Treatment De-Escalation in Squamous Cell Carcinoma of the Oropharynx

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The Problem

- Oropharynx cancer on the rise despite reduction in smoking rates
  - HPV
- Different phenotype, demographic
  - HPV-specific staging in AJCC 8th edition
- Improved prognosis
  - RTOG 0129- 8 year OS of 71% vs 30% for HPV-

Nguyen-Tan et al. J Clin Oncol 2014.

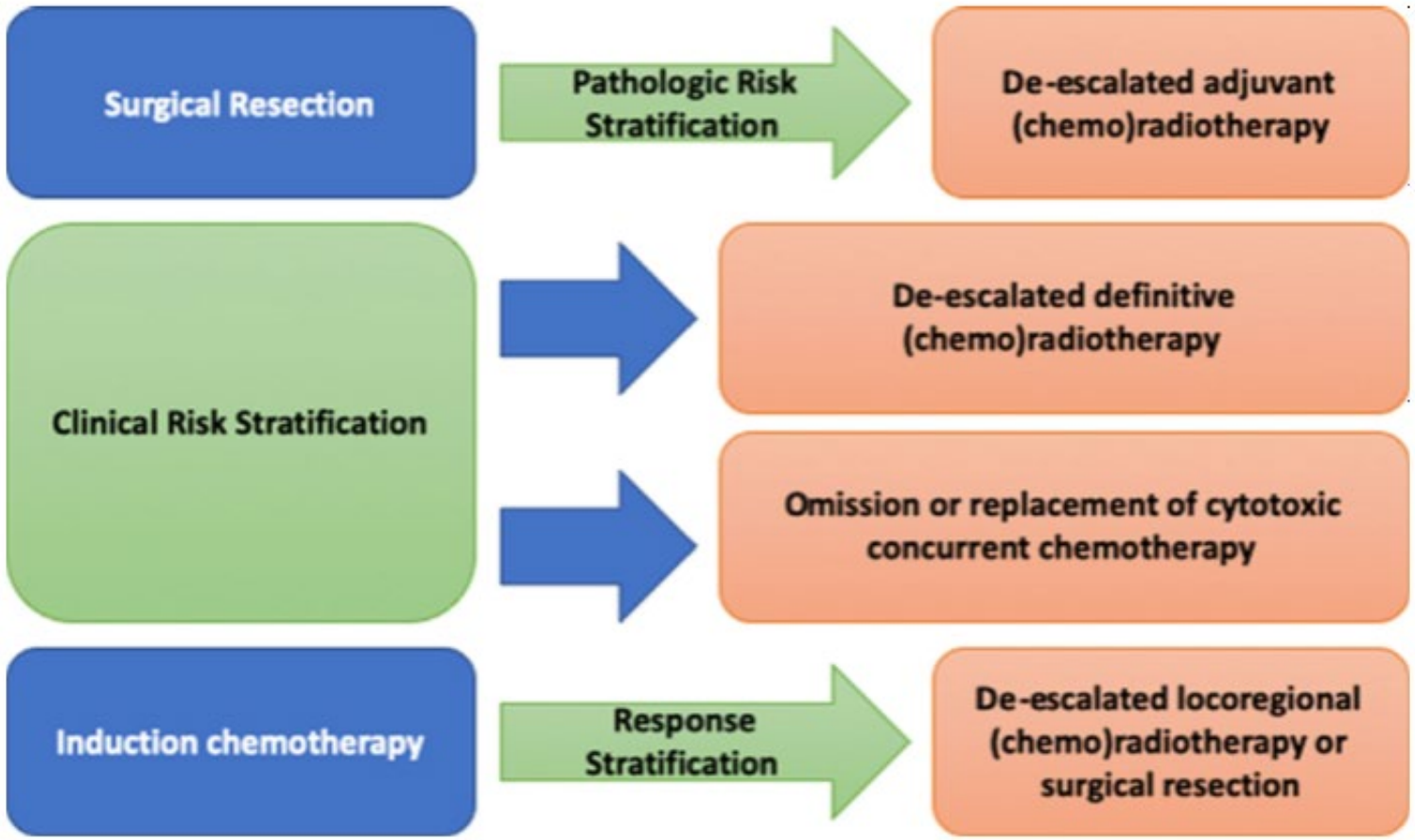
The Problem

- Treatment strategies have not evolved along with HPV+ disease
  - Acute and late complications of CRT remain significant
    - Speech
    - Swallowing
    - Hearing
    - Dental Health
    - QOL
- Pooled analysis of RTOG trials- 43% of those with locally advanced SCCHN had severe late toxicity

- Crux: New, highly curable disease. Is it safe to de-escalate?

