MULTIMODULAR TREATMENT IN HEAD AND NECK SQUAMOUS CELL CARCINOMA (HNSCC)

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Attikon University Hospital
Athens, Greece
LEARNING OBJECTIVES

After reading and reviewing this material, the participant should be able to:

Understand the new staging system (AJCC 8th Edition) for HNSCC

Evaluate the role of induction, definitive concurrent chemotherapy and sequential therapy in locally advanced HNSCC

Describe organ preservation strategies

Discuss the common indications for postoperative chemoradiation

Understand HPV-associated oropharyngeal cancers
OUTLINE

Introduction
Epidemiology
Oropharyngeal cancer
Staging (AJCC 8th Edition)
The role of chemotherapy in locally-advanced disease
Indications of postoperative chemoradiation
Bioradiotherapy with cetuximab
Deintensification strategies for HPV+ OPC
Immunotherapy for HNSCC
Surgical management of the neck
MANY SUBSITES

Heterogeneous group of tumours of varying primary sites

95% are HNSCC
- Oral cavity
- Oropharynx/hypopharynx
- Larynx
- Nasopharynx

Other anatomical sites
- Paranasal sinuses
- Salivary glands
- Lip

Image courtesy of Massachusetts General Hospital Cancer Center
Traditionally, tobacco and alcohol use account for the majority of HNSCC.

A growing proportion of oropharyngeal squamous cell carcinomas is caused by high-risk human papillomaviruses (HPV), especially HPV16.
EPIDEMIOLOGY
INCIDENCE IN THE USA

In 2019, 53,000 new cases of oral cavity and pharynx cancer and 10,860 deaths are expected to occur in the United States

5-year relative survival, 2008-2014
by stage at diagnosis, for oral cavity and pharynx
Among cases diagnosed from 2008 to 2014, followed through 2015

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All stages combined</td>
<td>65%</td>
</tr>
<tr>
<td>Localized</td>
<td>86%</td>
</tr>
<tr>
<td>Regional</td>
<td>63%</td>
</tr>
<tr>
<td>Distant</td>
<td>36%</td>
</tr>
</tbody>
</table>

Data Sources: Surveillance, Epidemiology, and End Results (SEER) 18 registries, National Cancer Institute, 2018
© 2020 American Cancer Society

## Estimated new cancer cases and deaths by sex, United States, 2020

<table>
<thead>
<tr>
<th></th>
<th>Estimated new cases</th>
<th>Estimated deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Both sexes</td>
<td>Male</td>
</tr>
<tr>
<td>All sites</td>
<td>1,806,590</td>
<td>893,660</td>
</tr>
<tr>
<td>Oral cavity and pharynx</td>
<td>53,260</td>
<td>38,380</td>
</tr>
<tr>
<td>Tongue</td>
<td>17,660</td>
<td>12,960</td>
</tr>
<tr>
<td>Mouth</td>
<td>14,320</td>
<td>8,430</td>
</tr>
<tr>
<td>Pharynx</td>
<td>17,950</td>
<td>14,630</td>
</tr>
<tr>
<td>Other oral cavity</td>
<td>3,330</td>
<td>2,360</td>
</tr>
</tbody>
</table>

### Stage distribution (US, 2009–2015)

<table>
<thead>
<tr>
<th>Stage</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>29</td>
<td>19</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>18</td>
<td>20</td>
<td>18</td>
</tr>
</tbody>
</table>

### 5-year relative survival

<table>
<thead>
<tr>
<th>Age</th>
<th>Series1</th>
<th>Series2</th>
<th>Series3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84</td>
<td>85</td>
<td>78</td>
</tr>
<tr>
<td>5</td>
<td>66</td>
<td>67</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>39</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>67</td>
<td>48</td>
</tr>
</tbody>
</table>
Lip and oral cavity cancer incidence rates highest in Melanesia and lowest in Western Africa, partly reflecting varying data quality worldwide.
Age standardised (World) incidence and mortality rates, oropharynx

- Incidence rates of oropharyngeal cancer highest in Western Europe and lowest in Western Africa

OROPHARYNGEAL CANCER (OPC)
OROPHARYNGEAL CANCER DISEASE VARIANTS: TOBACCO-RELATED, HPV-RELATED AND MIXED

Normal-appearing mucosa already harbours early genetic changes

EPIDEMIC OF HPV-ASSOCIATED OPC

Incidence rates for overall oropharyngeal cancer, HPV-positive oropharyngeal cancer, and HPV-negative oropharyngeal cancer from 1988 to 2004 in Hawaii, Iowa, and Los Angeles¹

Estimated age-standardised incidence of human papillomavirus (HPV)-positive and HPV-negative tonsillar cancer squamous cell carcinoma cases per 100,000 person-years, Stockholm, Sweden, 1970-2006²

Error bars indicate 95% CI.


PREVALENCE OF HPV IN OPC IS INCREASING, REGARDLESS OF SEX OR RACE
The relative survival for HPV-positive patient is independent of therapy, as long as this therapy is within the current standard of care.

Risk of death is consistently less than 60% that of HPV-negative cancers across studies.

The absolute survival difference is consistently higher than 30%.
# 7TH EDITION TNM

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>TisN0M0</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1N0M0</td>
</tr>
<tr>
<td>Stage II</td>
<td>T2N0M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3N0, T1-3N1, M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a N0-2, M0, T1-3N2, M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>Any T, N3, M0, T4b, Any N, M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>M1, any T or N</td>
</tr>
</tbody>
</table>

- T and N stages vary by anatomic site
- ≥N2 or T4 tumours → locoregionally advanced (Stage IV)
- Typically T1: ≤2 cm, T2: 2–4 cm, T3: ≥4 cm, T4: invades adj. structures
- N1: single LN ≤3 cm, N2: LN >3 cm but not >6 cm
- N3 >6 cm

TNM: tumour nodes metastases.
Suitable for tobacco-related OPC, not HPV+ disease

The 7th Edition lost the ability to differentiate between OPC stages in HPV era

HPV+OPC by 7th Edition TNM stage

Overall survival (%)

THE 7TH EDITION TNM IS BASED ON SMOKING-RELATED OPC

An Evolution in Demographics, Treatment, and Outcomes of Oropharyngeal Cancer at a Major Cancer Center

A Staging System in Need of Repair

Kristina R. Dahlstrom, MS; Gabriel Calzada, MD; Jennifer D. Hanby, MD; Adam S. Gerden, MD; Bonnie S. Glisson, MD; Guojun Li, MD, PhD; Dianna B. Roberts, PhD; Randal S. Weber, MD; and Erich M. Sturgis, MD, MPH

Stage I-II

It does not consider HPV status

MDACC Data (3891 OPC), 1955–2004, no consideration of tumour HPV status

Good performance for 40 years (1955–1994); inadequate performance in the recent decades

CHANGING PROGNOSTIC SIGNIFICANCE OF TUMOUR STAGE AND NODAL STAGE

In patients with squamous cell carcinoma of the oropharynx in the HPV era

SEER Database (13,328 OPC), 1997–2008, no consideration of tumour HPV status

- T stage retained a linear relationship with head and neck cancer specific mortality (HNCSM)
- The effect of N stage on HNCSM declined over time
AJCC 8TH EDITION TNM
Oral cavity cancers now incorporate depth of invasion as a criterion for T designation

Oropharyngeal cancers are now distinguished by the immunohistochemical stain, p16, into those that are associated with high-risk HPV and those that are not

A novel staging system has been introduced for HPV-associated HNSCC

Pathologic staging of HPV-associated oropharyngeal cancers differs from clinical staging by exclusively using node numbers

All sites except nasopharyngeal carcinoma and high-risk HPV OPC will now include the important parameter of extranodal extension

TNM: tumour nodes metastases.
P16-NEGATIVE OPC STAGING

Unchanged, except $T_0$ removed

N classification unchanged with the exception of extranodal extension (ENE)

N3 divided into N3a and N3b based on the absence or presence of ENE, respectively

M classification unchanged
### T CLASSIFICATION P16-NEGATIVE OPC

<table>
<thead>
<tr>
<th>T Category</th>
<th>T Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumour cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or smaller in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour larger than 2 cm but not larger than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced or very advanced local disease</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced local disease; tumour invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible(^a)</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced local disease; tumour invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery</td>
</tr>
</tbody>
</table>

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\(^a\) Mucosal extension to lingual surface of epiglottis from primary tumours of the base of the tongue and vallecula does not constitute invasion of the larynx.

