Thyroid and Salivary Cancer Updates

Prakash Neupane MD

3, 10, 11, 12, 15, 16, 20, 23, 24, 25, 27, 28, 29, 33, 34, 37, 38, 39, 42, 43.

Salivary Gland cancer

Occurs in glands of:

- »Parotid
- »Submandibular
- »Sublingual
- »Minor salivary glands

Salivary Gland cancer

Fewer than 10% of epithelial H&N cancers.

Association with prior Radiation exposure.[1]

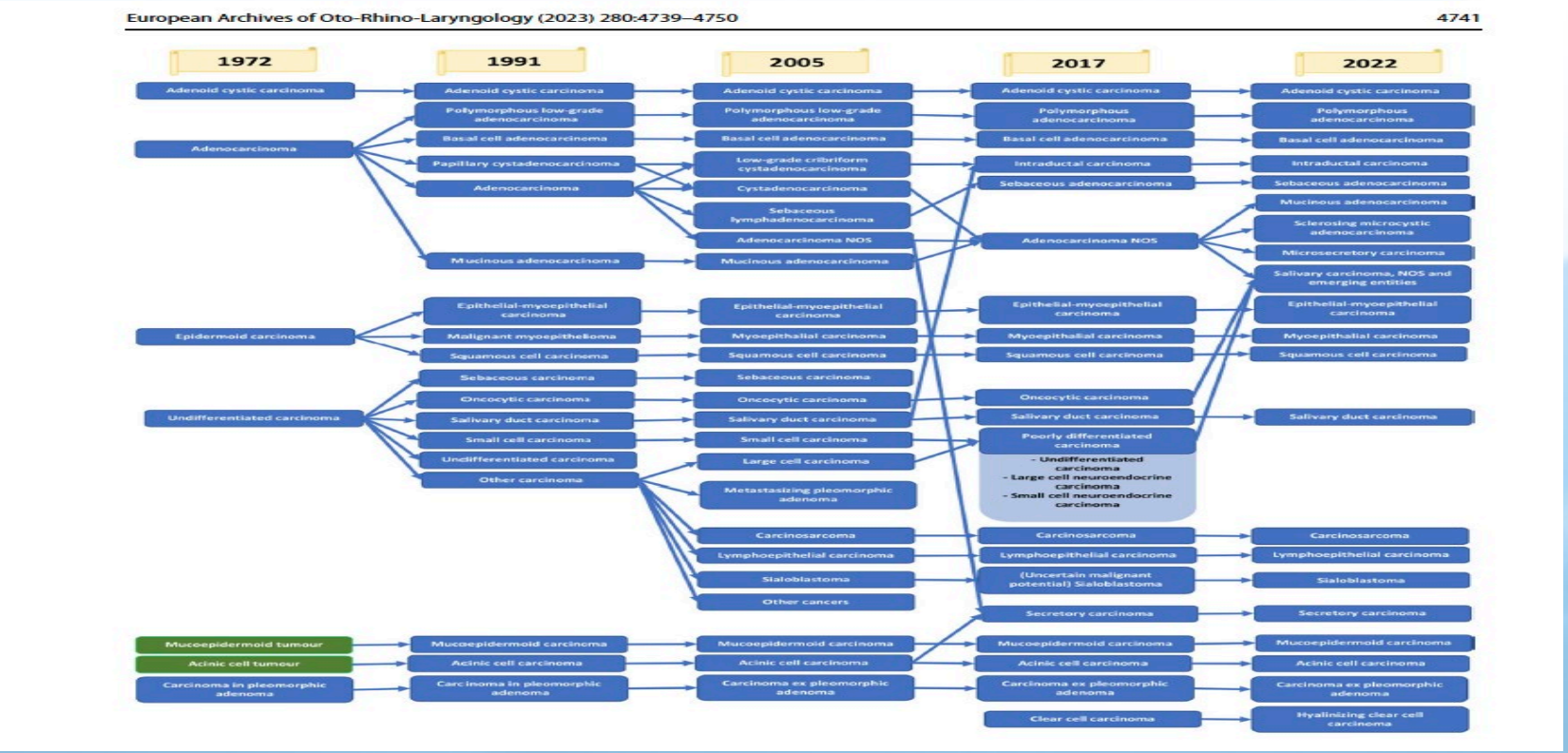
WHO classification lists more than 20 different subtypes of salivary gland cancers.[2]

Due to small numbers, histologic & prognostic heterogeneity, it is difficult to conduct trials

1. Belsky JL, Tachikawa K, Cihak RW, Yamamoto T. Salivary gland tumors in atomic bomb survivors, Hiroshima-Nagasaki, 1957 to 1970. JAMA. 1972 Feb 14;219(7):864-8

2. Skalova A et al (WHO classification of tumors series, 5th ed.; vol. 9). Available. from: https://tumourclassification.iarc.who.int/chapters/52

Classification of Salivary Cancers Over the Years.



Cancer Type and Molecular Alterations

Table 1 Selected genetic alterations in salivary gland malignancies [11, 14, 20]

Tumour type	Gene	Mechanism	Prevalenc
Acinic cell carcinoma	NR4A3	Fusion/activation	86%
Adenoid cystic carcinoma	MYB	Fusion/activation/amplification	80%
	MYBL1	Fusion/activation/amplification	10%
	NOTCH	Mutation	14%
Basal cell adenocarcinoma	CYLD	Mutation	29%
Carcinoma ex pleomorphic adenoma	PLAG1	Fusion/amplification	73%
	HMGA2	Fusion/amplification	14%
	TP53	Mutation	60%

Cancer Type and Molecular Alterations

*Eur Arch Otorhinolaryngol **280**, 4739–4750 (2023). https://doi.org/10.1007/s00405-023-08110-w*

Epithelial-myoepithelial carcinoma	HRAS	Mutation	78%
Hyalinizing clear cell carcinoma	EWSR1-ATF1	Fusion	93%
Intraductal carcinoma			
Intercalated duct subtype	NCOA4-RET	Fusion	47%
Apocrine subtype	PIK3CA	Mutation	High
	HRAS	Mutation	High
Salivary duct carcinoma	HER2	Amplification	31%
	FGFR1	Amplification	10%
	TP53	Mutation	56%
	PIK3CA	Mutation	33%
	HRAS	Mutation	33%
	AR	Copy gain	35%
	PTEN	Loss	38%
	CDKN2A	Loss	10%

Cancer Type and Molecular Alterations

Eur Arch Otorhinolaryngol **280**, 4739–4750 (2023). https://doi.org/10.1007/s00405-023-08110-w

Microsecretory adenocarcinoma	MEF2C-SS18	Fusion	>90%
Mucinous adenocarcinoma	AKT1 E17K	Mutation	100%
	TP53	Mutation	88%
Mucoepidermoid carcinoma	CRTC1-MAML2	Fusion	40–90%
	CRTC3-MAML2	Fusion	6%
	CDKN2A	Deletion	25%
Myoepithelial carcinoma	PLAG1	Fusion	38%
	EWSR1	Rearrangement	13%
Polymorphous adenocarcinoma			
Classic subtype	PRKD1	Mutation	73%
Cribriform subtype	PRKD1	Fusion	38%
	PRKD2	Fusion	14%
	PRKD3	Fusion	19%
Sebaceous adenocarcinoma	MSH2	Loss	10%
Secretory carcinoma	ETV6-NTRK3	Fusion	>90%
	ETV6-RET	Fusion	2–5%

NGS

Helpful to get tissue NGS that includes RNA fusion panel upfront on all high-risk disease.