Chen AM et al. JAMA Oto 2014.
El-Deiry M et al. Oto HNS 2005.
Duke RL et al. Arch Oto HNS 2005.
Funk GF et al Arch Oto HNS 2012.
Payakachat N et al. Head Neck 2013.

De-Escalation Approaches



Rosenberg AJ and Vokes EE. The Oncologist 2021.

Minimally invasive surgery

- Transoral robotic surgery
- Upfront surgery provides precise pathologic data upon which to base additional treatment decisions
  - ECOG 3311
    - 3 groups: low, intermediate and high risk
      - Low-risk: observation
      - Intermediate: randomized to 50 vs 60 Gy XRT
      - High: Weekly cisplatin, XRT to 66 Gy
    - Results:
      - PFS equivalent for intermediate risk
  - Future work: Compare surgery to upfront CRT, further investigation of ECS as an indication for adjuvant therapy

Ferris RL et al. J Clin Oncol 2020.

Our Approach

- TORS is selectively applied
  - T1 and T2 oropharynx cancer
    - HPV+ and HPV-
    - Minimal post-op morbidity anticipated
  - Limited to N1 disease

- Open question:
  Benefit of surgery in those requiring adjuvant CRT vs de-escalated CRT?

Reduction/Omission Cytotoxic Chemo

- Inferior survival, LRC outcomes demonstrated with Cetuximab vs Cisplatin with definitive RT
- Suggestion that Cisplatin dose reduction may be safe and feasible
- Role of immunotherapy with RT currently under investigation

Bonner JA et al. NEJM 2006.
Rosenthal DI et al. J Clin Oncol 2015.
Mehanna H et al. Lancet 2019.
Gillison ML et al. Lancet 2019
Nguyen-Tan PF et al. J Clin Oncol 2014.

Reduced XRT After Induction Chemo

- Response to induction predictive of response to XRT/CRT
- Numerous studies with similar approach:
  - Risk stratification
  - Induction
  - Assessment of response to induction
  - Reduced dose vs standard dose XRT

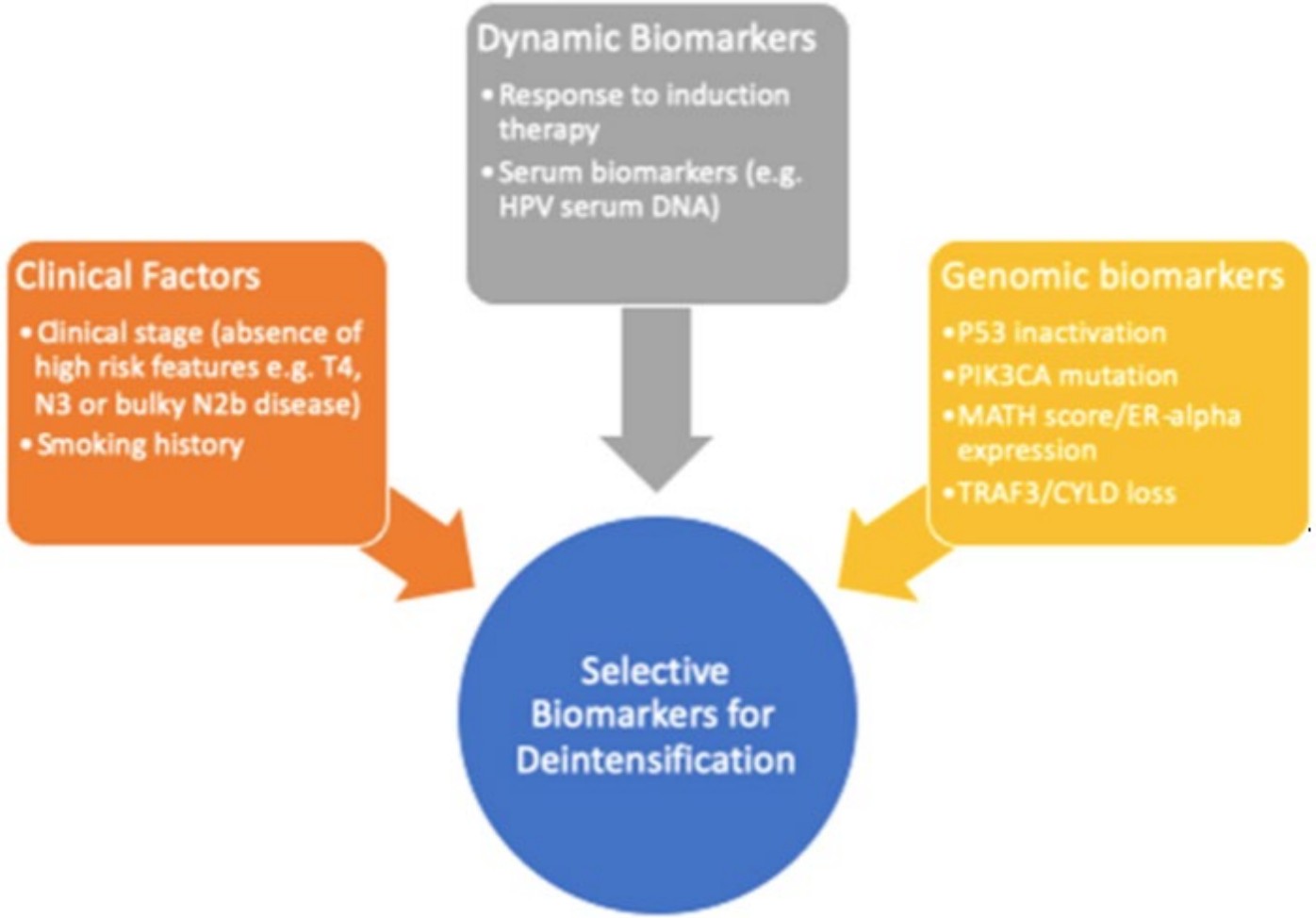
  - Overall outcomes: Excellent response to treatment, OS (80%) and PFS at 2 years especially in HPV +, low risk groups.