Similar to prior staging with the addition of extranodal extension

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2a</td>
<td>Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2b</td>
<td>Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N2c</td>
<td>Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in lymph node larger than 6 cm in greatest dimension and ENE-negative; or metastasis in any lymph node(s) and clinically overt ENE-positive</td>
</tr>
<tr>
<td>N3a</td>
<td>Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative</td>
</tr>
<tr>
<td>N3b</td>
<td>Metastasis in any node(s) and clinically overt ENE-positive</td>
</tr>
</tbody>
</table>
# OVERALL STAGE P16 NEGATIVE OPC

<table>
<thead>
<tr>
<th>T Category</th>
<th>N0</th>
<th>N1</th>
<th>N2a,b,c</th>
<th>N3a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>I</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T2</td>
<td>II</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T3</td>
<td>III</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T4a</td>
<td>IVA</td>
<td>IVA</td>
<td>IVA</td>
<td>IVB</td>
</tr>
<tr>
<td>T4b</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
<td>IVB</td>
</tr>
</tbody>
</table>
HPV POSITIVE OPC STAGING

T classification
- Largely unchanged except:
  - Tis removed
  - T4b removed

N classification
- Difference between clinical and pathologic staging
- Clinical staging based on laterality and size of nodes
- Pathologic staging based on number of nodes
- ENE not included

Overall stage: major change
- Stage IV reserved for M1 disease
**Re-termed ICON-S N**

<table>
<thead>
<tr>
<th>Gross lymph node</th>
<th>None</th>
<th>Unilateral neck, &lt;6 cm</th>
<th>Bilateral or contralateral neck, &lt;6 cm</th>
<th>&gt;6 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N0</td>
<td>N1, N2a, N2b</td>
<td>N2c, N3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ICON-S N category</th>
<th>7th edition TNM N category</th>
<th>ICON-S ST category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T1</td>
<td>T2</td>
</tr>
<tr>
<td>N0</td>
<td>1:00 (n=19)</td>
<td>1:20 (0.25-5.65), n=71</td>
</tr>
<tr>
<td>N1</td>
<td>1:57 (0.38-6.54), n=334</td>
<td>2:84 (0.69-14.60), n=478</td>
</tr>
<tr>
<td>N2</td>
<td>2:13 (0.44-10.31), n=61</td>
<td>3:51 (0.81-15.12), n=129</td>
</tr>
<tr>
<td>N3</td>
<td>8:85 (1.07-39.85), n=30</td>
<td>4:88 (1.03-23.19), n=38</td>
</tr>
</tbody>
</table>

Data are hazard ratio (95% CI), number of patients. Hazard ratios are adjusted for age, smoking pack-years, and use of cytotoxic chemotherapy (yes vs no). ICON-S=International Collaboration on Oropharyngeal cancer Network for Staging. ICON-S-7 ST definitions are unchanged from the 7th edition TNM classification, except there is no subdivision within T4 because survival was identical between T4a and T4b.

**Table S: Re-termed ICON-S and N categories and corresponding hazard ratios for risk of death within each T category**

<table>
<thead>
<tr>
<th>ICON-S stage classification</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


*ICON-S ‘N1’ = 7th edition N1 + N2a + N2b

‘N0’ remains distinct according to TNM convention
HPV+ OS BY T- AND N-CATEGORY
(MULTI-INSTITUTIONAL DATASET – N=1907 HPV+ OPC)


- HPV(+) T4a and T4b behave similarly
- HPV(+) N2c and N3 are clinically important as they have significant inferior OS compared to N0-N2b
## T STAGING HPV+ OPC

<table>
<thead>
<tr>
<th>T Category</th>
<th>T Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No primary identified</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or smaller in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour larger than 2 cm but not larger than 4 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis</td>
</tr>
<tr>
<td>T4</td>
<td>Moderately advanced local disease; tumour invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond</td>
</tr>
</tbody>
</table>
Number of lymph nodes is no longer important when radiation is the main treatment modality
ENE is not included

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>One or more ipsilateral lymph nodes, none larger than 6 cm</td>
</tr>
<tr>
<td>N2</td>
<td>Contralateral or bilateral lymph nodes, none larger than 6 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Lymph node(s) larger than 6 cm</td>
</tr>
</tbody>
</table>
# Pathologic N Classification for P16+ OPC

<table>
<thead>
<tr>
<th>N Category</th>
<th>N Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>pN0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>pN1</td>
<td>Metastasis in 4 or fewer lymph nodes</td>
</tr>
<tr>
<td>pN2</td>
<td>Metastasis in more than 4 lymph nodes</td>
</tr>
</tbody>
</table>
CHANGES BETWEEN 7TH AND 8TH EDITION TNM

Migration Stage III/IV to I: About 50% HPV+ OPC

7th edition
T1 N2b M0 = Stage IVa

8th edition
T1 N1 M0 = Stage I

7th edition
T4a N2c M0 = Stage IVa

8th edition
T4 N2 M0 = Stage III
THE ROLE OF CHEMOTHERAPY IN LOCALLY-ADVANCED DISEASE
META-ANALYSIS OF CHEMOTHERAPY IN HNC (MACH-NC)

63 randomised trials (1965–1993)
N=10,717 patients with SCC of the oropharynx, oral cavity, larynx, or hypopharynx
Comparison of locoregional treatment with and without chemotherapy
Median follow-up: 6 years
Overall benefit 4% at 5 years (32% vs. 36%)

<table>
<thead>
<tr>
<th>Trials</th>
<th>n</th>
<th>RR</th>
<th>P-value</th>
<th>Absolute benefit (5 years), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>1854</td>
<td>0.98</td>
<td>NS</td>
</tr>
<tr>
<td>Induction</td>
<td>31</td>
<td>5245</td>
<td>0.95</td>
<td>NS</td>
</tr>
<tr>
<td>Concomitant</td>
<td>26</td>
<td>3727</td>
<td>0.81</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

HNC, head and neck cancer; MACH-NC, Meta-analysis of Chemotherapy in Head and Neck Cancer; SCC, squamous cell carcinoma; ORR, overall risk reduction; RR, relative risk.
Adapted from Corey J. Langer, Clin Care Options 2010.
24 added trials – 87 studies, 16,485 patients

MACH-HN I: 8% absolute benefit concurrent; no significant effect of IC

No significant difference (p=0.19) was seen between monochemotherapy (HR 0.84) and polychemotherapy (HR 0.78)

In the monochemotherapy group, the effect of chemotherapy was significantly higher (p=0.006) with platin than with other types of monochemotherapies

Age matters

- Younger than 50 years of age: 24% increased survival
- Older than 70 years of age: 3% increased survival

MACH-NC, Meta-Analysis of Chemotherapy in Head and Neck Cancer; IC, induction chemotherapy.
Adapted from Corey J. Langer, Clin Care Options 2010.
PLUSES AND MINUSES OF CHEMORADIATION

Improves loco-regional control
- Facilitates organ preservation
- Beneficial impact on survival

Doubles the rate of severe acute mucositis

Use may be excessive based on stage

Long-term functional deficits in speech, swallowing, mobility

Adapted from Corey J. Langer, Clin Care Options 2010.
## RANDOMISED TRIALS OF INDUCTION PF ± TAXANE