Classification of Benign Salivary Epithelial Tumors

Eur Arch Otorhinolaryngol **280**, 4739–4750 (2023). https://doi.org/10.1007/s00405-023-08110-w

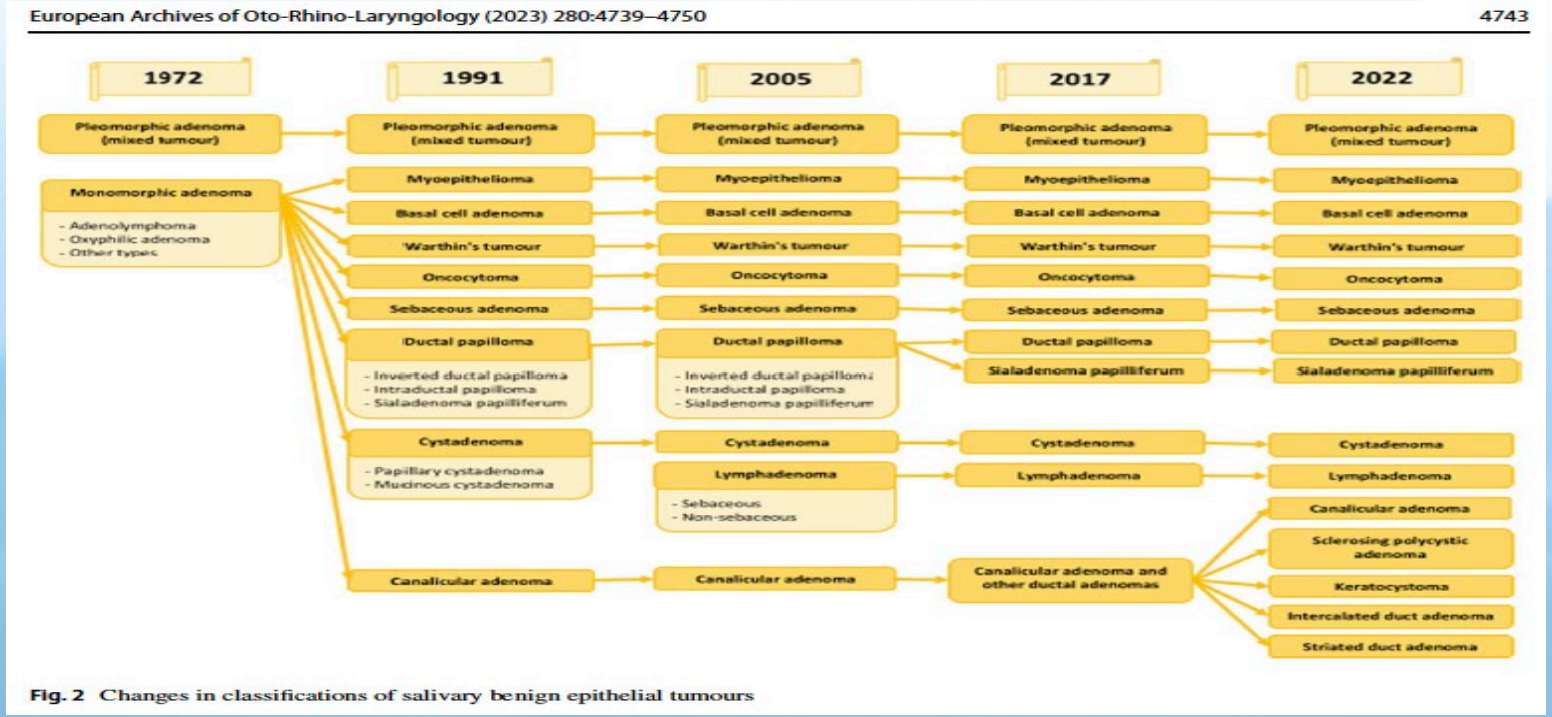
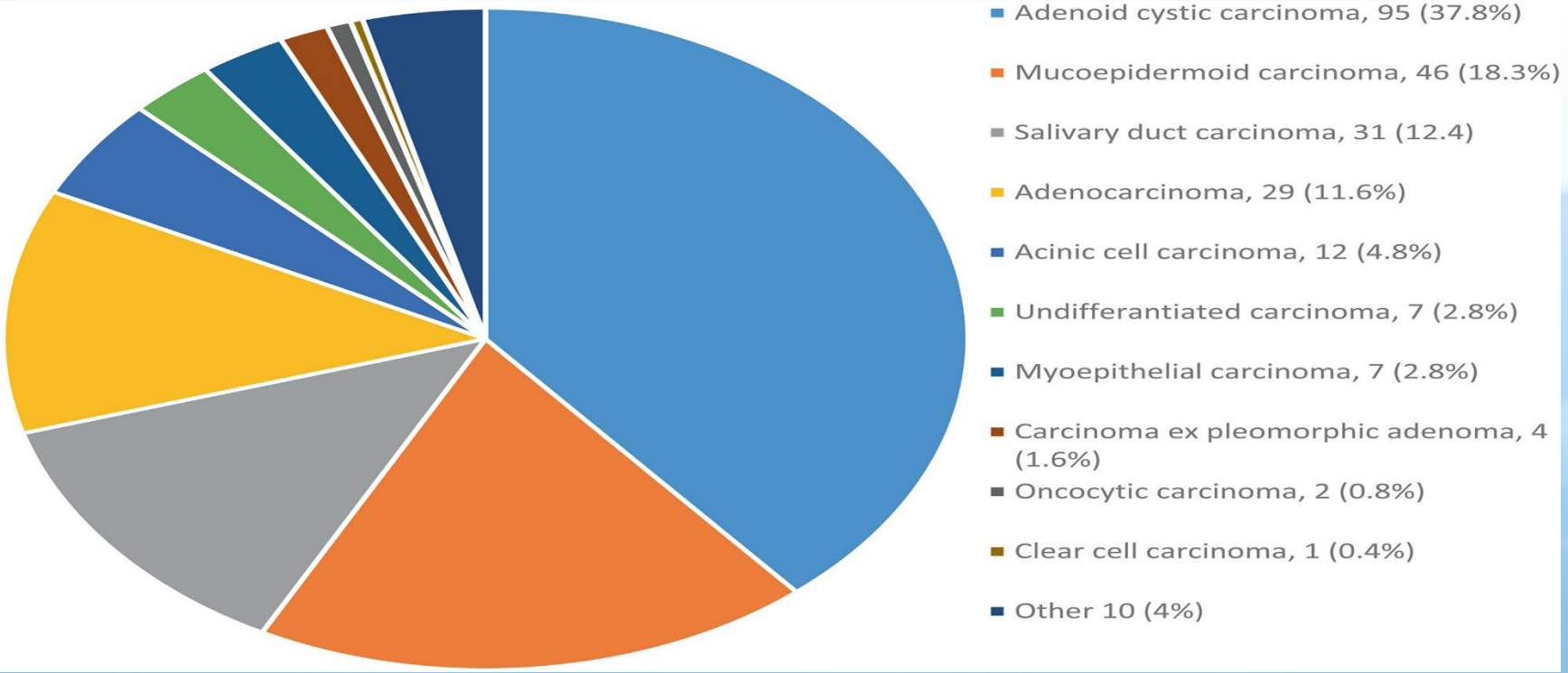