Reduced XRT After Induction Chemo

Trial name	Patient population	*n*	Design	Outcome measure	Reference
ECOG 2399	Stage III/IV oropharynx/larynx (40% HPV)	96	Carboplatin and paclitaxel ×2 cycles → CRT with weekly paclitaxel	2-yr OS 95% (HPV+) vs. 62% (HPV−) RR: 82% (HPV+) vs. 55% (HPV−)	Fakhry et al. [54]
ECOG 1308	HPV+ OPSCC	90	Cisplatin, paclitaxel, and cetuximab → CRT with concurrent cetuximab to 54 Gy (CR) or 69.3 Gy (<CR)	2-yr PFS 78%; 2-yr OS 91%	Marur et al. [58]
RAVD	Locally advanced HNSCC (63% HPV+)	94	Cisplatin, paclitaxel, cetuximab ± everolimus → volume de-escalation (>50% shrinkage)	G-tube dependence at 6 mo (5.7% in de-escalated vs. 32.6%; $p = .005$)	Villaflor et al. [59]
OPTIMA	Locally advanced HPV+ OPSCC	62	Carboplatin and nab-paclitaxel ×3 cycles → (a) 50 Gy (low risk, >50% shrinkage) (b) CRT 45 Gy (low 30%–50%; high risk >50%) (c) CRT 75 Gy (high risk <30%)	2-year PFS 94%	Seiwert et al. [60]
Chen et al.	Locally advanced HNSCC	45	Carboplatin and paclitaxel ×2 cycles → CRT with paclitaxel to 54 Gy (PR/CR) or 60 Gy (<PR)	2-yr PFS 92%	Chen et al. [61]
OPTIMA 2	Locally advanced HPV+ HNSCC		Carboplatin/nab-paclitaxel/ nivoumab ×3 cycles → risk and response-adapted locoregional therapy		NCT03107182
DEPEND	Locally advanced HPV- HNSCC		Carboplatin/nab-paclitaxel/ nivoumab ×3 cycles → risk and response-adapted locoregional therapy		NCT03944915

Abbreviations: −, negative; +, positive; CR, complete response; CRT, chemoradiotherapy; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; OPSCC, oropharyngeal squamous cell carcinoma; OS, overall survival; PFS, progression-free survival; PR, partial response.

