Treatment de-escalation after upfront surgery

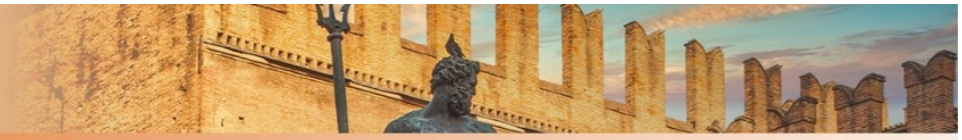
Domenico Attilio Romanello

Radiotherapy Service, South Tyrol Health Service, Bolzano

Südtiroler Sanitätsbetrieb
Azienda Sanitaria dell'Alto Adige
Azienda Sanitera de Sudtirol

Associazione Italiana Radioterapia e Oncologia clinica

Società Italiana di Radiobiologia



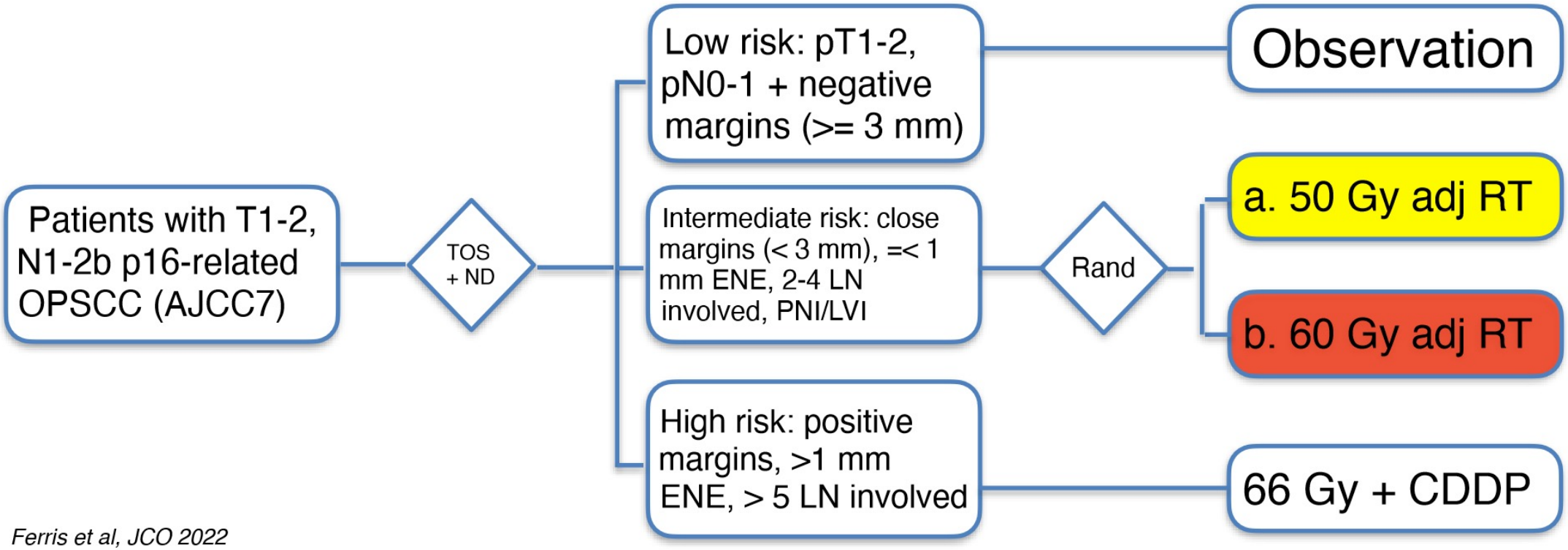
DICHIARAZIONE

Relatore: DOMENICO ATTILIO ROMANELLO

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro (relatore Webinar "Focus on carcinoma prostatico 2.0" per **SUMMEET S.R.L.**)

Surgery and de-escalation of adjuvant RT: E3311



Ferris et al, JCO 2022

TABLE 2. 2-Year PFS, Overall PFS Events, and Sites of Recurrence

Arm	Patients (No.)	2-Year PFS (%)	90% CI	Deaths (without recurrence)	Recurrences	LRF	DM
A	38	96.9	91.9 to 100	0	1	0	1
B	100	94.9	91.3 to 98.6	1	4	2	2
C	108	96.0	92.8 to 99.3	0	4	0	4
D	113	90.7	86.2 to 95.4	3	7	4	3

NOTE. In the past 2 years, arm A had three additional recurrences (two LRF and one DM), arm B had one additional death without recurrence, arm C had one additional recurrence (one LRF) and one death without recurrence, and arm D had one additional recurrence (one DM).
Abbreviations: DM, distant metastasis; LRF, local-regional failure; PFS, progression-free survival.

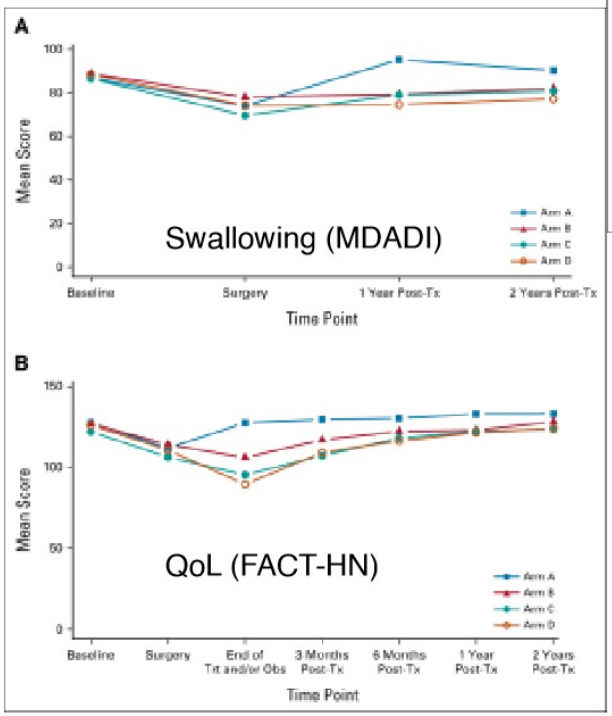
>=G3 toxicities:
B. 17/120
C. 31/127
p=.30