<table>
<thead>
<tr>
<th>Study</th>
<th>Eligibility</th>
<th>N</th>
<th>T + PF CR/PR, n/N (%)</th>
<th>PF CR/PR, n/N (%)</th>
<th>TPF/PF PFS, Mos</th>
<th>TPF/PF OS, Mos</th>
<th>p-value (HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hitt JCO 2005</td>
<td>Stage III-IV</td>
<td>382</td>
<td>33/47 (80)</td>
<td>14/54 (68)</td>
<td>20</td>
<td>12</td>
<td>0.035 (0.67)</td>
</tr>
<tr>
<td>TAX 323 NEJM 2007</td>
<td>Unresectable</td>
<td>358</td>
<td>(68)</td>
<td>(54)</td>
<td>11</td>
<td>8</td>
<td>0.005 (0.71)</td>
</tr>
<tr>
<td>Gortec ASCO 2006</td>
<td>L/HP II-IV</td>
<td>205</td>
<td>43/39 (82)</td>
<td>30/30 (60)</td>
<td>LP:</td>
<td></td>
<td>0.036</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>63%/41%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAX 324 NEJM 2007</td>
<td>III-IV</td>
<td>501</td>
<td>17/55 (72)</td>
<td>15/49 (64)</td>
<td>2-yr PFS:</td>
<td></td>
<td>0.006 (0.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53%/42%</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 yrs: 62%/48%</td>
<td></td>
</tr>
</tbody>
</table>

CR, complete response; HP, hypopharynx; HR, hazard ratio; L, larynx; LP, larynx preservation; OS, overall survival; PF, cisplatin, 5-fluorouracil; PFS, progression-free survival; PR, partial response; T, docetaxel; TPF, docetaxel, cisplatin, 5-fluorouracil.

Adapted from Corey J. Langer, Clin Care Options 2010.
RANDOMISED TRIALS OF SEQUENTIAL THERAPY*

Definitive chemo RT ± induction

*All powered to show survival difference of 10% to 15%.

Carbo, carboplatin; CB, concomitant boost; chemoRT, chemoradiation therapy; DFCI, Dana-Farber Cancer Institute; RT, radiation therapy; TPF, docetaxel, cisplatin, 5-fluorouracil. DHFX, docetaxel, fluorouracil, and hydroxyurea.

Adapted from Corey J. Langer, Clin Care Options 2010.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Eligibility</th>
<th>Target N*</th>
<th>Control Tx</th>
<th>Exp Tx</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>DeCIDE U Chicago</td>
<td>N2-3</td>
<td>400 / 285</td>
<td>DHFX</td>
<td>TPF x 2 DHFX</td>
<td>NS</td>
</tr>
<tr>
<td>Paradigm DFCI</td>
<td>Stages III-IV</td>
<td>300 / 145</td>
<td>Cisplatin CB-RT</td>
<td>TPF x 3 Carbo-RT or D-CB-RT</td>
<td>NS</td>
</tr>
<tr>
<td>SWOG</td>
<td>Oropharynx</td>
<td>400</td>
<td>Cisplatin RT</td>
<td>TPF x 1-3 surgery or cisplatin-RT</td>
<td></td>
</tr>
</tbody>
</table>
RTOG 9111: LARYNX PRESERVATION TRIAL

Phase 3 larynx preservation trial: Induction chemotherapy and radiation therapy vs. concomitant chemotherapy and radiation therapy vs. radiation therapy alone


Location
1. Glottic
2. Supraglottic

T Stage
1. T2
2. T3, fixed cord
3. T3, no cord fixation
4. T4, with base of tongue ≤1 cm

N Stage
1. N0, N1
2. N2, N3

Chemotherapy
Arm 1: cisplatin 100 mg/m²/5-FU 1 gm/m²/24 hrs CVI x 120° q3w x 3
Arm 2: cisplatin 100 mg/m² Days 1, 22, 43 of RT

Arm 1: CR, PR ↔ x 3 d cycle ↔ RT
Arm 2: Radiation therapy + CDDP
Arm 3: Radiation therapy
RTOG 9111: LARYNX PRESERVATION TRIAL

The median follow-up among surviving patients, 3.8 years
Demographics: median age 59 years; 94% KPS ≥ 80; 50% N0; 68% SGL; 28% N2-3

<table>
<thead>
<tr>
<th>Arm</th>
<th>cDDP/5-FU → RT</th>
<th>RT/cDDP</th>
<th>RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled, n (evaluable)</td>
<td>180 (173)</td>
<td>182 (172)</td>
<td>185 (173)</td>
</tr>
<tr>
<td>2-yr laryngectomy FS, %</td>
<td>59</td>
<td>66</td>
<td>53</td>
</tr>
<tr>
<td>5-yr DMFS, %</td>
<td>85</td>
<td>88</td>
<td>78</td>
</tr>
<tr>
<td>5-yr DFS, %</td>
<td>38</td>
<td>36</td>
<td>27</td>
</tr>
<tr>
<td>5-yr OS, %</td>
<td>55</td>
<td>54</td>
<td>56</td>
</tr>
</tbody>
</table>

Conclusions
- RT/cDDP: statistically significant ↑ in laryngectomy-free survival (p=0.01)
- No statistically significant diff in survival

5-FU, 5-fluorouracil; cDDP, cisplatin; DFS, disease-free survival; DMFS, distant metastasis-free survival; FS, free survival; KPS, Karnofsky performance score; OS, overall survival; RT, radiation therapy; SGL, supraglottal larynx.
LONG-TERM RESULTS OF RTOG 9111

Laryngeal preservation

Laryngectomy-free survival

Overall survival

Locoregional control

P<0.001

P=0.53

P=0.02

P=0.0015

SURVIVAL

(A) and (B) according to treatment group

Limited to deaths from study cancer

Limited to deaths not caused by study cancer

P = 0.03

Conc., concomitant; ind., induction; RT, radiation therapy.
TOTAL LARYNGECTOMY AND LARYNX PRESERVATION
STRATEGIES IN PATIENTS WITH LOCALLY ADVANCED
LARYNGEAL (T3–4) CANCER

INDICATIONS FOR POSTOPERATIVE CHEMORADIATION
### ADJUVANT TRIALS: HNSCC RT ± CT (DDP)

<table>
<thead>
<tr>
<th>Trial</th>
<th>RT (Gy)</th>
<th>F/U (mos)</th>
<th>LRC (%)</th>
<th>DFS (%)</th>
<th>OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RTOG 9501</strong> †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 LN, ECE, + margins</td>
<td>n=459</td>
<td>46</td>
<td>81 vs. 70 (P=0.01)</td>
<td>33 vs. 25 (P=0.04)</td>
<td>45 vs. 38 (P=0.19)</td>
</tr>
<tr>
<td></td>
<td>(60–66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EORTC 22931</strong> ‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N2–3, ECE, + margins</td>
<td>n=350</td>
<td>60</td>
<td>82 vs. 69 (P=0.007)</td>
<td>47 vs. 36 (P=0.04)</td>
<td>53 vs. 40 (P=0.002)</td>
</tr>
<tr>
<td></td>
<td>(66)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bachaud</strong> §</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ ECE</td>
<td>n=83</td>
<td>60</td>
<td>70 vs. 55 (P=0.05)</td>
<td>45 vs. 23 (P&lt;0.02)</td>
<td>36 vs. 13 (P&lt;0.01)</td>
</tr>
<tr>
<td></td>
<td>(&gt;60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DDP, cisplatin; CT, chemotherapy; DFS, disease-free survival; ECE, extracapsular extension; F/U, follow-up; LN, lymph node; LRC, locoregional control; OS, overall survival; RT, radiation therapy; HNSSC, head and neck squamous cell carcinoma.