Novel Strategies

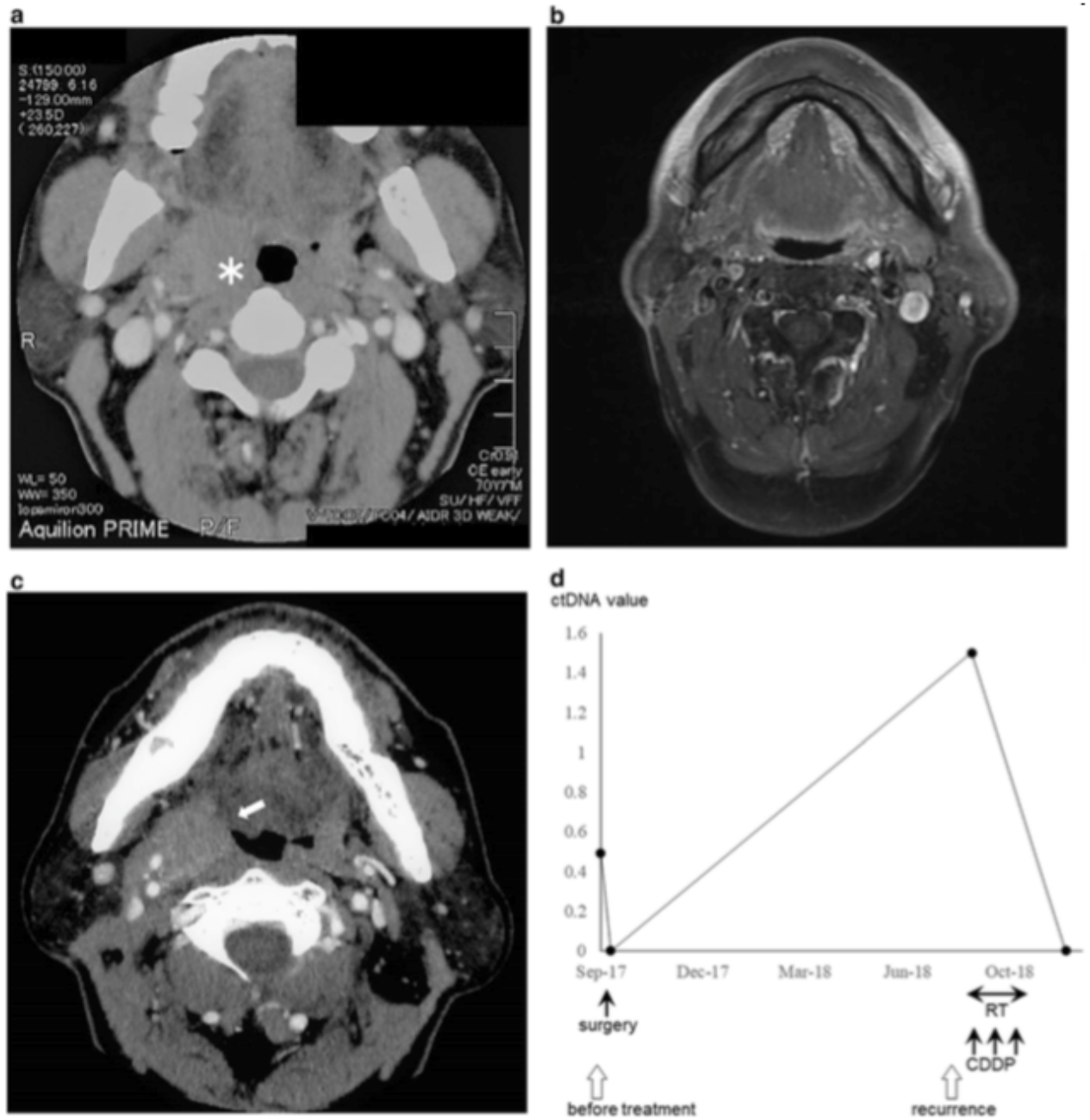


Rosenberg AJ and Vokes EE. The Oncologist 2021

Circulating HPV DNA

- Circulating tumor DNA (ctDNA)
  - New biomarker for various cancers
  - Present in up to 87% of HPV+ OP SCCA
- 25 patients with p16 + OP SCCA
  - Observed- mean of 15 mos
  - 11 treated primarily with surgery, 14 with XRT
  - CR achieved in all
- 14 ctDNA + at dx, all negative after treatment
  - 2 recurred- ctDNA+ at recurrence

Akashi et al. Nature Scientifc Reports 2022
Wang et al. Sci Transl Med 2015.


a
b
c
d
ctDNA value
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Sep-17
Dec-17
Mar-18
Jun-18
Oct-18
surgery
RT
CDDP
before treatment
recurrence
Aquilion PRIME
R/F
R

Summary

- Area of active study but still largely investigational
- HPV-staging and prognostic implications based on standard treatments
- May be safe, feasible to reduce dose of cytotoxic chemo
- May be able to de-escalate XRT after response to induction
- Promise in reduced radiation after surgery if risk-stratified- must compare to de-escalated definitive CRT
- Biomarkers show promise, may offer future guidance