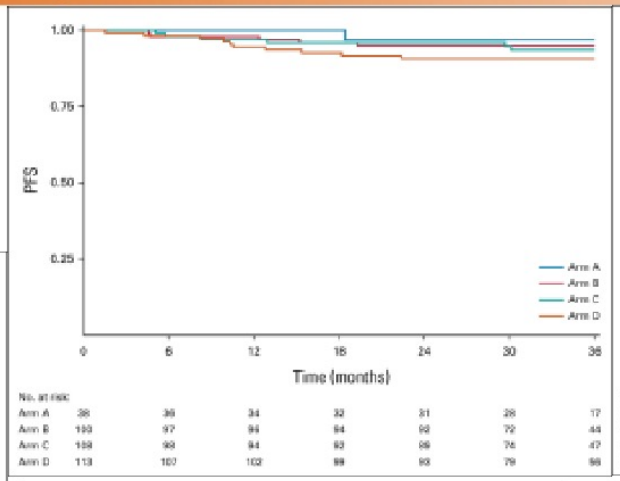
1 G5 hemorrage (among 495 pts)

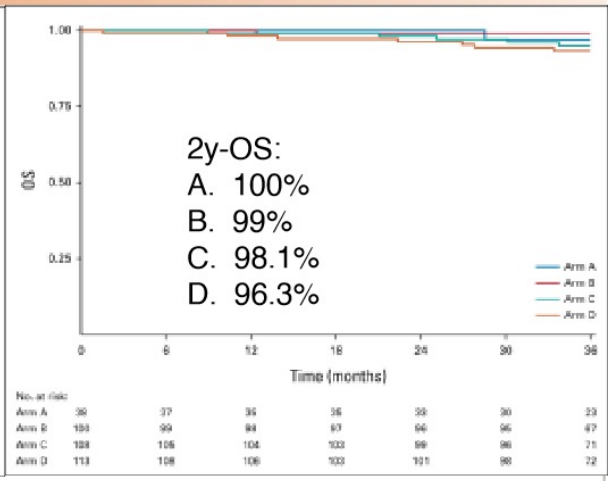
PROs did not differ between B. And C.