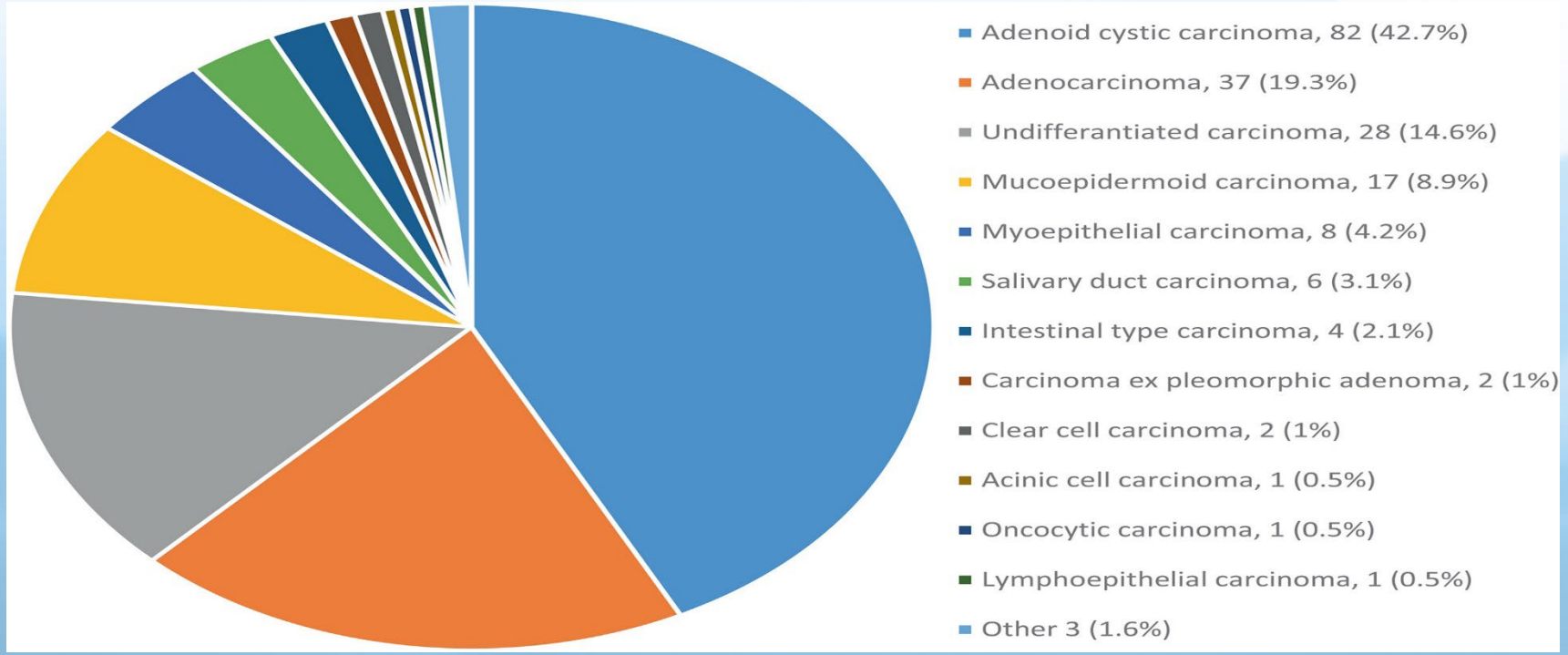
Fig. 2 Changes in classifications of salivary benign epithelial tumours

Major Salivary Gland Cancers



Head and Neck 21 April 2023 https://doi.org/10.1002/hed.27376

Minor Salivary Gland Cancers



Head and Neck 21 April 2023 https://doi.org/10.1002/hed.27376

Salivary Gland cancer

Most common types

- Adenoid cystic carcinoma
- Adenocarcinoma / ductal

Common Targets

- Ductal – AR, Her2 neu
- MASC -Mammary analogue secretory carcinoma (MASC) of the salivary gland: **(NTRK)**

Low-grade tumors

- Indolent course
- Curable with local Tx

High-grade mucoepidermoid or adeno

- Aggressive and Frequently metastasize

Treatment

Surgery

- Mainstay of Tx for all resectable primary & nodal metastasis
- Add adjuvant XRT if adverse pathologic features

Radiation based Tx- mostly palliative.

- For unresectable tumors

Adjuvant Treatment

No randomized trials so far.

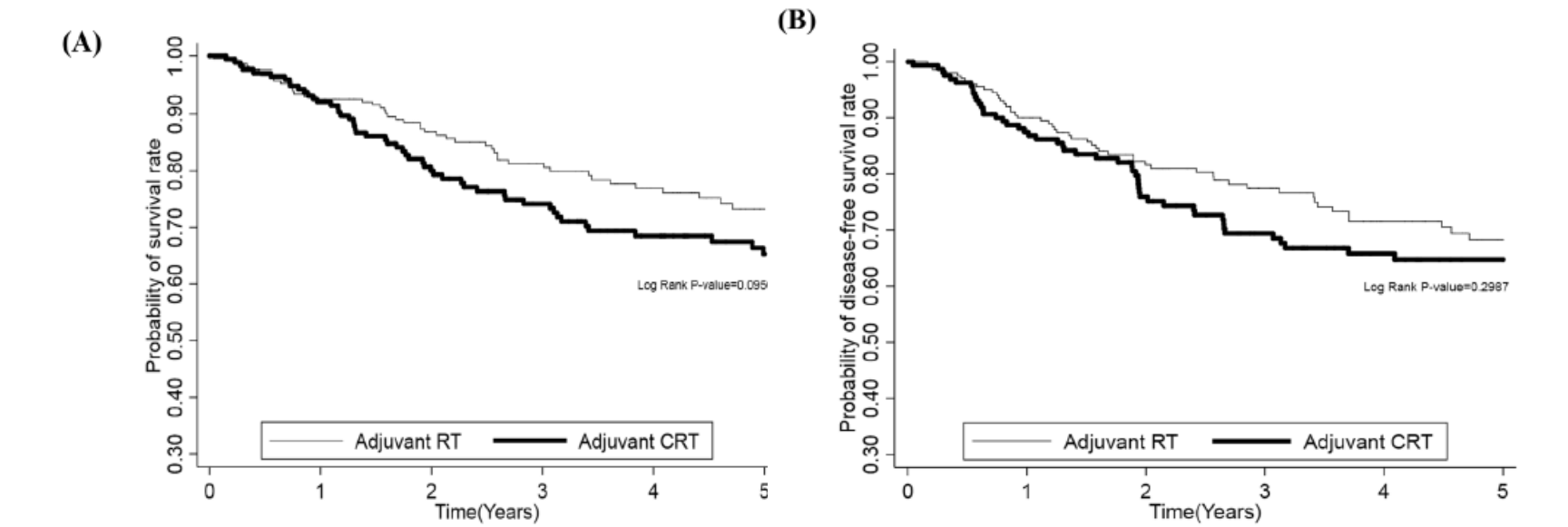
Radiation alone remains the standard of care in high risk of recurrence after surgery.

RTOG 1008 Phase II/ III trial still enrolling.

High Risk Factors (RTOG 1008)