EORTC VS. RTOG ELIGIBILITY

EORTC

- Stage III–IV
- OP, OcW Level 4 or 5 pos. nodes
- Perineural disease
- Vascular embolisms

RTOG

- Margins+
- ECE
- 2+ pos. nodes

## Refining Adjuvant Therapy

Separate trials are currently designed for intermediate-risk and high-risk groups

<table>
<thead>
<tr>
<th>Risk stratification</th>
<th>Standard of care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>None</td>
</tr>
<tr>
<td>Low</td>
<td>56–60 Gy</td>
</tr>
<tr>
<td>Intermediate (ECE−/margin−)</td>
<td>60–66 Gy</td>
</tr>
<tr>
<td>High (ECE+/margin+)</td>
<td>60–66 Gy + cisplatin</td>
</tr>
</tbody>
</table>


Adapted from Corey J. Langer, Clin Care Options 2010.
BIORADIOTHERAPY WITH CETUXIMAB
EGFR expression linked to poorer outcome\(^1\) and reduced response to radiotherapy\(^2,3\)

<table>
<thead>
<tr>
<th>Type of tumor</th>
<th>Tumors with EGFR expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>90–100%</td>
</tr>
<tr>
<td>Colon</td>
<td>75–89%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Up to 95%</td>
</tr>
<tr>
<td>Breast</td>
<td>Up to 91%</td>
</tr>
<tr>
<td>Renal</td>
<td>Up to 90%</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Up to 80%</td>
</tr>
<tr>
<td>Ovary</td>
<td>Up to 77%</td>
</tr>
<tr>
<td>Bladder</td>
<td>Up to 72%</td>
</tr>
<tr>
<td>Glioma</td>
<td>Up to 63%</td>
</tr>
</tbody>
</table>

CETUXIMAB

IgG1 mAb
Chimeric protein
Specifically binds with high affinity to FcγRI (EC50 = 0.13 nM) and FcγRIIIa (EC50 = 6 nM)
Induces apoptosis and antibody dependent cellular cytotoxicity (ADCC)
Preclinical synergistic activity in combination with chemotherapy and radiotherapy
PHASE 3 STUDY DESIGN

Eligibility
Patients with locoregionally advanced squamous cell carcinoma of either the oropharynx, hypopharynx, or larynx

Stratified by
Karnofsky score: 90–100 vs. 60–80
Regional nodes: Negative vs. positive
Tumour stage: AJCC T1–3 vs. T4
RT fractionation: Concomitant boost vs. once daily vs. twice daily

Arm 1 (RT)
Radiation therapy

Arm 2 (RT + C)
Radiation therapy + cetuximab wkly

Primary endpoints: Overall survival, locoregional control

# MOST COMMON ADVERSE EVENTS

<table>
<thead>
<tr>
<th>Toxicity (%)</th>
<th>RT (n=212)</th>
<th></th>
<th>RT + C (n=208)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grades 3/4</td>
<td>All Grades</td>
<td>Grades 3/4</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>91</td>
<td>18</td>
<td>97‡</td>
<td>34‡</td>
</tr>
<tr>
<td>Mucositis/stomatitis</td>
<td>93</td>
<td>52</td>
<td>91</td>
<td>54</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>63</td>
<td>30</td>
<td>64</td>
<td>25</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>70</td>
<td>3</td>
<td>64</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue/malaise</td>
<td>50</td>
<td>5</td>
<td>52</td>
<td>4</td>
</tr>
<tr>
<td>Infusion reaction*</td>
<td>--</td>
<td>–</td>
<td>14‡</td>
<td>3†</td>
</tr>
</tbody>
</table>

*Listed for its relationship to cetuximab; †P<0.05; ‡P<0.001, Fisher's exact test.

ERBITUX + RT: OVERALL SURVIVAL
5 YEAR UPDATE

ERBITUX + RT improves significantly long-term survival, with nearly half of the patients alive at 5 years

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Dead</th>
<th>Alive</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erbitux + RT</td>
<td>211</td>
<td>110</td>
<td>101</td>
<td>49.0</td>
</tr>
<tr>
<td>RT</td>
<td>213</td>
<td>130</td>
<td>83</td>
<td>29.3</td>
</tr>
</tbody>
</table>

HR=0.73 (95% CI: 0.56, 0.95)

p=0.02

5-year OS rate

<table>
<thead>
<tr>
<th></th>
<th>ERBITUX + RT</th>
<th>RT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS rate</td>
<td>46%</td>
<td>36%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

DEINTENSIFICATION STRATEGIES FOR HPV+ OPC
TREATMENT DE-INTENSIFICATION

Aims to reduce treatment-related morbidity and improve patient quality of life without compromising treatment effectiveness

Patients with HPV+ OPSCC are younger and expected to live longer; therefore, morbidity resulting from late toxicity is a concern in these patients

Deintensification strategies include: administering radiotherapy alone, reducing the dose of radiotherapy and substituting chemotherapy with cetuximab
DE-INTENSIFYING WITH CETUXIMAB

Randomised Trials
- RTOG 1016
- De-Escalate
- TROG 12.01

Primary Endpoints
- Overall Survival
- Toxicity
- Symptom Severity
Determination of Epidermal growth factor receptor-inhibitor (cetuximab) versus Standard chemotherapy (Cisplatin) early And Late Toxicity Events in human papillomavirus-positive oropharyngeal squamous cell carcinoma

De-ESCALaTE HPV
DE-ESCALATE: TOXICITY

Same rates of serious (G3–5) and all grade toxicity

Overall severe toxicity events per patient:

Cisplatin: 4.81 (4.23 to 5.40)
Cetuximab: 4.82 (95% CI: 4.22, 5.43)

p=0.98

Mehanna H, et al. Lancet 2018;393(10166):51–60 Reproduced under the terms of the Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/; accessed July 2020).
DE-ESCALATE: SURVIVAL
Improved OS with cisplatin

![Overall survival graph](image)

2-year OS:
97.5% vs 89.4%,
p=0.001

HR=4.99, 95% CI: 1.70, 14.67

Mehanna H, et al. Lancet 2018;393(10166):51–60. Reproduced under the terms of the Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0; accessed July 2020).
DE-ESCALATE: RECURRENCE

Worse loco-regional and distant control with cetuximab

All recurrences

2 yr RR = 6.0% vs. 16.1%, p = 0.0007
HR = 3.39 (1.61 to 7.19)

Mehanna H, et al. Lancet 2018;393(10166):51–60. Reproduced under the terms of the Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/; accessed July 2020).
**RADIATION THERAPY ONCOLOGY GROUP 1016**

**Study Design**

Stage III/IV
Oropharynx
p16+

**Stratification factors:**
- cN-stage (cN0-2a vs. cN2b- cN3),
- cT-stage (T1-2 vs. T3-4) Zuprod
- Performance Status (0 vs. 1),
- smoking history (<10 py vs. >10 py)

**I: Accelerated IMRT 70 Gy/6 weeks (cisplatin 100 mg/m², d1, 22)**

**II: Accelerated IMRT 70 Gy/6 weeks (cetuximab x8)**

Radiotherapy plus cetuximab showed inferior OS and PFS compared with cisplatin chemoradiotherapy

ECOG 1308: PHASE 2 SCHEMA

**Eligibility**
- OPSCC
- resectable
- HPV ISH + and / or p16+
- Stage III, IVA

**Induction chemotherapy**
- Cisplatin 75/m² d1
- Paclitaxel 90/m² d1, 8, 15
- Cetuximab 250/m² d1, 8, 15
- Q 21 days for 3 cycles

**Concurrent chemoradiation**
- **CLINICAL CR**
  - Low dose IMRT 54 Gy / 27 fx* + Cetuximab qw
- **CLINICAL PR/SD**
  - Full dose IMRT 69.3 Gy / 33 fx* + Cetuximab qw

**IMRT margins for primary:** 1.0 to 1.5 cm around gross disease

**Nodal margin:** 1 cm margin minimum, treat entire nodal level

**Primary objective:** 2-year PFS after low-dose IMRT (stat aim: 2-year 85% or better)

IMRT, intensity modulated radiation therapy.
# ENDPOINTS: 2-YEAR PFS AND OS

<table>
<thead>
<tr>
<th>Cohort (n)</th>
<th>2-year PFS (90% CI)</th>
<th>2-year OS (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All low dose patients (62)</td>
<td>0.80 (0.70, 0.88)</td>
<td>0.93 (0.85, 0.97)</td>
</tr>
<tr>
<td>T4a (7)</td>
<td>0.54 (0.19, 0.79)</td>
<td>0.86 (0.45, 0.97)</td>
</tr>
<tr>
<td>Non-T4a (55)</td>
<td>0.84 (0.73, 0.91)</td>
<td>0.94 (0.86, 0.98)</td>
</tr>
<tr>
<td>N2c (19)</td>
<td>0.77 (0.56, 0.89)</td>
<td>0.95 (0.76, 0.99)</td>
</tr>
<tr>
<td>Non-N2c (43)</td>
<td>0.82 (0.69, 0.90)</td>
<td>0.93 (0.82, 0.97)</td>
</tr>
<tr>
<td>Smoker &gt;10 pack-years (22)</td>
<td>0.57 (0.35, 0.73)</td>
<td>0.86 (0.67, 0.94)</td>
</tr>
<tr>
<td>Smoker ≤10 pack-years (40)</td>
<td>0.92 (0.81, 0.97)</td>
<td>0.97 (0.87, 0.995)</td>
</tr>
<tr>
<td>Smoker ≤10 pack-years, &lt;T4, N2c (27)</td>
<td>0.96 (0.82, 0.99)</td>
<td>0.96 (0.82, 0.99)</td>
</tr>
<tr>
<td>All high-dose patients (15)*</td>
<td><strong>0.65 (0.41, 0.82)</strong></td>
<td><strong>0.87 (0.63, 0.96)</strong></td>
</tr>
</tbody>
</table>

*3 high-dose patients did not go on to receive RT.