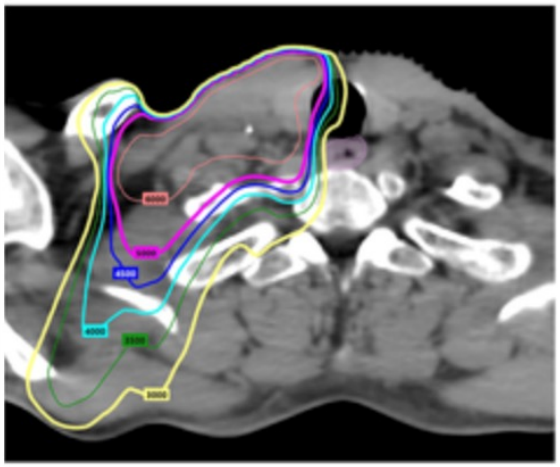
Ferris et al, JCO 2022

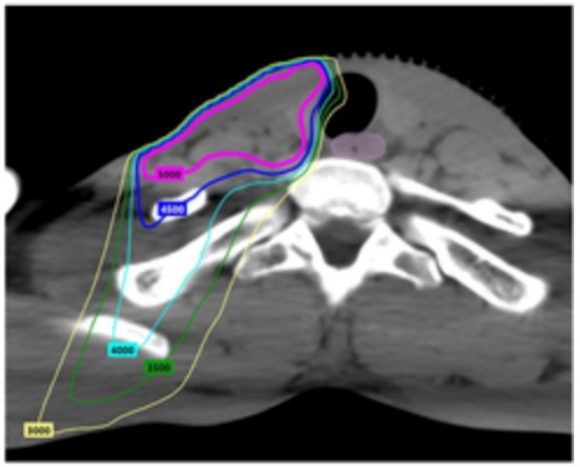
Kang et al, CA Cancer J Clin. 2022



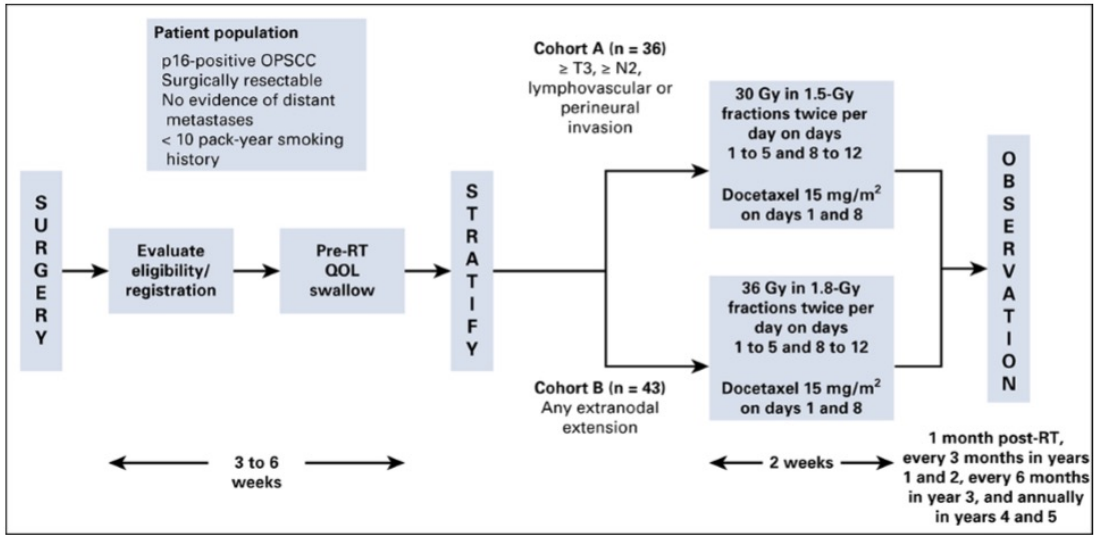


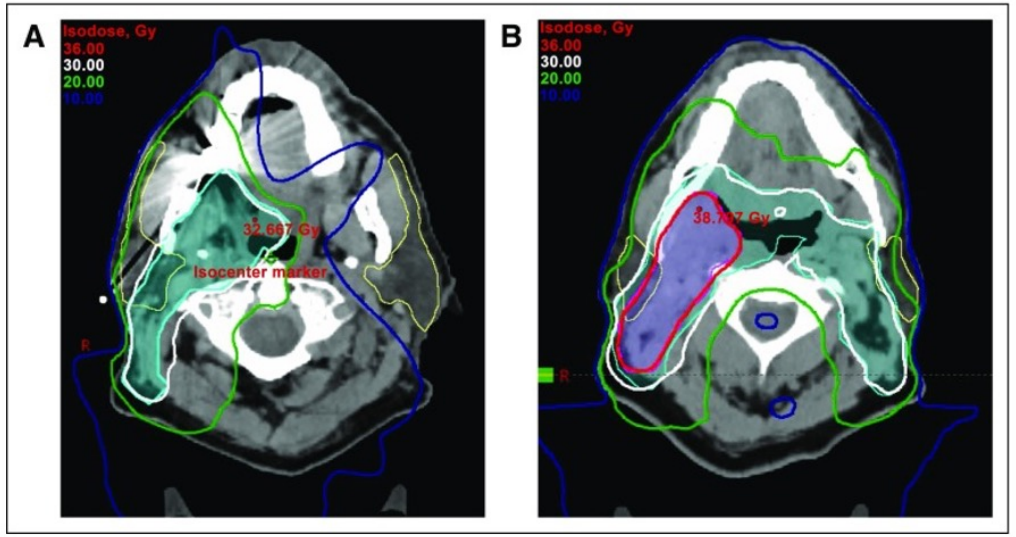




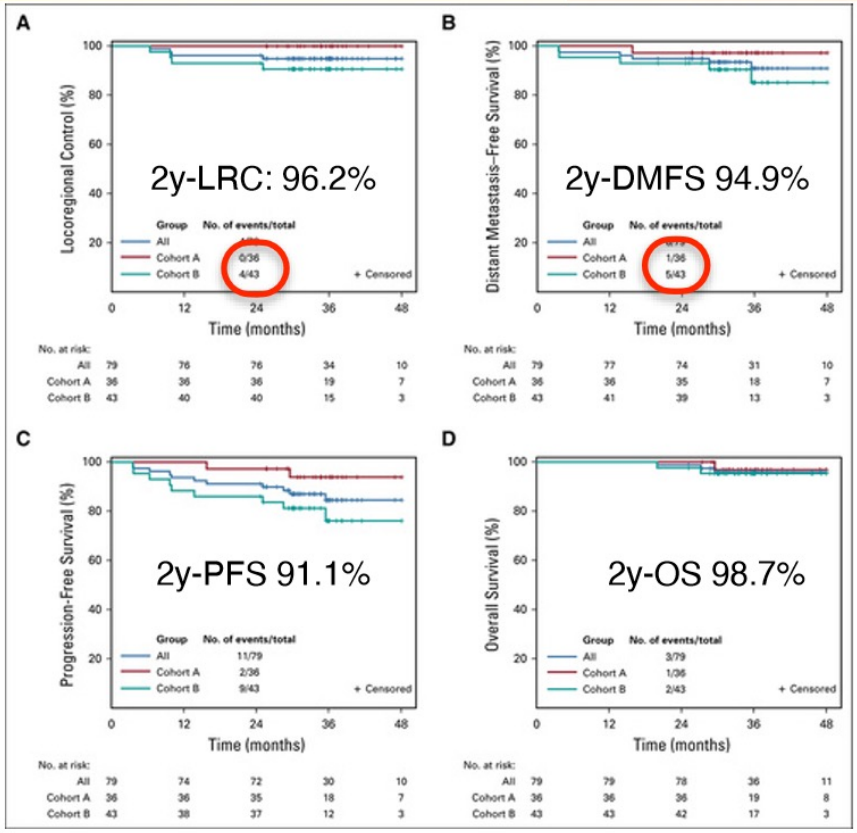


Aggressive Dose De-Escalation: MC1273

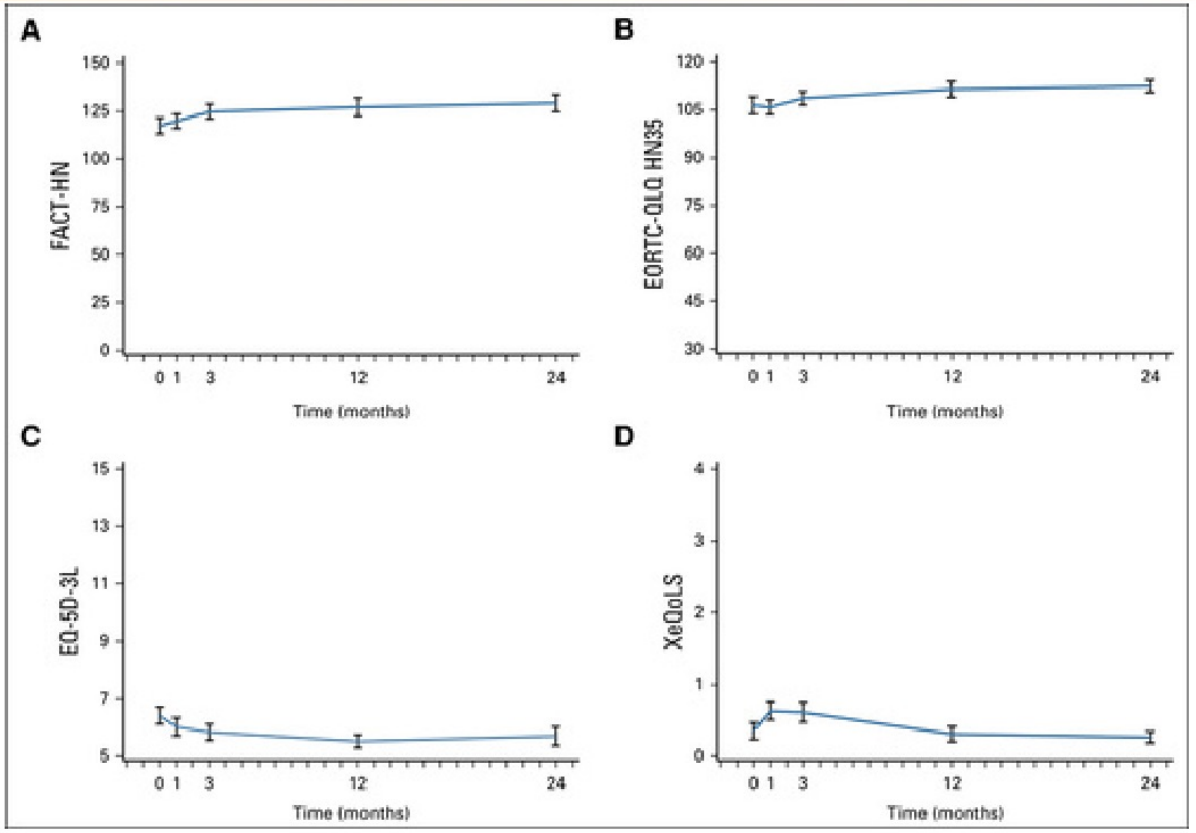




Ma et al, JCO 2019



FUP 35.7 months



16 >= G3 toxicities
1 temporary feeding tube during RT

Ma et al, JCO 2019

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International Journal of Radiation Oncology*Biology*Physics
Volume 111, Issue 5, 1 December 2021, Page 1324

LBA-1

MC1675, a Phase III Evaluation of De-Escalated Adjuvant Radiation Therapy (DART) vs. Standard Adjuvant Treatment for Human Papillomavirus Associated Oropharyngeal Squamous Cell Carcinoma

D.M. Ma [1], K. Price [2], E.J. Moore [3], S.H. Patel [4], M.L. Hinni [5], B. Fruth [6], N.R. Foster [6], K. Van Abel [3], L.X. Yin [3], M.A. Neben-Wittich [1], L.A. McGee [7], J.C. Rwigema [8], D.M. Routman [9], S.C. Lester [9], D.L. Price [3], J.R. Janus [10], J.L. Kasperbauer [11], T.H. Nagel [5] ... R.L. Foote [9]

- 30-36 Gy DART BID+Docetaxtel (n=130) vs SOC 60 Gy PORT + CDDP 40 mg/mq weekly (n= 64)
- ENE+ (n= 115), non-smokers (n=139)
- 3-mo >= G3 toxicities: DART 1.6% vs SOC 7.1% (p=0.058)