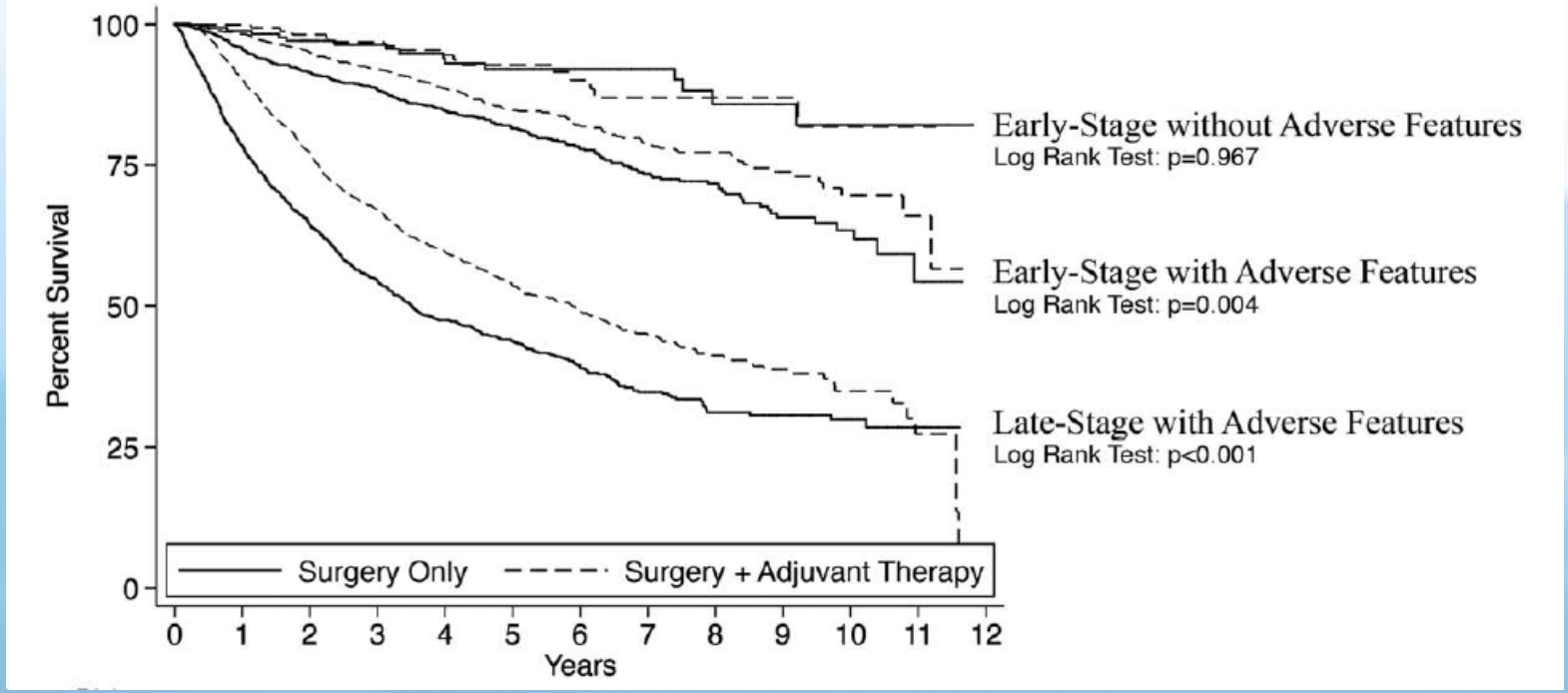
- Intermediate-grade adenocarcinoma or intermediate-grade mucoepidermoid carcinoma;
- High-grade adenocarcinoma or high-grade mucoepidermoid carcinoma or salivary duct carcinoma;
- High-grade acinic cell carcinoma or high-grade (>30% solid component) adenoid cystic carcinoma.
- Pathologic stage T3-4 or N1-3 or T1-2, N0 with a close (≤1mm) or microscopically positive surgical margin

Adjuvant CRT vs Radiation Alone
A National database Taiwan retrospective review from Taiwan



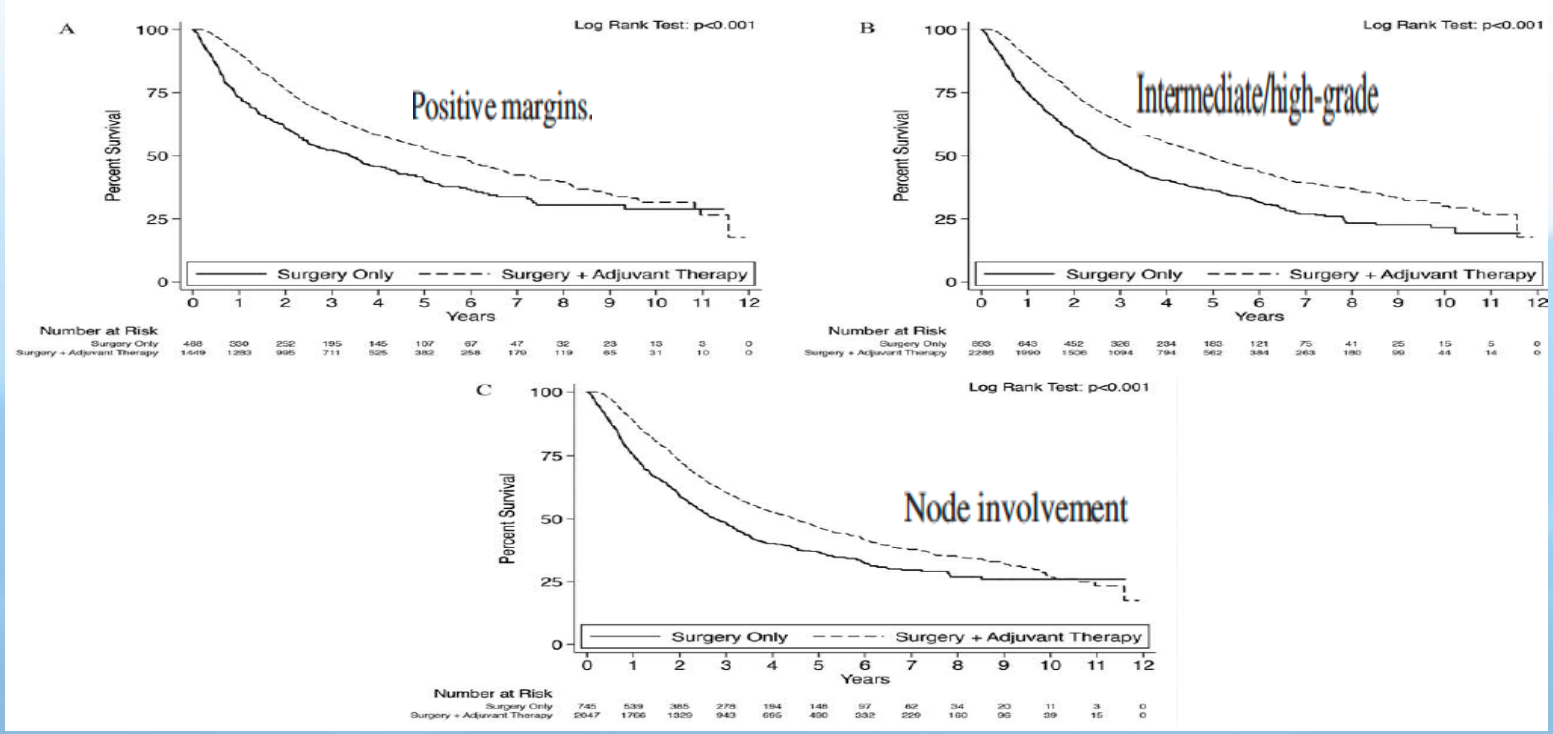
Scientific Reports | (2022) 12:20862 *https://doi.org/10.1038/s41598-022-25468-9*

NCDB review of adjuvant therapy



Cheraghlou et al Head & Neck. 2018;40:1343–1355 DOI: 10.1002/hed.24984

Survival According to Risk Factors



Cheraghlou et al Head & Neck. 2018;40:1343–1355 DOI: 10.1002/hed.24984

CRT vs Radiation Alone in Adjuvant

Head & Neck. Gordon et al DOI: 10.1002/hed.27222

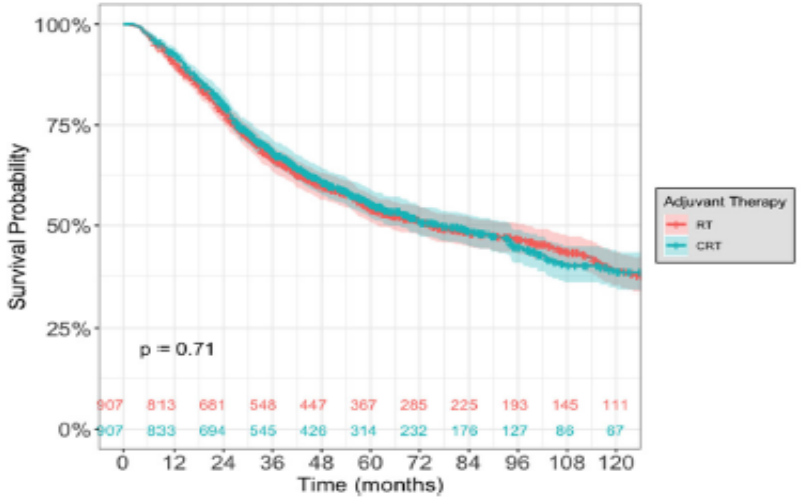


FIGURE 3 Kaplan–Meier survival curves of propensity-score matched groups receiving adjuvant radiotherapy or adjuvant chemoradiation. CRT, chemoradiation; RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