IMMUNOTHERAPY FOR HNSCC
HNSCC TREATMENT

First-line Recurrent/Metastatic (R/M) setting
- EXTREME regimen of cetuximab + platinum + 5-FU is standard of care, but median OS is only about 10 months, and incidence of grade 3-4 AEs is high\(^1,2\)

Second-line R/M setting
- Historic standards of care include cetuximab, docetaxel, and methotrexate
- Monotherapy with the Programmed Death 1 (PD1) inhibitors pembrolizumab\(^3\) and nivolumab\(^4\) improved OS and had manageable safety versus investigator’s choice of cetuximab, docetaxel, or methotrexate

BLOCKING PROGRAMMED DEATH 1 (PD1) AXIS BLOCKS OR RESTORES LOSS OF T CELL ACTIVITY

PD-1/PD-L1 interaction inhibits T cell activation, attenuates effector function, maintains immune homeostasis

Tumours and surrounding cells upregulate PD-L1 in response to T cell activity

TWO PD1 CHECKPOINT INHIBITORS WERE APPROVED FOR HNSCC IN 2016

FDA Approves Pembrolizumab for Head and Neck Cancer

The Food and Drug Administration (FDA) approved pembrolizumab (Keytruda®) on August 5 for the treatment of some patients with an advanced form of head and neck cancer. The approval is for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) that has continued to progress despite standard-of-care treatment with chemotherapy.

FDA Approves Nivolumab for Head and Neck Cancer

The Food and Drug Administration (FDA) approved nivolumab (Opdivo®) on November 10 for the treatment of squamous cell cancer of the head and neck (SCCHN).

Nivolumab is already approved for the treatment of several other cancers. This new approval is for the use of nivolumab in patients with SCCHN that has progressed during chemotherapy with a platinum-based drug or that has recurred or metastasized after platinum-based chemotherapy.

Nivolumab is the second immunotherapy drug approved to treat SCCHN. In August of this year, the FDA approved pembrolizumab (Keytruda®) for patients with SCCHN whose tumor expressed PD-L1.

Both pembrolizumab and nivolumab for treatment of platinum-refractory recurrent/metastatic HNSCC are included in the latest NCCN recommendations.
**Key Eligibility Criteria**

- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment\(^a\)
- Known p16 status in the oropharynx\(^b\)

**Stratification Factors**

- PD-L1 expression\(^a\)
  (TPS ≥50% vs. <50%)
- p16 status in oropharynx
  (positive vs. negative\(^b\))
- ECOG performance status (0 vs. 1)

---

\(^a\) Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS, tumour proportion score = % of tumour cells with membranous PD-L1 expression.

\(^b\) Assessed using the CINtec p16 Histology assay (Ventana) with a cutpoint for positivity of strong and diffuse nuclear and cytoplasmic staining in ≥70% of cells; non- oropharyngeal tumours were considered p16 negative.

\(^c\) Following a loading dose of 400 mg/m\(^2\).

Overall alpha controlled at one-sided 2.5% across all comparisons

- Hypotheses in top row tested first and in parallel
- Remaining hypotheses tested only if the hypothesis immediately above was positive
- Prespecified analysis plan allows alpha from successful hypotheses to be passed to other hypotheses

Second interim analysis: per protocol, performed 17 months after the last patient enrolled
- Data cut-off date: June 13, 2018
KEYNOTE-048 STUDY DESIGN (NCT02358031)

Key Eligibility Criteria
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment
- Known p16 status in the oropharynx

Stratification Factors
- PD-L1 expression (TPS ≥50% vs. <50%)
- p16 status in oropharynx (positive vs. negative)
- ECOG performance status (0 vs. 1)

Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent) – TPS, tumour proportion score = % of tumour cells with membranous PD-L1 expression;
Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%;
Following a loading dose of 400 mg/m².

OVERALL SURVIVAL
P vs. E, CPS ≥20 population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>62%</td>
<td>0.61 (0.45, 0.83)</td>
</tr>
<tr>
<td>EXTREME</td>
<td>78%</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
14.9 mo (11.6, 21.5)
10.7 mo (8.8, 12.8)

Data cut-off date: Jun 13, 2018.
OVERALL SURVIVAL
P vs. E, CPS ≥1 population

<table>
<thead>
<tr>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro alone</td>
<td>69%</td>
<td>0.78 (0.64, 0.96)</td>
</tr>
<tr>
<td>EXTREME</td>
<td>81%</td>
<td></td>
</tr>
</tbody>
</table>

Median (95% CI)
12.3 mo (10.8-14.9)
10.3 mo (9.0-11.5)

Data cut-off date: Jun 13, 2018.
PROGRESSION-FREE SURVIVAL

P vs. E

CPS ≥20

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>86%</td>
<td>0.99</td>
<td>0.5</td>
</tr>
<tr>
<td>EXTREME</td>
<td>91%</td>
<td>(0.75, 1.29)</td>
<td></td>
</tr>
</tbody>
</table>

CPS ≥1

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro</td>
<td>88%</td>
<td>1.16</td>
<td></td>
</tr>
<tr>
<td>EXTREME</td>
<td>91%</td>
<td>(0.96, 1.39)</td>
<td></td>
</tr>
</tbody>
</table>

Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cut-off date: Jun 13, 2018.

RESPONSE SUMMARY
P vs. E

CPS ≥20

<table>
<thead>
<tr>
<th>Confirmed Response, n (%)</th>
<th>Pembro N = 133</th>
<th>EXTREME N = 122</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>31 (23.3)</td>
<td>44 (36.1)</td>
</tr>
<tr>
<td>CR</td>
<td>10 (7.5)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>PR</td>
<td>21 (15.8)</td>
<td>40 (32.8)</td>
</tr>
<tr>
<td>SD</td>
<td>40 (30.1)</td>
<td>42 (34.4)</td>
</tr>
<tr>
<td>PD</td>
<td>42 (31.6)</td>
<td>13 (10.7)</td>
</tr>
<tr>
<td>Non-CR/non-PD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8 (6.0)</td>
<td>6 (4.9)</td>
</tr>
<tr>
<td>Not evaluable or assessed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 (9.0)</td>
<td>17 (13.9)</td>
</tr>
</tbody>
</table>

CPS ≥1

<table>
<thead>
<tr>
<th>Confirmed Response, n (%)</th>
<th>Pembro N = 257</th>
<th>EXTREME N = 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>49 (19.1)</td>
<td>89 (34.9)</td>
</tr>
<tr>
<td>CR</td>
<td>14 (5.4)</td>
<td>7 (2.7)</td>
</tr>
<tr>
<td>PR</td>
<td>35 (13.6)</td>
<td>82 (32.2)</td>
</tr>
<tr>
<td>SD</td>
<td>72 (28.0)</td>
<td>83 (32.5)</td>
</tr>
<tr>
<td>PD</td>
<td>100 (38.9)</td>
<td>34 (13.3)</td>
</tr>
<tr>
<td>Non-CR/non-PD&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11 (4.3)</td>
<td>11 (4.3)</td>
</tr>
<tr>
<td>Not evaluable or assessed&lt;sup&gt;b&lt;/sup&gt;</td>
<td>25 (9.7)</td>
<td>38 (14.9)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Patients without measurable disease per central review at baseline who did not have CR or PD. <sup>b</sup>Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cut-off date: Jun 13, 2018.