- 2y-PFS: DART 86.5% [95% CI, 80.2%-93.3%] vs SOC 95.1% [95% CI, 88.8%-100%)
- Feeding tubes: DART 1.6% vs SOC 27.4%
- > 4 N+ /ENE+ 2y-PFS: 42.9% (DART) vs 100% (SOC)

ELSEVIER
International Journal of Radiation Oncology*Biology*Physics
Volume 112, Issue 5, 1 April 2022, Pages e3-e4

2

Non-Inferiority Margin and Nodal Analysis of De-Escalated Adjuvant Radiation Therapy (DART) for HPV-Related Oropharyngeal Squamous Cell Carcinoma (OPSCC): A Preplanned Pooled Analysis of MC1273 & MC1675

D.J. Ma [1], K. Price [2], E.J. Moore [3], S.H. Patel [4], M.L. Hinni [5], B. Fruth [6], N.R. Foster [6], K. Van Abel [3], L.X. Yin [7], M.A. Neben-Wittich [8], Y. Garces [9], L.A. McGee [10], J.C. Rwigema [11], D.M. Routman [8], S.C. Lester [8], D.L. Price [7], J.R. Janus [12], A.V. Chintakuntlawar [2] ... R.L. Foote [9]

Cohort	N	OS	LRC	PFS
Total	202	97.8 (95.7-100.0%)	96.9 (94.5-99.4%)	91.1 (87.2-95.3)
ENE-	93	100.0 (100.0-100.0)	100.0 (100.0-100.0)	97.7 (94.6-100)
ENE+	109	95.9 (91.9-99.9)	94.2 (89.8-98.8)	85.2 (78.6-92.5)
pN0-1	180	98.6 (96.8-100.0)	98.3 (96.3-100.0)	95.1 (91.9-98.5)
pN2	22	90.7 (79.2-100.0)	85.2 (71.1-100.0)	58.7 (41.3-83.6)
ENE-/pN0-1	92	100.0 (100-100)	100.0 (100-100)	97.5 (94.7-100)
ENE+/pN1	88	97.2 (100.0-93.5)	96.4 (92.5-100)	92.5 (86.9-98.5)
ENE-/pN2	2	100.0 (100-100)	100.0 (100-100)	100.0 (100-100)
ENE+/pN2	20	89.7 (100.0-77.2)	83.6 (68.2-100)	54.5 (36.4-81.7)