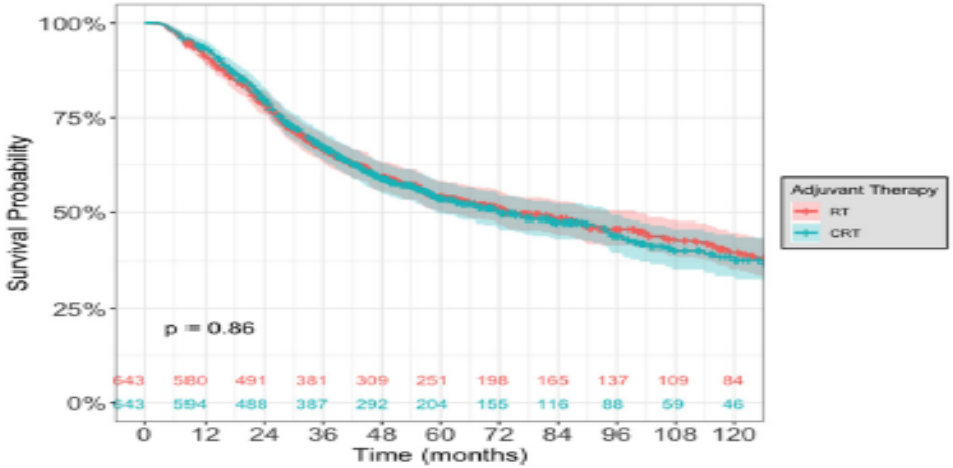


FIGURE 4 Kaplan–Meier survival curves of propensity-score matched groups with mucoepidermoid carcinoma, adenocarcinoma, adenoid cystic carcinoma, acinar cell carcinoma, or intraductal receiving adjuvant radiotherapy or adjuvant chemoradiation. CRT, chemoradiation; RT, radiotherapy [Color figure can be viewed at wileyonlinelibrary.com]

Adjuvant radiation vs Chemoradiation

- To date, No evidence of clear benefit to add chemotherapy to radiation in adjuvant setting. No prospective trial data available.

- In practice, high risk group is still considered for concurrent chemoradiation if no significant comorbidity exists and have good performance status.

- Result from a phase III randomized trial (RTPG 1008) is expected to help for better guidance and stronger evidence.

Recurrent and Metastatic Disease
HER2 Positivity as a Target

Histological Subtype	Study Included	Number of patients	HER2 positivity estimate (95% CI)
Salivary duct carcinoma	37	1105	43% (95% CI: 36% – 51%)
Carcinoma ex pleomorphic adenoma	14	218	39% (95% CI: 32% – 45%)
Squamous cell carcinoma	5	39	17% (7.5%-33%)
Adenocarcinoma NOS	14	274	13% (7.6% – 21%)
Intraductal carcinoma	1	9	11% (0.28% – 48%)
Poorly differentiated carcinoma	4	15	6.7% (0.17%-32%).
Mucoepidermoid carcinoma	15	591	5.5% (2.9% – 9.6%).
Myoepithelial carcinoma	9	70	4.3% (1.4% – 13%)
Epithelial-myoepithelial carcinoma	2	56	1.8% (0.04%-9.6%)
Acinic cell carcinoma	10	274	0.45% (0.0097% – 18%)
Adenoid cystic carcinoma	14	541	0.15% (0.037% – 5.4%)
Polymorphus adenocarcinoma	3	50	0%
Basal cell carcinoma	5	33	0%
Oncocytic carcinoma	3	14	0%
Lymphoepithelial carcinoma	2	5	0%
Clear cell carcinoma	1	1	0%
Total	50	3372	

Egebjerg et al Front Oncol. 2021; 11: 693394. Jun 24. doi: 10.3389/fonc.2021.693394

Systemic Therapy - NCCN

SYSTEMIC THERAPY FOR SALIVARY GLAND TUMORS

Recurrent, Unresectable, or Metastatic Salivary Gland Tumors (with no surgery or RT option)

- **The choice of systemic therapy should be individualized based on patient characteristics (eg, PS, goals of therapy).**

Preferred Regimens

- None

Other Recommended Regimens

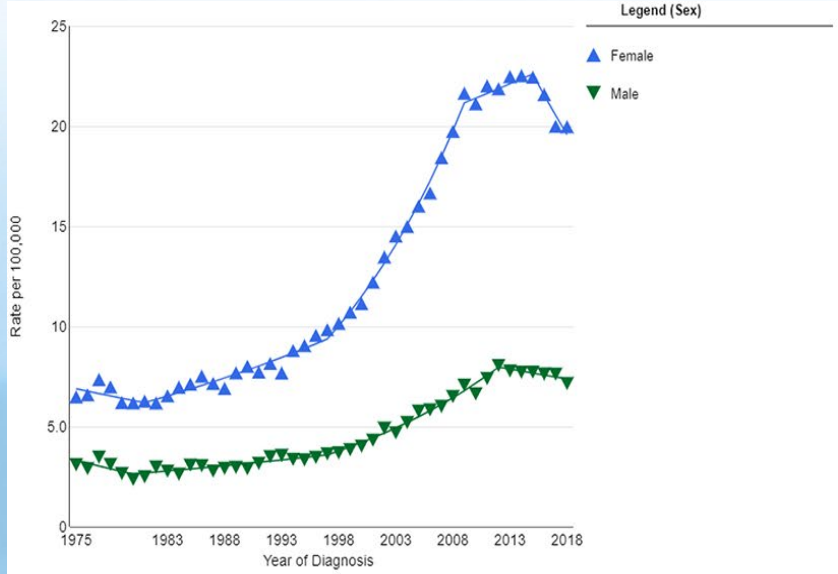
- Cisplatin/vinorelbine[1]
- Cisplatin/doxorubicin/cyclophosphamide[2] (category 2B)
- Paclitaxel (category 2A for non-adenoid cystic carcinoma [ACC]; category 2B for ACC)[3]
- Carboplatin/paclitaxel[4,5]
- Carboplatin/gemcitabine[6]

Useful in Certain Circumstances

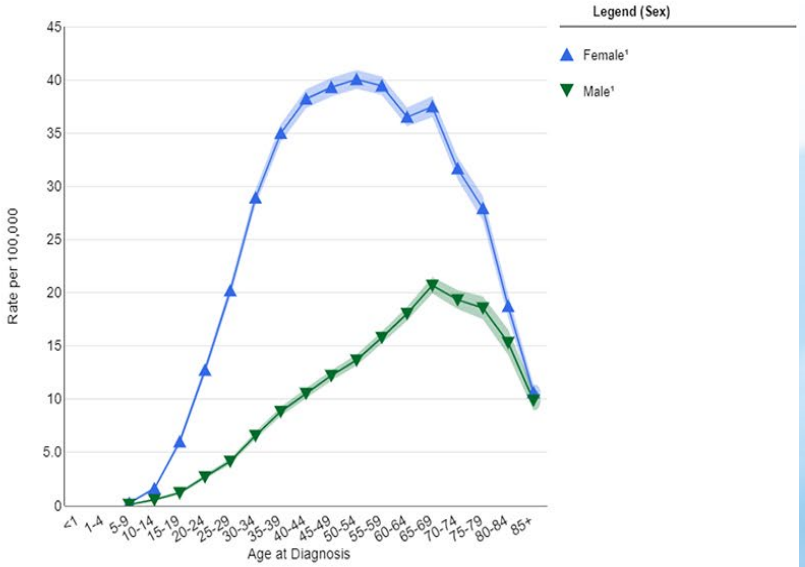
- Androgen receptor (AR) therapy for AR+ tumors
  - Leuprolide[7]
  - Bicalutamide[8]
  - Abiraterone[9]
  - Goserelin (category 2B)[10,11,12]
- *NTRK* therapy for *NTRK* gene fusion-positive tumors
  - Larotrectinib[13,14]
  - Entrectinib[15]
- HER2-targeted therapy for HER2+ tumors[a]
  - Trastuzumab[b,16]
  - Ado-trastuzumab emtansine (TDM-1)[17]
  - Trastuzumab/pertuzumab[b,18]
  - Docetaxel/trastuzumab[b,19]
  - Fam-trastuzumab deruxtecan-nxki[20]
- Sorafenib (category 2B)[21]
- Axitinib (category 2B)[22]
- Axitinib + avelumab for ACC (category 2B)[23]
- Lenvatinib for ACC (category 2B)[24]
- Pembrolizumab (for microsatellite instability-high [MSI-H], mismatch repair deficient [dMMR], TMB-H [≥10 mut/Mb] tumors)[25]
- Dabrafenib/trametinib for *BRAF* V600E-positive tumors[26]
- Selpercatinib for *RET* gene fusion-positive tumors[27]

Thyroid Cancer

Incidence of Thyroid Carcinoma.



a.



b.