Duration of response, median (range)

P: 20.9 mo (2.7 to 34.8+)
E: 4.2 mo (1.2+ to 22.3+)

Duration of response, median (range)

P: 20.9 mo (1.5+ to 34.8+)
E: 4.5 mo (1.2+ to 28.6+)
## EXPOSURE AND AE SUMMARY

**P vs. E, total**

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab (n=300)</th>
<th>EXTREME (n=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exposure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, median (range), months</td>
<td>3.5 (0.03–24.2)</td>
<td>4.9 (0.03–35.3)</td>
</tr>
<tr>
<td>Administrations, median (range)</td>
<td>6 (1–35)</td>
<td>7 (1–48)</td>
</tr>
<tr>
<td><strong>Treatment-related adverse events, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>175 (58.3)</td>
<td>278 (96.9)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>50 (16.7)</td>
<td>198 (69.0)</td>
</tr>
<tr>
<td>Led to death</td>
<td>3 (1.0)(^a)</td>
<td>8 (2.8)(^b)</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>14 (4.7)</td>
<td>57 (19.9)</td>
</tr>
<tr>
<td><strong>Immune-mediated adverse events and infusion reactions, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>91 (30.3)</td>
<td>68 (23.7)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>20 (6.7)</td>
<td>30 (10.5)</td>
</tr>
<tr>
<td>Led to death</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Led to discontinuation</td>
<td>7 (2.3)</td>
<td>19 (6.6)</td>
</tr>
</tbody>
</table>

\(^a\)Autoinflammatory disease, disseminated intravascular coagulation, and pneumonitis (n=1 each);  
\(^b\)Pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each). Data cut-off date: Jun 13, 2018.  
**KEYNOTE-048 STUDY DESIGN (NCT02358031)**

**Key Eligibility Criteria**
- SCC of the oropharynx, oral cavity, hypopharynx, or larynx
- R/M disease incurable by local therapies
- ECOG PS 0 or 1
- Tissue sample for PD-L1 assessment\(^a\)
- Known p16 status in the oropharynx\(^b\)

**Stratification Factors**
- PD-L1 expression\(^a\) (TPS ≥50% vs. <50%)
- p16 status in oropharynx (positive vs. negative)\(^b\)
- ECOG performance status (0 vs. 1)

![Diagram showing study design and treatment regimens](image)

- **Pembrolizumab 200 mg Q3W for up to 35 cycles**
  - Pembrolizumab 200 mg + Carboplatin AUC 5 OR Cisplatin 100 mg/m\(^2\) + 5-FU 1000 mg/m\(^2\)/d for 4 days for 6 cycles (each 3 wks)
- **Cetuximab 250 mg/m\(^2\) Q1W\(^c\) + Carboplatin AUC 5 OR Cisplatin 100 mg/m\(^2\) + 5-FU 1000 mg/m\(^2\)/d for 4 days for 6 cycles (each 3 wk)**
- **Pembrolizumab 200 mg Q3W for up to 29 cycles**

---

\(^a\)Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent) – TPS = tumour proportion score = % of tumour cells with membranous PD-L1 expression;
\(^b\)Assessed using the CINtec p16 Histology assay (Ventana); cut-point for positivity = 70%;
\(^c\)Following a loading dose of 400 mg/m\(^2\).

OVERALL SURVIVAL
P+C vs. E, total population

Data cut-off date: Jun 13, 2018.

Events | HR (95% CI) | P
--- | --- | ---
Pembro + Chemo | 70% | 0.77 (0.63-0.93) | 0.0034
EXTREME | 80% | Median (95% CI)
13.0 mo (10.9-14.7)
10.7 mo (9.3-11.7)
OVERALL SURVIVAL IN SUBGROUPS
P+C vs. E, total population

The p16-negative subgroup includes participants with non-oropharyngeal tumours. Data cut-off date: Jun 13, 2018.
PROGRESSION-FREE SURVIVAL

P+C vs. E, total population

Progression-free survival assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cut-off date: Jun 13, 2018

RESPONSE SUMMARY
P+C vs. E, total population

<table>
<thead>
<tr>
<th>Confirmed Response, n (%)</th>
<th>Pembro + Chemo N = 281</th>
<th>EXTREME N = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>100 (35.6)</td>
<td>101 (36.3)</td>
</tr>
<tr>
<td>CR</td>
<td>17 (6.0)</td>
<td>8 (2.9)</td>
</tr>
<tr>
<td>PR</td>
<td>83 (29.5)</td>
<td>93 (33.5)</td>
</tr>
<tr>
<td>SD</td>
<td>78 (27.8)</td>
<td>94 (33.8)</td>
</tr>
<tr>
<td>PD</td>
<td>48 (17.1)</td>
<td>34 (12.2)</td>
</tr>
<tr>
<td>Non-CR/non-PD(^a)</td>
<td>13 (4.6)</td>
<td>9 (3.2)</td>
</tr>
<tr>
<td>Not evaluable or assessed(^b)</td>
<td>42 (14.9)</td>
<td>40 (14.4)</td>
</tr>
</tbody>
</table>

\(^a\)Patients without measurable disease per central review at baseline who did not have CR or PD. \(^b\)Patients who did not have a post-baseline imaging assessment evaluable for response or who did not have post-baseline imaging. Response assessed per RECIST v1.1 by blinded, independent central radiologic review. Data cut-off date: Jun 13, 2018.


### Duration of response

**Confirmed Response, n (%)**

- **P+C**: N = 281
  - **ORR**: 100 (35.6)
  - **CR**: 17 (6.0)
  - **PR**: 83 (29.5)
  - **SD**: 78 (27.8)
  - **PD**: 48 (17.1)
  - **Non-CR/non-PD\(^a\)**: 13 (4.6)
  - **Not evaluable or assessed\(^b\)**: 42 (14.9)

- **EXTREME**: N = 278
  - **ORR**: 101 (36.3)
  - **CR**: 8 (2.9)
  - **PR**: 93 (33.5)
  - **SD**: 94 (33.8)
  - **PD**: 34 (12.2)
  - **Non-CR/non-PD\(^a\)**: 9 (3.2)
  - **Not evaluable or assessed\(^b\)**: 40 (14.4)

**Median (range)**

- **P+C**: 6.7 mo (1.6+ to 30.4+)
- **E**: 4.3 mo (1.2+ to 27.9+)
### EXPOSURE AND AE SUMMARY

**P+C vs. E, total**

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Pembro + Chemo N=276</th>
<th>EXTREME N=287</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, median (range), months</td>
<td>5.8 (0.1–24.2)</td>
<td>4.9 (0.03–35.3)</td>
</tr>
<tr>
<td>Administrations, median (range)</td>
<td>8 (1–35)</td>
<td>7 (1–48)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-related adverse events, n (%)</th>
<th>Pembro + Chemo N=276</th>
<th>EXTREME N=287</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>263 (95.3)</td>
<td>278 (96.9)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>196 (71.0)</td>
<td>198 (69.0)</td>
</tr>
<tr>
<td>Led to death</td>
<td>10 (3.6)a</td>
<td>8 (2.8)b</td>
</tr>
<tr>
<td>Led to discontinuation of any drug</td>
<td>63 (22.8)</td>
<td>57 (19.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Immune-mediated adverse events and infusion reactions, n (%)</th>
<th>Pembro + Chemo N=276</th>
<th>EXTREME N=287</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any grade</td>
<td>71 (25.7)</td>
<td>68 (23.7)</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>13 (4.7)</td>
<td>30 (10.5)</td>
</tr>
<tr>
<td>Led to death</td>
<td>1 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Led to discontinuation of any drug</td>
<td>8 (2.9)</td>
<td>19 (6.6)</td>
</tr>
</tbody>
</table>