HN005 2y-PFS thresholds: 86.9-92.3%

Mucosal spare irradiation: AVOID

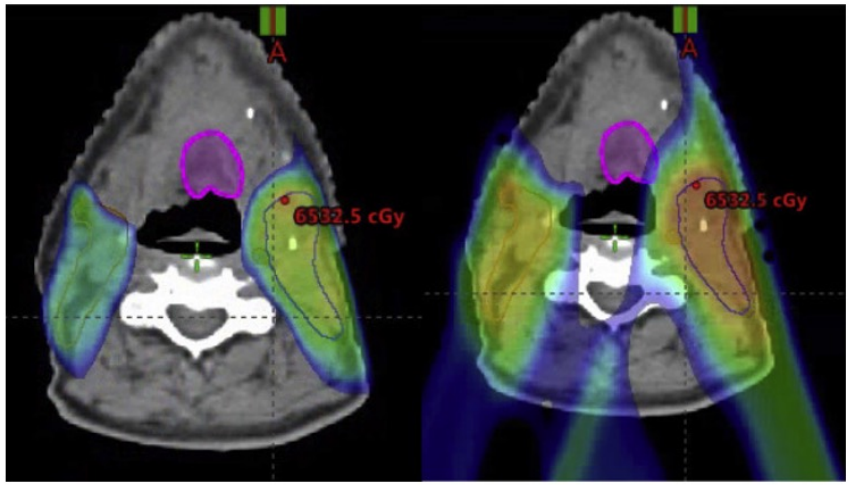
AJCC7 pT1-2, pN1-3 p16+ OPSCC

↓

TORS + ND, R > 2 mm, no PNI/LVI

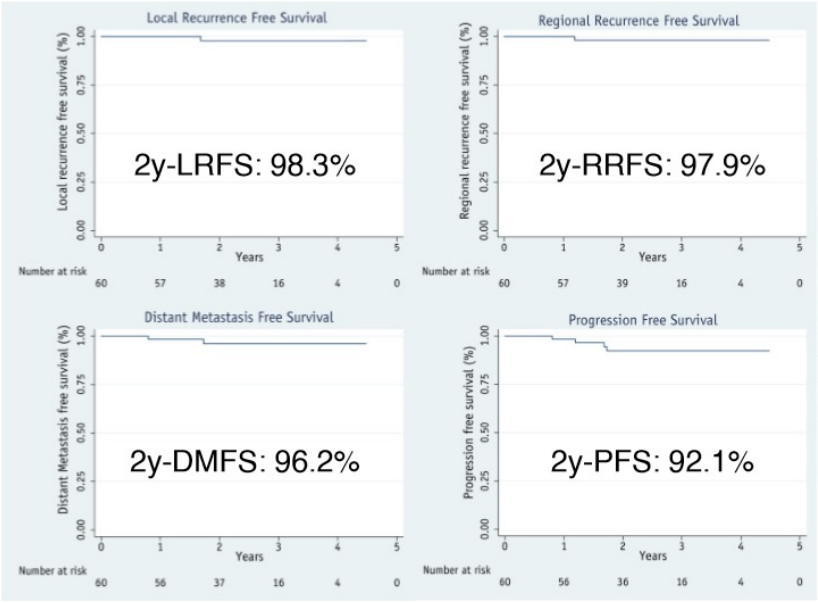
↓

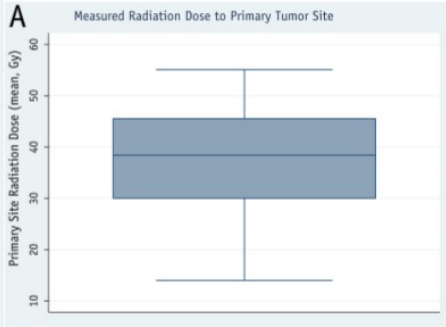
IMRT/IMPT to neck only
60/66 Gy N+
54 Gy N0



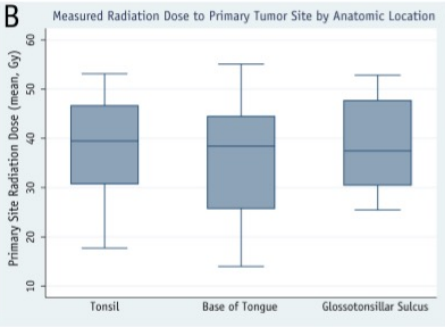
Swisher-McClure et al, IJROBP 2020

60 pts (27 PT, 32 IMRT, 1 IMRT/PT), 13 CRT
FUP 2.4 years
Recurrences: 1 T, 1 N, 2 M
2 late soft tissues necroses in the primary site
2 feeding tubes at 3 months, definitely removed

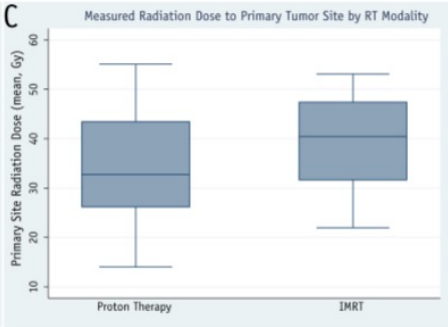




36.9 Gy



37.8 Gy 38.7 Gy
35.4 Gy



33.9 Gy (RBE) 39.16 Gy

Swisher-McClure et al, IJROBP 2020

A Prospective Study of Mucosal Sparing Radiation Therapy in Resected Oropharyngeal Cancer Patients

Justin D. Anderson, MD • Todd A. DeWees, PhD • Daniel J. Ma, MD • ... Michele Y. Halyard, MD • Michael L. Hinni, MD • Samir H. Patel, MD • Show all authors

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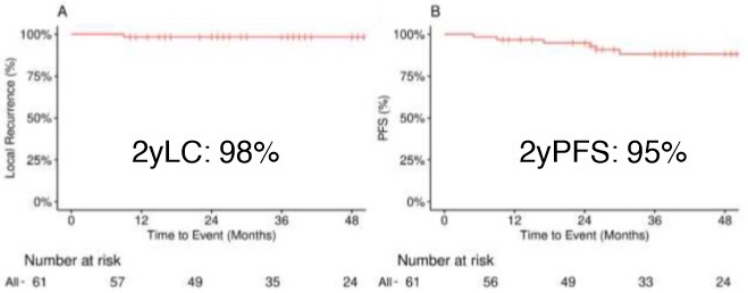
61 patients, 44 PT, 17 IMRT
AJCC7 pT1-2, pN1-N3, cM0 p16+ OPSCC
No PNI (solitary nerve < 2mm within tumor confines)
no LVSI (single focus within tumor confines)
60 Gy (RBE)/54 Gy (RBE)