Surveillance, Epidemiology, and End Results Program (SEER) Cancer Statistics Review, 1975–2018 [Internet]. Bethesda (MD): National Cancer Institute; 2021. Apr 15 [cited 2021 Nov 24]. Available from: http://seer.cancer.gov/csr/1975_2018.

Thyroid

- 2.4-fold increase in incidence between 1973 and 2002
- Mortality rate stable at 0.5 deaths per 100,000 people
- Papillary thyroid cancer is increasing (not other types)
  - Nearly 90% of cancers are subclinical or smaller than 2 cm in size
  - Early-stage cancers may account for most of the observed changes in incidence

Classification – 2 types

Cells of origin:

• Papillary thyroid carcinomas (PTC)	90%
• Follicular thyroid carcinomas (FTC)	4%
• Hürthle-cell carcinomas	2%
• Medullary thyroid carcinomas (MTC)	2% (parafollicular cells)
• Anaplastic thyroid carcinomas (ATC)	1%

Surveillance, Epidemiology, and End Results Program (SEER) Cancer Statistics Review, 1975–2018 [Internet]. Bethesda (MD): National Cancer Institute; 2021. Apr 15 [cited 2021 Nov 24]. Available from: http://seer.cancer.gov/csr/1975_2018.

Histologic Subtypes

Well-differentiated types

- Papillary
- Follicular
- Mixed tumors (papillary & follicular)
- Follicular variant of papillary
- Hurthle cell (variant of follicular ca)

Prognosis

10 yr survival rate for differentiated

thyroid cancer = 90%

Treatment

Differentiated thyroid cancer : papillary and follicular

- Surgery
  - Extent of removal is controversial
  - Many experts recommends removal of the entire thyroid
    - Complications: recurrent laryngeal nerve injury vocal cord paralysis
    - Hypocalcemia 2/2 hypoparathyroidism
  - Partial removal [the affected lobe and isthmus]
    - for better risk pts (young, small tumors)

- Levothyroxine suppression

- Radioactive iodine

- External beam XRT and chemo : reserved for palliation for refractory metastatic disease

Gordon et al JAMA Otolaryngol Head Neck Surg. 2022;148(12):1156-1163. doi:10.1001/jamaoto.2022.3360

Metastatic Disease, Iodine Refractory

Systemic Therapy Regimens for Metastatic Disease		
Preferred Regimens		
Dabrafenib/trametinib[2] (*BRAF* V600E mutation positive)	Dabrafenib 150 mg PO and Trametinib 2 mg PO	Twice daily Once daily
Larotrectinib[3] (*NTRK* gene fusion positive)	100 mg PO	Twice daily
Entrectinib[4] (*NTRK* gene fusion positive)	600 mg PO	Once daily
Pralsetinib[5] (*RET* gene fusion-positive)	400 mg PO	Once daily
Selpercatinib[6] (*RET* gene fusion-positive)	120 mg PO (<50 kg) or 160 mg PO (≥50 kg)	Twice daily
Other Recommended Regimens		
Paclitaxel[8]	60–90 mg/m² IV or 135–200 mg/m²	Weekly Every 3–4 weeks
Doxorubicin[8]	20 mg/m² IV or 60–75 mg/m² IV	Weekly Every 3 weeks
Paclitaxel/carboplatin[1] (category 2B)	Paclitaxel 60–100 mg/m² IV, carboplatin AUC 2 IV or Paclitaxel 135–175 mg/m² IV, carboplatin AUC 5–6 IV	Weekly Every 3–4 weeks
Docetaxel/doxorubicin[1] (category 2B)	Docetaxel 60 mg/m² IV, doxorubicin 60 mg/m² IV (with G-CSF) or Docetaxel 20 mg/m² IV, doxorubicin 20 mg/m² IV	Every 3–4 weeks Weekly
Useful in Certain Circumstances		
Doxorubicin/cisplatin[8]	Doxorubicin 60 mg/m² IV, cisplatin 40 mg/m² IV	Every 3 weeks
Pembrolizumab[a,7]	200 mg IV or 400 mg IV	Every 3 weeks Every 6 weeks
Pembrolizumab/lenvatinib[9]	Pembrolizumab 200 mg IV (or 400 mg IV every 6 weeks) + Lenvatinib 20–24 mg PO daily	Every 3 weeks
Nivolumab[10,11]	240 mg IV or 480 mg IV	Every 2 weeks Every 4 weeks

NCCN version 2 2024

Anaplastic or Poorly Differentiated Thyroid Carcinoma

SYSTEMIC THERAPY

Adjuvant/Radiosensitizing Chemotherapy Regimens[1]		
Other Recommended Regimens		
Paclitaxel/carboplatin	Paclitaxel 50 mg/m² IV, carboplatin area under the curve (AUC) 2 IV	Weekly
Docetaxel/doxorubicin	Docetaxel 20 mg/m² IV, doxorubicin 20 mg/m² IV	Weekly
Paclitaxel	30–60 mg/m² IV	Weekly
Docetaxel	20 mg/m² IV	Weekly

NCCN version 2 2024

Consideration of Kinase Inhibitors

Oral kinase inhibitors demonstrate clinically significant activity in randomized, placebo-controlled clinical trials in locally recurrent unresectable and metastatic MTC and in radioiodine-refractory differentiated thyroid cancer (DTC).

Kinase inhibitor therapy can be associated with improved progression-free survival, but is not curative.

Kinase inhibitor therapy is expected to cause side effects that may have a significant effect on quality of life.

The natural history of MTC and DTC is quite variable with rates of disease progression ranging from a few months to many years.

The pace of disease progression should be factored into treatment decisions. Patients with very indolent disease who are asymptomatic