Superscript:
- aSeptic shock (n=5) and cerebral ischemia, hemorrhage, interstitial lung disease, sepsis, and tumour hemorrhage (n=1 each);  
- Pneumonia (n=3), sepsis (n=2), and hypoxia, osteomyelitis, and pulmonary artery thrombosis (n=1 each). Data cut-off date: Jun 13, 2018.  
SUMMARY AND CONCLUSIONS
Pembrolizumab + chemotherapy vs. EXTREME

Pembrolizumab plus chemotherapy with a platinum and 5-FU significantly improved OS vs. EXTREME in the total population (HR 0.77, P=0.0034)
- No PFS or ORR benefit for pembrolizumab plus chemotherapy
- Responses to pembrolizumab plus chemotherapy were more durable

Pembrolizumab plus chemotherapy had a comparable safety profile vs. EXTREME
- Similar incidence of any-grade, grade 3-4, and grade 5 treatment-related AEs
- No unexpected toxicity in the pembrolizumab + chemotherapy arm

Data support pembrolizumab plus platinum-based chemotherapy as a new first-line standard-of-care for R/M HNSCC

It has been shown that immunotherapy works better in the setting of minimal residual disease.

Moving immunotherapy in the curative setting may increase cure rates.

Several studies are currently testing the incorporation of PD1 checkpoint inhibitors in cisplatin chemoradiotherapy regimens given as definitive or postoperative therapy.

PD1 checkpoint inhibitors are being tested as a substitute to cisplatin in cisplatin-unfit patients or good prognosis HPV+ patients.
EVOLVING ROLE OF IMMUNOTHERAPY IN HEAD AND NECK CANCERS
A systemic review

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Name of study</th>
<th>Primary site</th>
<th>Standard arm</th>
<th>Experimental arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT02764593</td>
<td>Safety Testing of Adding Nivolumab to Chemotherapy in Patients With Intermediate and High-Risk Local-Regionally Advanced Head and Neck Cancer</td>
<td>Locally advanced head and neck cancers</td>
<td>-</td>
<td>Arm 1 (nivolumab + cisplatin)</td>
</tr>
<tr>
<td></td>
<td>(RTOG 3304)</td>
<td></td>
<td></td>
<td>Arm 2 (nivolumab + High-dose cisplatin)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm 3 (nivolumab + cetuximab)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arm 4 (nivolumab + IMRT)</td>
</tr>
<tr>
<td>NCT02998087</td>
<td>Phase III Randomized Trial of Avelumab-cetuximab-Radiotherapy Versus Standards of Care</td>
<td>Locally advanced head and neck cancers</td>
<td>Arm A: IMRT + cisplatin 100 mg/m²</td>
<td>Arm B (Patient FIT) and Arm C (Patient UNFIT): IMRT + cetuximab + avelumab f/u avelumab maintenance for 1 year</td>
</tr>
<tr>
<td>(REACH)</td>
<td></td>
<td></td>
<td></td>
<td>Arm D Patient UNFIT: IMRT + cetuximab + avelumab</td>
</tr>
<tr>
<td>NCT02707588</td>
<td>Phase II Randomized Study to determine the tolerance and efficacy of Pembrolizumab or Cetuximab combined with radiotherapy</td>
<td>Locally advanced head and neck cancers</td>
<td>Cetuximab + RT</td>
<td>Pembrolizumab + RT</td>
</tr>
<tr>
<td>(Pembrolizumab)</td>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab + RT</td>
</tr>
<tr>
<td>NCT02952586</td>
<td>Phase III Randomized Study of Avelumab in Combination With Standard of Care Chemoradiotherapy (Cisplatin Plus Definitive RT) Versus Standard Of Care Chemoradiotherapy</td>
<td>Locally advanced head and neck cancers</td>
<td>Placebo + cisplatin + RT</td>
<td>Avelumab + cisplatin + RT</td>
</tr>
<tr>
<td>(JAVELIN Head and Neck 100)</td>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab + cisplatin + RT</td>
</tr>
<tr>
<td>NCT02421640</td>
<td>Phase II Study of TIL following CCRT in Patients With Locoregionally Advanced NPC</td>
<td>Locally advanced nasopharyngeal cancers</td>
<td>Cisplatin + RT</td>
<td>Cisplatin + RT with TIL-tumour infiltrating lymphocytes</td>
</tr>
<tr>
<td>NCT02398584</td>
<td>Immunotherapy With MK-3475 in Surgically Resectable Head and Neck Squamous Cell Carcinoma</td>
<td>Resectable squamous cell carcinoma of the head and neck</td>
<td>-</td>
<td>Neoadjuvant MK-3475 and adjuvant MK-3475</td>
</tr>
<tr>
<td>NCT03040999</td>
<td>Randomized Phase III Study of Pembrolizumab Given Concomitantly With Chemoradiation and as Maintenance Therapy Versus Chemoradiation Alone</td>
<td>Locally advanced head and neck cancer</td>
<td>Placebo + cisplatin + RT</td>
<td>Pembrolizumab + cisplatin + RT</td>
</tr>
<tr>
<td>(KEYNOTE-412)</td>
<td></td>
<td></td>
<td></td>
<td>Pembrolizumab + cisplatin + RT</td>
</tr>
<tr>
<td>NCT02841748</td>
<td>Randomized Phase II Study of Adjuvant Pembrolizumab versus Placebo in Head and Neck Cancers at High Risk for Recurrence - the pathway Study</td>
<td>Head and neck cancers</td>
<td>Placebo</td>
<td>Pembrolizumab</td>
</tr>
</tbody>
</table>

RT: Radiation therapy, IMRT: Intensity-modulated radiotherapy, TIL: Tumor-infiltrating lymphocytes, NPC: Nasopharyngeal carcinoma

JAVELIN HEAD AND NECK 100: STUDY DESIGN

Phase 3 study of avelumab + CRT vs. CRT alone in LA SCCHN

Press release on April 21, 2020: Bavencio Seen as Ineffective in Phase 3 Head and Neck Cancer Trial

NECK DISSECTION
MANAGEMENT OF THE NECK IN SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

Evidence

Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer

Table 1. Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Elective-Surgery Group (N=243)</th>
<th>Therapeutic-Surgery Group (N=233)</th>
<th>All Patients (N=496)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number (percent)</td>
<td>Number (percent)</td>
<td>Number (percent)</td>
</tr>
<tr>
<td>Mean age (range) — yr</td>
<td>48 (21–73)</td>
<td>48 (20–73)</td>
<td>48 (20–73)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>187 (77.0)</td>
<td>187 (79.9)</td>
<td>374 (75.4)</td>
</tr>
<tr>
<td>Female</td>
<td>56 (23.0)</td>
<td>66 (21.1)</td>
<td>122 (24.6)</td>
</tr>
<tr>
<td>Site of primary tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue</td>
<td>207 (85.2)</td>
<td>216 (85.4)</td>
<td>423 (85.3)</td>
</tr>
<tr>
<td>Buccal mucosa</td>
<td>33 (13.6)</td>
<td>35 (13.8)</td>
<td>68 (13.7)</td>
</tr>
<tr>
<td>Floor of mouth</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
<td>5 (1.0)</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>105 (43.2)</td>
<td>114 (45.1)</td>
<td>219 (44.2)</td>
</tr>
<tr>
<td>T2</td>
<td>138 (56.8)</td>
<td>139 (54.9)</td>
<td>277 (55.8)</td>
</tr>
<tr>
<td>Baseline ultrasonography</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>222 (91.4)</td>
<td>234 (92.5)</td>
<td>456 (91.9)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>19 (7.8)</td>
<td>17 (6.7)</td>
<td>36 (7.3)</td>
</tr>
<tr>
<td>Suspicious</td>
<td>2 (0.8)</td>
<td>2 (0.8)</td>
<td>4 (0.8)</td>
</tr>
</tbody>
</table>

Panel A shows Kaplan–Meier estimates of overall survival and the corresponding hazard ratio in the elective-surgery group and the therapeutic-surgery group. At 3 years, the rates of overall survival were 80.0% (95% confidence interval [CI], 74.1 to 85.8) in the elective-surgery group and 67.5% (95% CI, 61.0 to 73.9) in the therapeutic-surgery group. There were 50 deaths in the elective-surgery group and 79 deaths in the therapeutic-surgery group. Panel B shows Kaplan–Meier estimates of disease-free survival and the corresponding hazard ratio. At 3 years, the rates of disease-free survival were 69.5% (95% CI, 63.1 to 76.0) in the elective-surgery group and 45.9% (95% CI, 39.4 to 52.3) in the therapeutic-surgery group. There were 81 and 146 recurrences in the two groups, respectively.

