio (95% CI)	*P* value
Age > 60 years	OS	1.7 (1.0–3.1)	0.071[a]
Lymphovascular invasion	OS	2.1 (1.2–3.8)	0.010[a]
	DSS	2.1 (0.9–5.0)	0.082
	RFS	2.7 (1.3–5.8)	0.010
Close/positive margin	OS	2.1 (1.1–3.9)	0.020[a]
	DSS	3.2 (1.3–7.9)	0.015[a]
	RFS	1.6 (0.7–3.4)	0.234
N-positive neck	DSS	0.5 (0.1–1.9)	0.300
Extra-capsular extension	OS	1.7 (1.0–2.9)	0.053[a]
	DSS	4.7 (1.3–17.1)	0.019[a]
	RFS	1.5 (0.8–3.1)	0.244



Evaluation

* Physical exam and health history:
* Neurological exam:
* Biopsy
* Endoscopy
* Laryngoscopy:
* CT scan
* PET CT Scan
* HPV


Oropharyngeal carcinoma
HPV- positive
HPV-negative
≤10 pack years
>10 pack years
≤10 pack years
>10 pack years
N0-2a
N2b-3
T2-3
T4
Low risk
3-y OS 93%
Intermediate risk
3-y OS 71%
High risk
3-y OS 46%

* Updated staging system for oropharyngeal cancer now also includes the p16 (HPV) status of the tumor. Treatment strategies are slowly changing with this new staging System.

Treatment for oropharyngeal cancer is based on

* The stage (extent)
* HPV infection (p16-positive),
* Smoking History

* The trend toward greater emphasis on organ preservation is occurring largely in response to the results of several randomized trials that have demonstrated better survival and local control in patients who were treated with CRT compared with those treated with radiotherapy alone or with open surgical approaches followed by adjuvant radiotherapy.

* A meta-analysis by Parsons et al found that patients with oropharyngeal carcinoma experienced similar local control and overall survival rates regardless of whether they were treated initially with surgery or radiotherapy, although they did experience significantly more complications with the former.
* As a result definitive CRT was adopted as the standard treatment at many centers.

* Data have emerged showing that patients with human papillomavirus (HPV)-negative oropharyngeal cancer experience significantly worse outcomes than do their HPV-positive counterparts.
* Patients with HPV-negative cancer have also frequently reported higher rates of tobacco smoking and alcohol use than HPV-positive patients have.

* Preclinical studies have found that HPV-negative head and neck squamous cell carcinoma cell lines exhibit greater radioresistance than do HPV-positive cell lines.
* This effect might be mediated by increased epidermal growth factor receptor (EGFR) expression.
* It has been hypothesized that cells with greater EGFR expression repair radiotherapy-induced DNA damage more proficiently, which results in a greater risk of local recurrence.

TREATMENT

* Stage 0 (carcinoma in situ) oropharyngeal cancer

* Although cancer in this stage is on the surface layer and has not started to grow into deeper layers of tissue, it can do so if not treated. The usual treatment is surgery (usually Mohs surgery, surgical stripping, or thin resection) to remove the top layers of tissue along with a small margin (edge) of normal tissue. Close follow-up is important to watch for any signs that the cancer has come back. Carcinoma in situ that keeps coming back after surgery may need to be treated with radiation therapy.

Early-stage oropharyngeal cancer

* **T1 and T2**
* **Radiation therapy** aimed at Primary and the draining lymph node (66-70 Gy)
* **Surgery** – Excision of primary along with lymph node dissection. Post Operative Chemo radiotherapy can be advised as per extent of tumor.

Locally advanced oropharyngeal cancer

* T3 and T4
* (p16/HPV-positive or p16/HPV-negative) are treated with chemoradiation.
* Once weekly or Three weekly chemo with Cisplatin
* Radiotherapy to primary and draining lymph nodes (66-70Gy)
* If Operable Surgery followed by ChemoRadiation can be given.

Metastatic oropharyngeal cancer

* These are usually treated with chemo, cetuximab, or both.
* Immunotherapy alone or with chemo, might be another option.
* Treatment of the Primary may be done with Short term Radiotherapy which may help relieve symptoms.

Recurrent oropharyngeal cancer

* Treatment options for recurrent cancers depend on the location and size of the cancer, what treatments have already been used, and the person's general health. Because these cancers can be hard to treat, clinical trials of newer treatments may be a good option for some people.


Thank you