NCCN version 2 2024

RAI Refractory- Lenvatinib

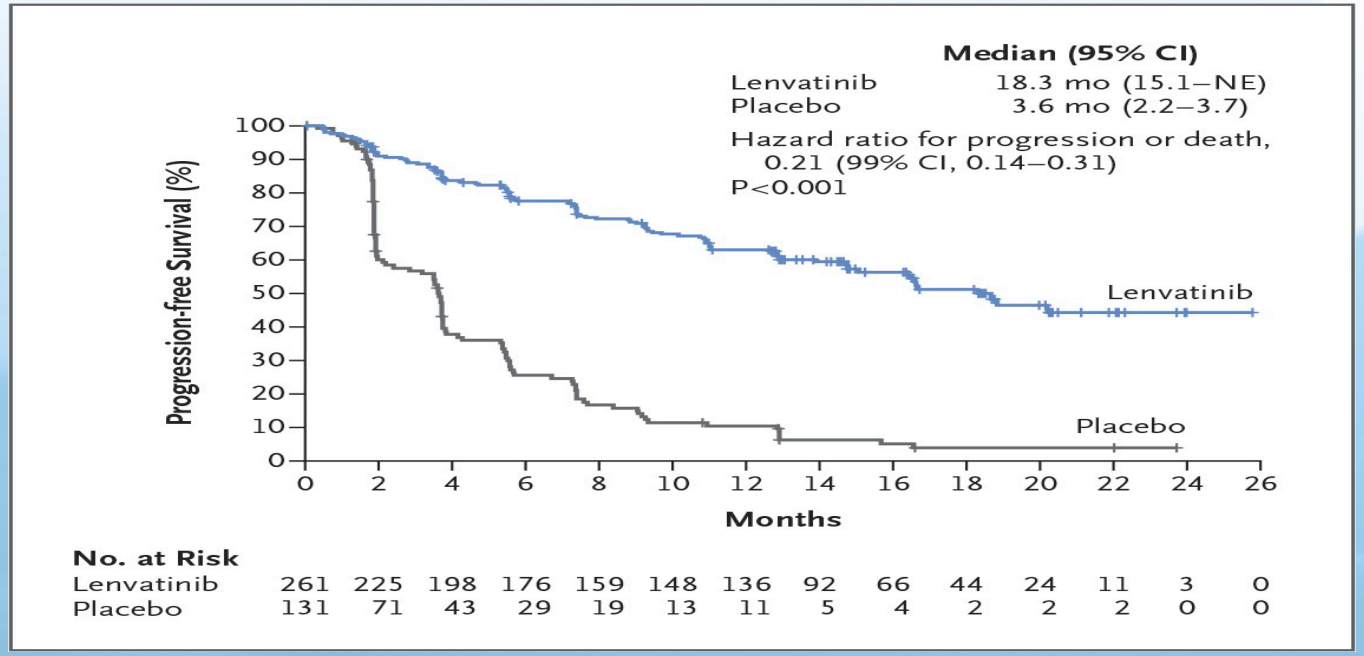
- Lenvatinib is an oral, multitargeted tyrosine kinase inhibitor of the VEGFRs 1, 2, and 3, FGFRs 1 through 4, PDGFR α, RET, and KIT signaling networks.

- Phase III trial- Inclusion, at least one measurable lesion that had progressed according to the Response Evaluation Criteria In Solid Tumors [RECIST], version 1.1, criteria within 12 months after iodine-131 therapy

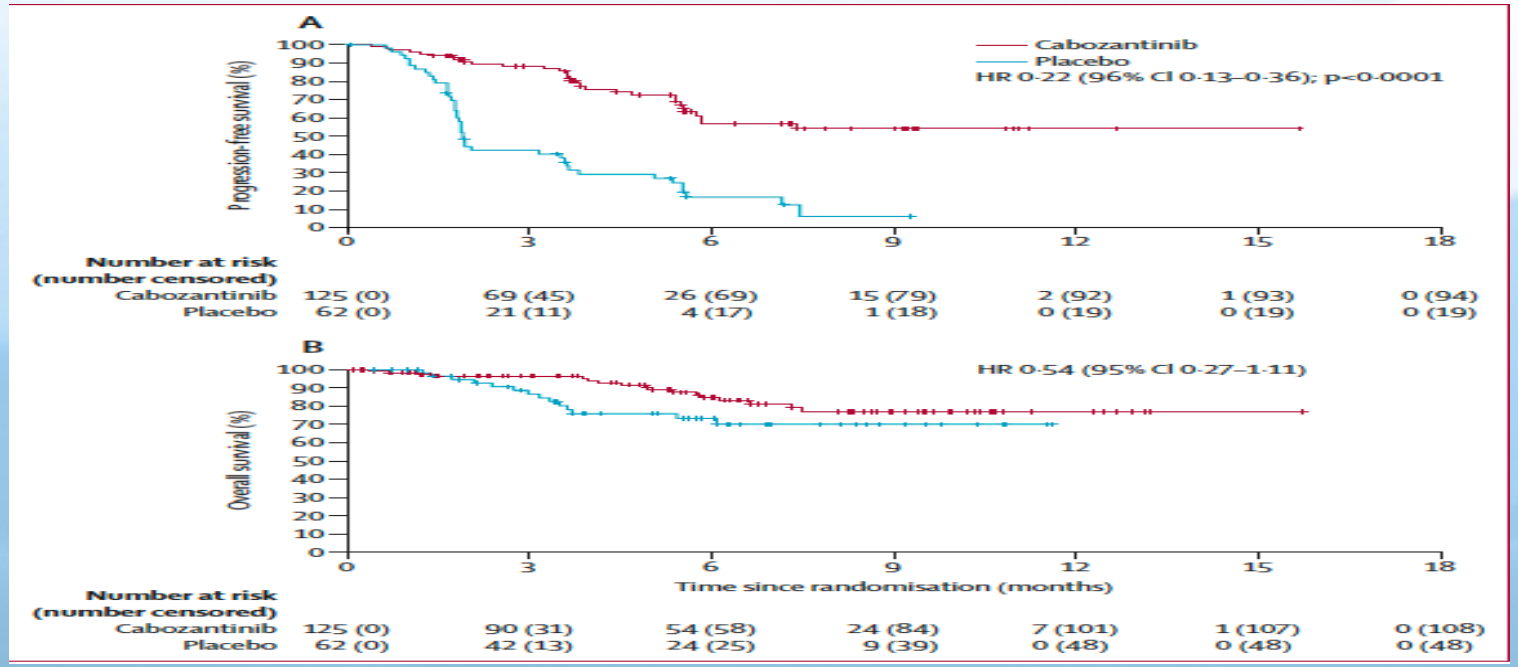
February 12, 2015, N Engl J Med 2015; 372:621-630 DOI: 10.1056/NEJMoa1406470

Lenvatinib vs placebo

February 12, 2015, N Engl J Med 2015; 372:621-630 DOI: 10.1056/NEJMoa1406470



Cabozantinib for radioiodine-refractory differentiated thyroid cancer



The Lancet Oncology COSMIC - 311 DOI:https://doi.org/10.1016/S1470-2045(21)00332-6

Medullary Thyroid cancer

Neoplasm of the calcitonin-producing cells (para-follicular)

5-9% of all thyroid cancer

Both sporadic and familial types occur

- Sporadic more common (60-70%)
- Familial more common in 15-25 years of age

Medullary Thyroid cancer

Familial Medullary Ca

- mutation in RET proto-oncogene
- Dominant pattern of inheritance

- May be part of MEN
  - MEN 2A
    - Medullary thyroid cancer
    - Pheochromocytoma
    - Parathyroid hyperplasia
  - MEN 2B
    - Medullary thyroid cancer
    - Pheochromocytoma
    - Intestinal and mucosal ganglioneuromatosis
- May be a familiar form not associated with MEN

Thakker et al, J Clin Endocrinol Metab. 2012;97(9):2990. Epub 2012 Jun 20.

Treatment MTC

- **Total thyroidectomy with LN dissection** (risk of multifocal disease is high)
  - Bilateral central compartment node dissection
  - unilateral neck dissection at the very least.

- XRT
  - Not routinely given post-operatively
  - Disappointing efficacy for macroscopic disease

Wells et al. ATA Guidelines Thyroid. 2015;25(6):567.

Monitoring After Tx

Follow 2 tumor markers

- **Calcitonin**
- **CEA**

10-year survival rates

- 70-80% for familial and sporadic types combined

Wells et al. ATA Guidelines Thyroid. 2015;25(6):567.

Systemic therapy

Indicted for rapidly progressive or symptomatic disease.

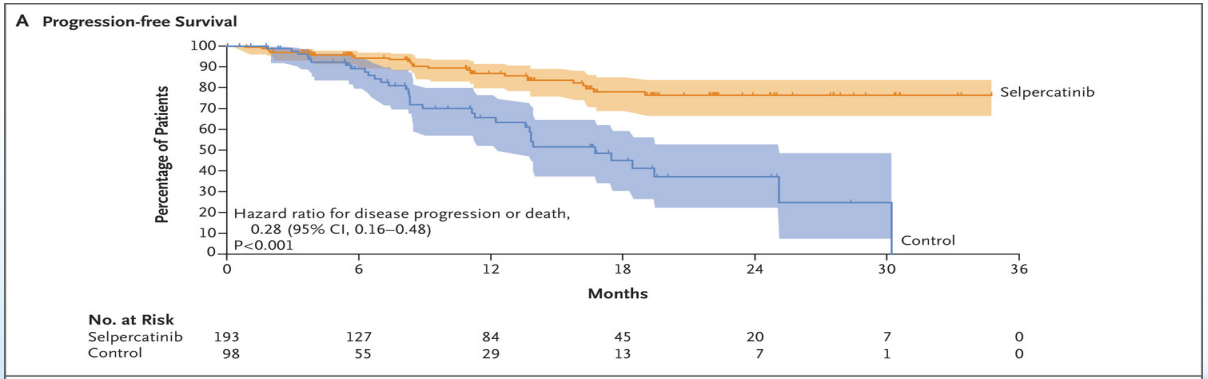
NGS is key in guiding therapy.