BACKGROUND: Guidelines remain unclear over whether patients with early stage oral cancer without overt neck disease benefit from upfront elective neck dissection (END), particularly those with the smallest tumours.

METHODS: We conducted a randomised trial of patients with stage T1/T2 NO disease, who had their mouth tumour resected either with or without END. Data were also collected from a concurrent cohort of patients who had their preferred surgery. Endpoints included overall survival (OS) and disease-free survival (DFS). We conducted a meta-analysis of all six randomised trials.

RESULTS: Two hundred fifty fifty randomised and 346 observational cohort patients were studied (27 hospitals). Occult neck disease was found in 18.1% (77) and 34.6% (72) patients respectively. Five-year intention-to-treat hazard ratios (HR) were: OS HR = 0.71 (p = 0.18), and DFS HR = 0.66 (p = 0.04). Corresponding per-protocol results were: OS HR = 0.59 (p = 0.054), and DFS HR = 0.56 (p = 0.007). END was effective for small tumours. END patients experienced more facial/neck nerve damage; QoL was largely unaffected. The observational cohort supported the randomised findings. The meta-analysis produced HR OS 0.64 and DFS 0.54 (p < 0.001).

CONCLUSION: SEND and the cumulative evidence show that within a generalisable setting oral cancer patients who have an upfront END have a lower risk of death/recurrence, even with small tumours.

CLINICAL TRIAL REGISTRATION: NCT01723109 (registered on 17/02/2008), ISRCTN number: 45018955, ClinicalTrials.gov Identifier: NCT00371883.

**Intention-to-treat analyses**

Hutchison IL, et al. Br J Cancer 2019;121:287–36. Reproduced under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/; accessed July 2020).
Purpose
Multiple smaller studies have demonstrated an association between overall survival and lymph node (LN) count from neck dissection in patients with head and neck cancer. This is a large cohort study to examine these associations by using a national cancer database.

Patients and Methods
The National Cancer Database was used to identify patients who underwent upfront nodal dissection for mucosal head and neck squamous cell carcinoma between 2004 and 2013. Patients were stratified by LN count into those with < 18 nodes and those with ≥ 18 nodes on the basis of prior work. A multivariable Cox proportional hazards regression model was constructed to predict hazard of mortality. Stratified models predicted hazard of mortality both for patients who were both node negative and node positive.

Results
There were 45,113 patients with ≥ 18 LNs and 18,865 patients with < 18 LNs examined. The < 18 LN group, compared with the ≥ 18 LN group, had more favorable tumor characteristics, with a lower proportion of T3 and T4 lesions (27.9% vs 39.8%), fewer patients with positive nodes (46.6% vs 60.5%), and lower rates of extracapsular extension (9.3% vs 15.1%). Risk-adjusted Cox models predicting hazard of mortality by LN count showed an 18% increased hazard of death for patients with < 18 nodes examined (hazard ratio [HR] 1.18; 95% CI, 1.13 to 1.22). When stratified by clinical nodal stage, there was an increased hazard of death in both groups (node negative: HR, 1.24; 95% CI, 1.17 to 1.32; node positive: HR, 1.12; 95% CI, 1.05 to 1.19).

Conclusion
The results of our study demonstrate a significant overall survival advantage in both patients who are clinically node negative and node positive when ≥ 18 LNs are examined after neck dissection, which suggests that LN count is a potential quality metric for neck dissection.
MANAGEMENT OF THE NECK IN SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

ASCO Clinical Practice Guideline: Evidence

ABSTRACT

BACKGROUND

The role of image-guided surveillance as compared with planned neck dissection in the treatment of patients with squamous-cell carcinoma of the head and neck who have advanced nodal disease (stage N2 or N3) and who have received chemoradiotherapy for primary treatment is a matter of debate.

METHODS

In this prospective, randomized, controlled trial, we assessed the noninferiority of positron-emission tomography–computed tomography (PET-CT)–guided surveillance (performed 12 weeks after the end of chemoradiotherapy, with neck dissection performed only if PET-CT showed an incomplete or equivocal response) to planned neck dissection in patients with stage N2 or N3 disease. The primary end point was overall survival.

RESULTS

From 2007 through 2012, we recruited 364 patients (282 patients in the planned-surgery group and 282 patients in the surveillance group) from 37 centers in the United Kingdom. Among these patients, 17% had nodal stage N2a disease and 67% had stage N2b disease. A total of 84% of the patients had oropharyngeal cancer, and 7% had tumors that staged positive for the p16 protein, an indicator that human papillomavirus had a role in the causation of the cancer. The median follow-up was 36 months. PET-CT–guided surveillance resulted in fewer neck dissections than did planned dissection surgery (54 vs. 221); rates of surgical complications were similar in the two groups (42% and 38%, respectively). The 2-year overall survival rate was 84.9% (95% confidence interval [CI], 80.7 to 89.1) in the surveillance group and 85.9% (95% CI, 82.6 to 88.3) in the planned-surgery group. The hazard ratio for death slightly favored PET-CT–guided surveillance and indicated noninferiority (upper boundary of the 95% CI for the hazard ratio, <1.50; P=0.0004). There was no significant difference between the groups with respect to p16 expression. Quality of life was similar in the two groups. PET-CT–guided surveillance, as compared with neck dissection, resulted in savings of $3,495 (approximately $2,290 in U.S. dollars) per person over the duration of the trial.

CONCLUSIONS

Survival was similar among patients who underwent PET-CT–guided surveillance and those who underwent planned neck dissection, but surveillance resulted in considerably fewer operations and it was more cost-effective. (Funded by the National Institute for Health Research Health Technology Assessment Programme and Cancer Research UK; PET-NECK Current Controlled Trials number, ISRCTN13733460)


PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer
PET-CT Surveillance versus Neck Dissection in Advanced Head and Neck Cancer

Figure 2. Kaplan-Meier Estimates of Overall Survival, According to Trial Group.

In Panel B, the numbers of patients shown are the numbers of patients in those groups at randomization.

MANAGEMENT OF THE NECK IN SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY

ASCO Clinical Practice Guideline: Oral Cancer Treatment Algorithm

FIG 2. Treatment algorithm for management of the neck in patients with oral cavity squamous cell carcinoma (SCC) of the head and neck. cN0, clinically node negative; cN+, clinically node positive; END, elective neck dissection; pN1, single pathologically node positive.
MANAGEMENT OF THE NECK IN SQUAMOUS CELL CARCINOMA OF THE OROPHARYNX

ASCO Clinical Practice Guideline: Oropharyngeal Cancer Treatment Algorithm

**FIG. 3.** Treatment algorithm for management of the neck in patients with oropharyngeal squamous cell carcinoma of the head and neck. cN+, clinically node positive; CT, computed tomography; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography.
CONCLUSIONS

Cisplatin chemoradiotherapy remains the standard of care for locally advanced (LA) HNSCC

TPF is the preferred induction regimen

Sequential therapy is not superior to chemoradiotherapy alone

HPV-positive OPC patients constitute a separate prognostic and therapeutic cohort and are staged differently from HPV-negative ones

Cetuximab-RT is inferior to cisplatin-RT in terms of OS and PFS in HPV-associated locally advanced oropharynx cancer

The new staging system for OPC does not affect treatment decisions

Randomised trials testing the addition of PD1 checkpoint inhibitors to cisplatin chemoradiation are ongoing in locally advanced setting and results are awaited with great interest
THANK YOU!