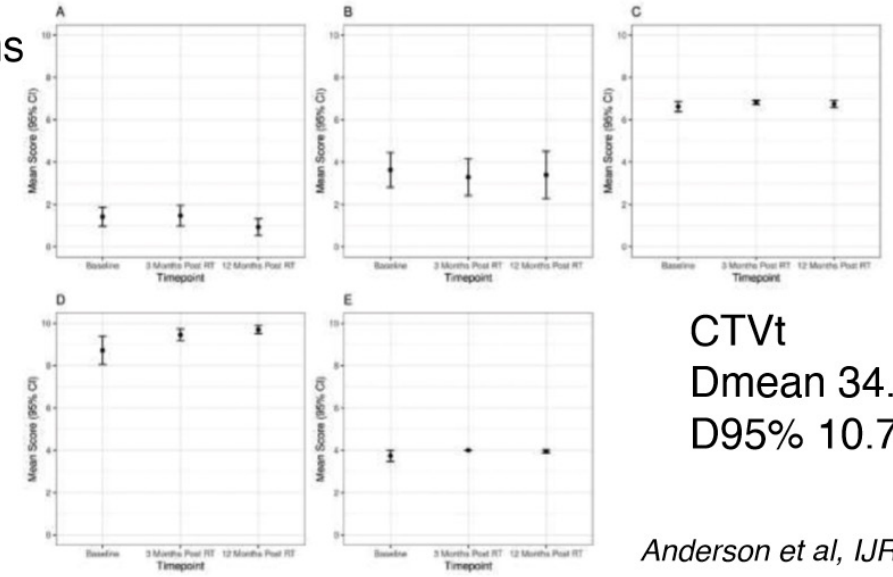


FUP 38 months

Table 2 Treatment-related grade ≥3 adverse events

Technique	Time point	Toxicity
Proton	During treatment	Dermatitis radiation
IMRT	During treatment	Dermatitis radiation
Proton	During treatment	Dermatitis radiation
Proton	During treatment	Dermatitis radiation
IMRT	During treatment	Nausea
Proton	During treatment	Dermatitis radiation

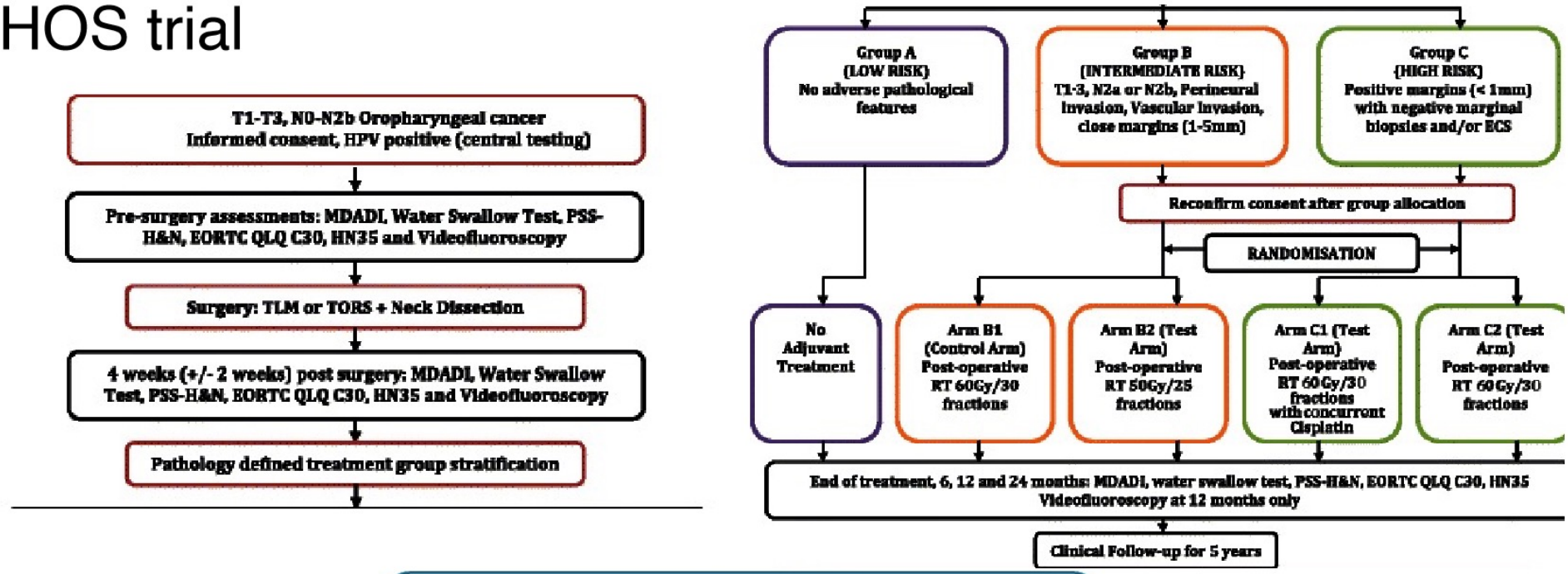
Abbreviation: IMRT = intensity modulated radiation therapy.