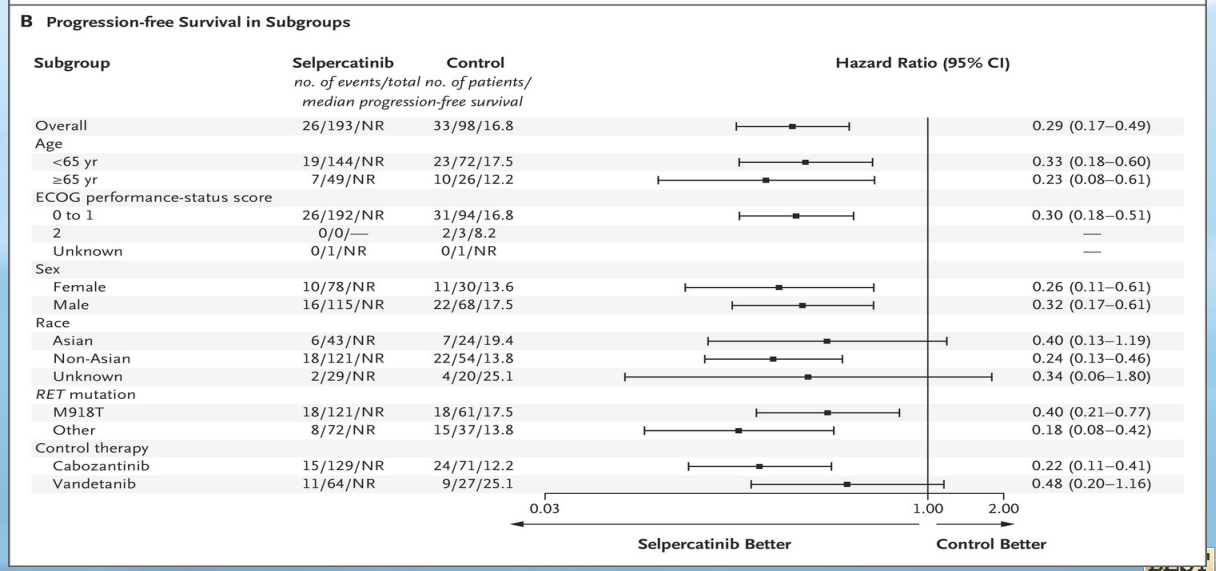
Activating RET gene abnormalities occur in over 90% of hereditary and approximately 40%-60% of sporadic medullary thyroid carcinoma cases.

Selpercatinib and Pralsetinib are options for RET abnormality.

RET Gene Abnormality

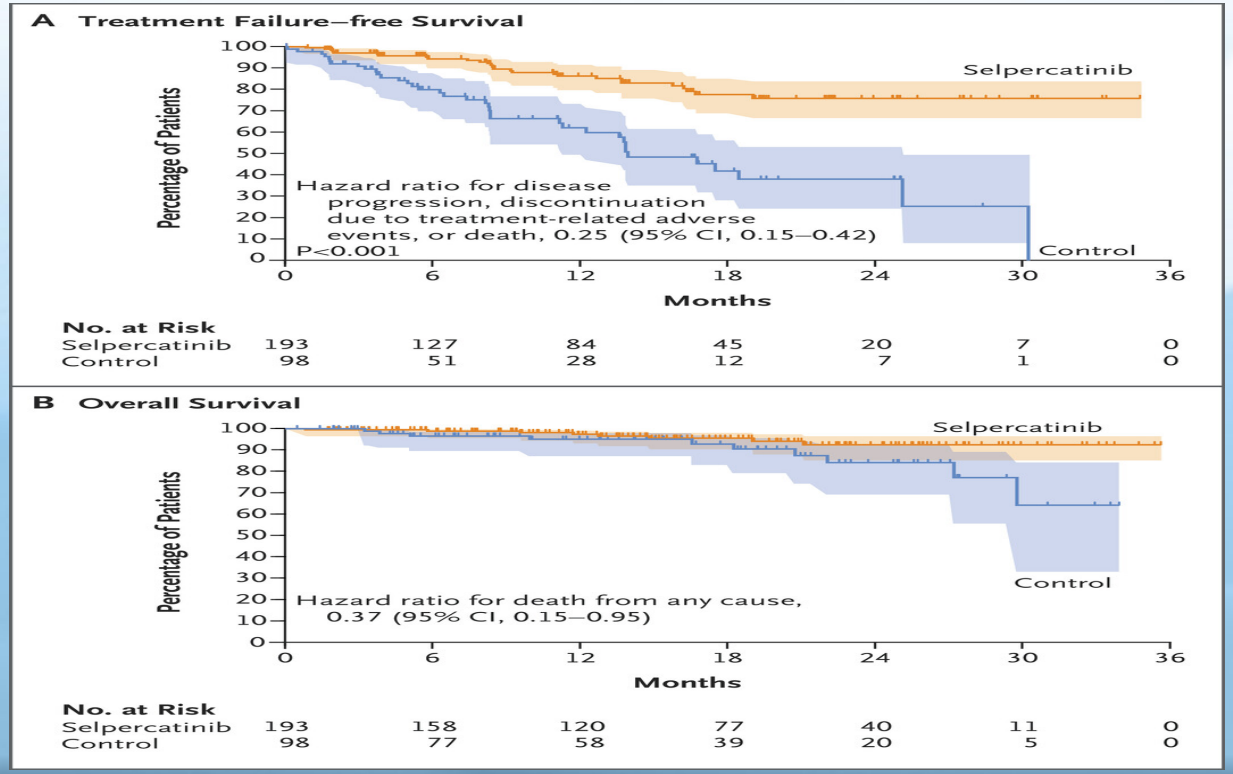
Phase 3 Trial of Selpercatinib in Advanced *RET*-Mutant Medullary Thyroid Cancer- N Engl J Med 2023;389:1851-1861 DOI: 10.1056/NEJMoa2309719
VOL. 389 NO. 20





Phase 3 Trial of Selpercatinib in Advanced *RET*-Mutant Medullary Thyroid Cancer-

N Engl J Med 2023;389:1851-1861 DOI: 10.1056/NEJMoa2309719 VOL. 389 NO. 20



Vandetanib (Oral TKI)

J Clin Oncol. 2012 Jan 10;30(2):134-41. doi: 10.1200/JCO.2011.35.5040.

Targets VEGF, RET, EGFT

Randomized Phase III

- 300mg Vandetanib daily vs placebo
  - Better PFS (HR 0.46, p<0.001)
  - Also V better in objective response rate, Disease control rate
    ** No OS benefit reported yet
  - Boxed warning: Risk of QT prolongation

FDA approval (April, 6, 2011):
-Vandetanib for symptomatic or progressive medullary thyroid cancer in patients with unresectable, locally advanced, or metastatic disease.

Cabozantinib (Oral TKI)

J Clin Oncol. 2011 Jul;29(19):2660-6. Epub 2011 May 23

Targets

MET, VEGF receptor 2, RET

Randomized Phase III (n=330) with

- 140mg PO daily vs placebo
  - Better PFS (11.2 m vs 4 m)
  - Better response rate (28% vs 0%)

** No OS benefit reported yet **

FDA approval (November, 29, 2012):
-Cabozantinib for metastatic medullary thyroid cancer

Thank you