CTVt
Dmean 34.6 Gy
D95% 10.7 Gy

Anderson et al, IJROBP 2022

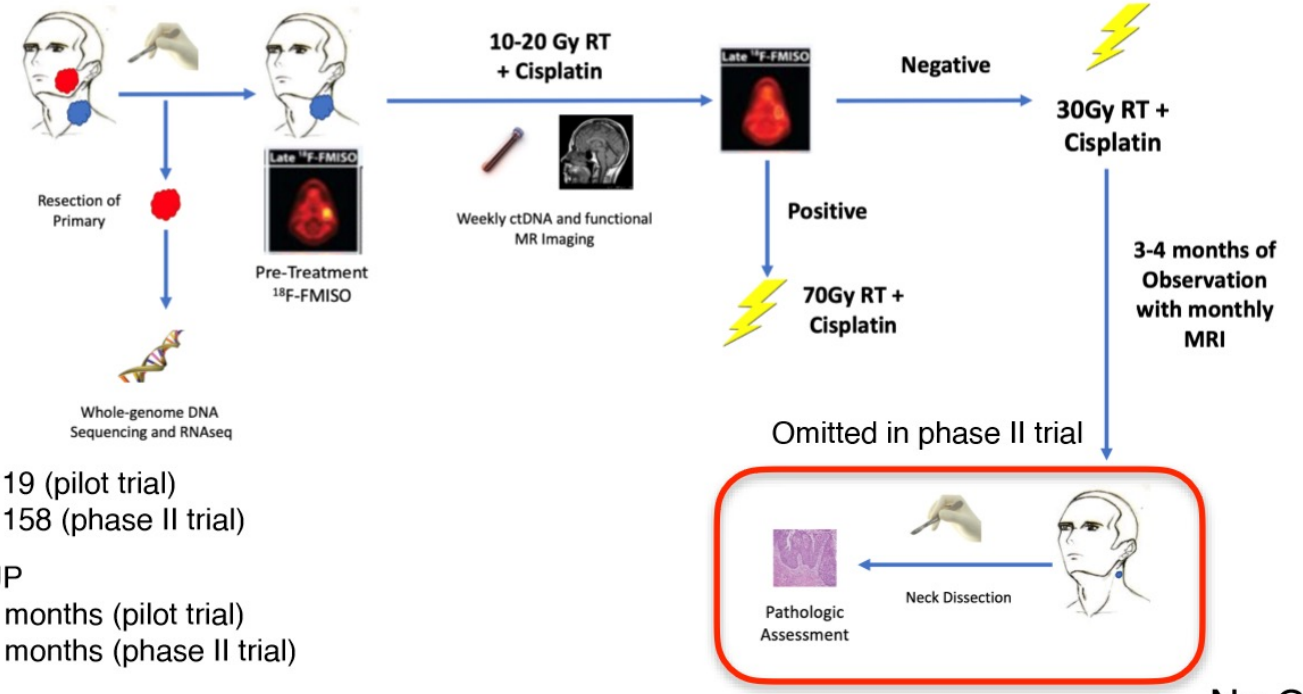
PATHOS trial



Primary Outcome Measure:
Phase II – Swallowing function (MDADI) at 12 months; **Phase III** – Overall Survival
Secondary Outcome Measure:
Swallowing panel measurements including qualitative and quantitative swallowing assessments, QOL (EORTC QLQ C30 and HN35), acute and late toxicity, disease-free survival, locoregional control and distant metastases.
Phase II – Overall Survival; **Phase III** - Swallowing function (MDADI) at 12 months.

Owadally et al, BMC Cancer 2015

MSKCC 30 ROC/NCT03323463



n= 19 (pilot trial)
n= 158 (phase II trial)

FUP
34 months (pilot trial)
12 months (phase II trial)

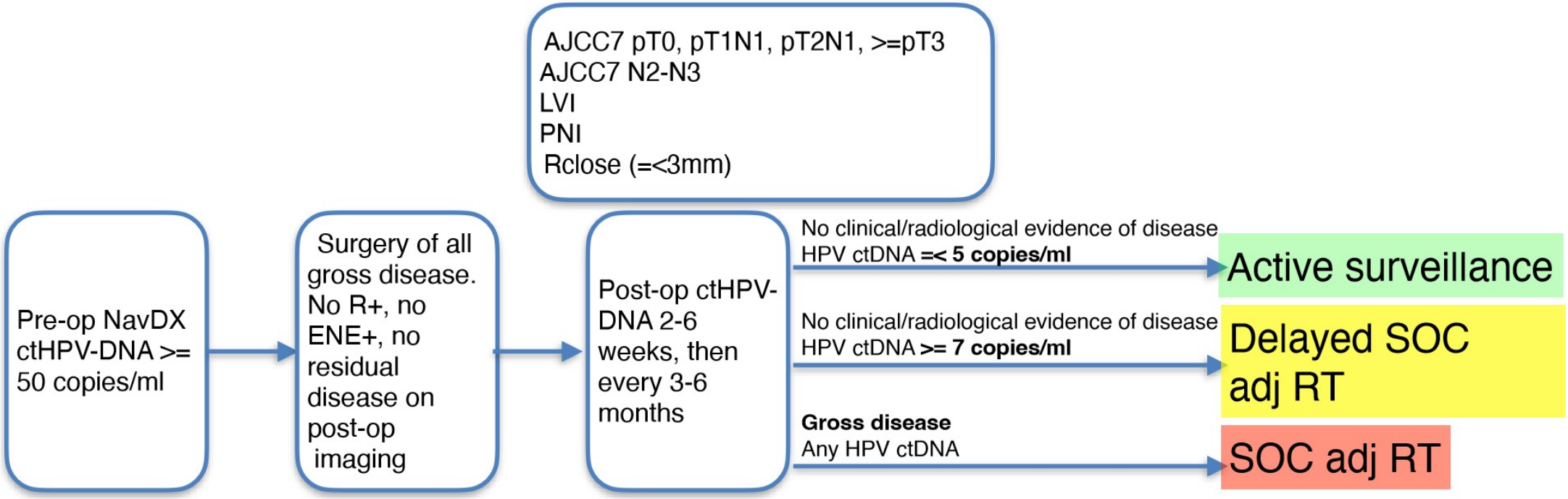
Riaz et al, JNCI 2021
Lee et al, JCO 2021

Pilot trial:
- 2y OS, 92.9%
- 2y PFS, 92.9%
- 2y LRC, 100.0%
- 11/15 pCR

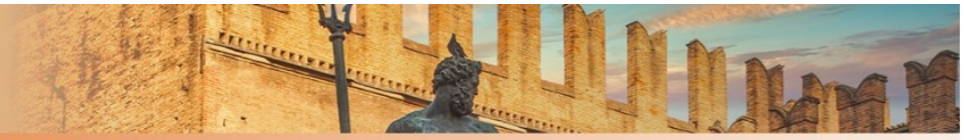
Phase 2:
- 1y OS, 100.0%
- 1y PFS 94.0%
- 1y LRC, 94.0%
- 1y DMFS, 100.0%
- No T recurrences
- 8/128 N recurrences

No G3 RT toxicities in the pilot trial
No G3 mucositis, 0 PEG tubes in phase 2 trial

Post-op cfDNA-guided adjuvant RT: MSKCC/NCT05307939



https://clinicaltrials.gov/ct2/show/study/NCT05307939



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140

ctHPVDNA and Recurrence Risk in MC1675, a Secondary Analysis of a Phase III Evaluation of De-Escalated Adjuvant Radiation Therapy (DART) vs. Standard Adjuvant Treatment for HPV Associated Oropharyngeal Squamous Cell Carcinoma

D.M. Routman [1], K. Van Abel [2], K.A. Price [3], S.H. Patel [4], M.L. Hinni [5], B. Fruth [6], S. Kumar [7], C. Del Vecchio Fitz [8], C. Kuperwasser [8], M.A. Neben-Wittich [1], L.A. McGee [4], S.C. Lester [1], D.L. Price [9], J.R. Janus [10], T.H. Nagel [5], A.V. Chintakuntlawar [11], P. Savvides [12], R.L. Foote [13], E.J. Moore [14], D.J. Ma [1]

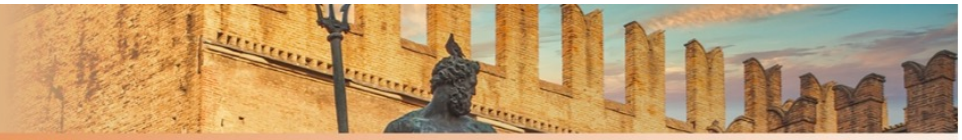
MRD: molecular residual disease

Results

Of the 194 patients (DART: 130, SOC: 64), 150 had plasma available for analysis at any timepoint. Of 44 pts with pre-surgery plasma available, 37 (84%) had detectable TTMV-HPV DNA, with a median value of 250 frgs/mL (range 5-31092). Post-op, 137 pts had plasma available (median 21 days post-op), of which 16 (11%) had detectable post op TTMV-HPV DNA, median 10 frgs/mL. Three months after completion of RT, 114 pts had plasma available, of which 8 pts (7%) had detectable TTMV-HPV DNA median 43 frgs/mL. At 18 months, PFS was 73.1% for patients with post-op detectable MRD compared to 95.8% of patients with no MRD ($p<0.01$). Similarly, MRD at 3 months post treatment was associated with a PFS of only 25% at 18 months compared to 97.2% PFS in patients without MRD ($p<0.0001$). For pts receiving DART with ENE and pN1 disease, 18-month PFS was 66.7% in the setting of MRD compared to 88.8% for no MRD ($p=0.08$).

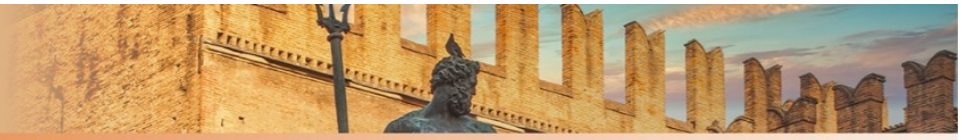
Conclusion

This secondary analysis of MC1675 validates post-op detectable TTMV-HPV DNA as a risk factor for recurrence and demonstrates 3-month post treatment TTMV-HPV DNA as an additional highly significant MRD timepoint identifying at least 50% of all recurrences. Assay standardization is paramount to future studies as well as pre-op collection on all patients. For patients with clinical risk factors such as ENE, our data support the hypothesis that post-op TTMV-HPV DNA could aid in patient selection for de-escalation.



Study Name	NCT Code	Phase	Status	Eligibility	De-Escalation Strategy	Outcomes
PATHOS	NCT02215265	II/III	Accrual	T1–3, N0–2b HPV-related OPSCC (7th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1–2, no adverse features: observe 2. Intermediate risk = T1–3, N2a-b, PNI, LVI, 1–5 mm margins: randomized to adjuvant RT of 50 Gy or 60 Gy 3. High risk = positive margins (<1 mm), >1 mm ENE: randomized to adjuvant 60 Gy RT or 60 Gy RT with concurrent cisplatin	N/A
ADEPT	NCT01687413	III	Accrual	Resectable T1–4a HPV-related OPSCC, ENE positive	All patients undergo TORS and ND, nodal disease with ENE randomized to 60 Gy RT alone or with concurrent weekly cisplatin	N/A Terminated because of poor accrual
MINT	NCT03621696	II	Complete, no published results	Stage I-III resectable HPV-related OPSCC (8th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = <T4, <cN3, no ENE, negative margins: 42 Gy adjuvant RT 2. Intermediate risk = <T4, <cN3, ENE, or positive margins = 42 Gy adjuvant RT with one dose cisplatin 3. High risk = T4, cN3: 60 Gy RT with concurrent cisplatin	Preliminary results available on clinicaltrials.gov

University of Pittsburgh/NCT03715946 Phase 2 p16+ OPC resected by TORS T0–T3 with at least 1 IR factor <10 PYSH: >N2b (>5 LNs), >1 mm ECE, margin+ >10 PYSH: N2, > 1 mm ECE, margin+	*Reduced PORT (45 or 50 Gy)* Plus immunotherapy (concurrent plus adj nivolumab)	Ongoing, not reported	Ongoing, not reported	*Silver et al, CO 2022* *Kang et al, CA Cancer J Clin. 2022*



ADAPT	NCT03875716	II	Accrual	Resectable HPV-related OPSCC, T0–2, N0–1, M0 (8th edition)	All patients undergo TOS and ND. Post-operative risk stratification: 1. Low risk = pT1–2, N0–1, minimum of 15 LNs examined, ≤2 LN involved, no ENE: observation 2. Intermediate risk = pT1–2, N0–2, >2 LNs involved, <15 LNs examined, positive LNs in levels Ib, IV, or V, ≤1 mm ENE, contralateral LNs, close margins: reduced adjuvant RT 3. High risk = pT1–4, N0–2 with >1 mm ENE and positive margins: adjuvant RT (standard dose)	N/A
DELPHI	NCT03396718	I	Accrual	Patients with resected primary and ND with indication for adjuvant therapy	Patients are randomized to: 1. Intermediate risk = HPV + pT3 and R0 +/− 1–2 LN involvement and no ECE: 54/59.4 Gy 2. High risk = HPV + with R1, pT4, 3+ nodes, and/or ECE: 60/66 Gy 3. Comparative group 1 (HPV−) = 60/66 Gy 4. Comparative group 2 (HPV+) = 60/66 Gy	N/A
	NCT03729518	II	Accrual	Resectable T1–3, N0–2c HPV-related OPSCC (7th edition)	All patients undergo TORS and ND. If post-operative pathology demonstrates <5 involved LN, patients undergo reduced adjuvant RT to nodal areas, avoiding primary site, with or without chemotherapy	N/A
	NCT02784288	I	Active, not recruiting	Potentially resectable T1–3, N0–2c HPV-related OPSCC	All patients undergo ND and biopsy of primary site. Post-operative pathology determining treatment pathway: 1. Low risk = ≤1 LN < 6 cm, no ENE, no LVI, no PNI: TOS 2. Intermediate risk = >/=2 LNs, presence of PNI/LVI, no ENE: RT 3. High risk = ENE or positive margins: concurrent CRT	N/A

Silver et al, CO 2022

Summary

Treatment de-escalation after upfront surgery: feasible, several modalities

Early promising results, however coming from phase-II trials (NO SOC)

Biomarkers approaches to improve patient selection

Grazie per l'attenzione

Ich bedanke mich