12th Annual Otolaryngology Literature Update
Head & Neck Oncology IV

W. Greer Albergotti, III, M.D.
Assistant Professor
Head & Neck Oncology
Department of Otolaryngology - Head & Neck Surgery
Medical University of South Carolina
albergot@musc.edu

W. Greer Albergotti, M.D. is an Assistant Professor of Otolaryngology and Head and Neck Surgery at the Medical University of South Carolina. A native of Anderson, SC, Dr. Albergotti completed his undergraduate training at Washington and Lee University in Lexington, Virginia with a B.A. in Economics (cum laude). He then returned to South Carolina to complete his Doctor of Medicine with Alpha Omega Alpha honors at the Medical University of South Carolina. He completed his Otolaryngology Residency at the University of Pittsburgh Medical Center before pursuing and completing the Head & Neck and Reconstructive Surgery Fellowship at MUSC.

After training, Dr. Albergotti joined the faculty at the Medical College of Georgia at Augusta University as an Assistant Professor. During his time there, he served as Associate Residency Program Director, the Chief of the Otolaryngology service at the Charlie Norwood VA Medical Center, and Associate Fellowship Director of Endocrine Surgery. He also received awards for his teaching, including the 2019 Exemplary Teaching Award.

Dr. Albergotti has clinical interests in all aspects of head and neck surgery (oral cavity tumors, oropharyngeal cancer including transoral robotic surgery, conservation laryngeal surgery, thyroid, and parathyroid disorders, salivary gland tumors, skin cancer, sentinel node biopsy, and transoral laser surgery). He also has an interest in the advanced reconstruction of the head and neck including microvascular reconstructive surgery.

Dr. Albergotti has published widely in the field of head and neck surgery, particularly as it relates to functional outcomes after surgery.

12th Annual Otolaryngology Literature Update
Medical University of South Carolina

Head & Neck Oncology IV

W. Greer Albergotti, III, M.D.

Gross ND, Miller DM, Khushalani NI, Divi V, Ruiz ES, Lipson EJ, Meier F, Su YB, Swiecicki PL, Atlas J, Geiger JL, Hauschild A, Choe JH, Hughes BGM, Schadendorf D, Patel VA, Homsi J, Taube JM, Lim AM, Ferrarotto R, Kaufman HL, Seebach F, Lowy I, Yoo SY, Mathias M, Fenech K, Han H, Fury MG, Rischin D. Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma. N Engl J Med. 2022 Oct 27;387(17):1557-1568. doi: 10.1056/NEJMoa2209813. Epub 2022 Sep 12. PMID: 36094839; PMCID: PMC9844515.

Liu JB, Ramonell KM, Carty SE, McCoy KL, Schaitkin BM, Karslioglu-French E, Morariu EM, Ohori NP, Seethala RR, Chiosea SI, Nikiforova MN, Nikiforov YE, Yip L. Association of comprehensive thyroid cancer molecular profiling with tumor phenotype and cancer-specific outcomes. Surgery. 2023 Jan;173(1):252-259. doi: 10.1016/j.surg.2022.05.048. Epub 2022 Oct 20. PMID: 36272768.

Mechera R, Maréchal-Ross I, Sidhu SB, Campbell P, Sywak MS. A Nod to the Nodes: An Overview of the Role of Central Neck Dissection in the Management of Papillary Thyroid Carcinoma. Surg Oncol Clin N Am. 2023 Apr;32(2):383-398. doi: 10.1016/j.soc.2022.10.012. PMID: 36925192.

Patel SP, Othus M, Chen Y, Wright GP Jr, Yost KJ, Hyngstrom JR, Hu-Lieskovan S, Lao CD, Fecher LA, Truong TG, Eisenstein JL, Chandra S, Sosman JA, Kendra KL, Wu RC, Devoe CE, Deutsch GB, Hegde A, Khalil M, Mangla A, Reese AM, Ross MI, Poklepovic AS, Phan GQ, Onitilo AA, Yasar DG, Powers BC, Doolittle GC, In GK, Kokot N, Gibney GT, Atkins MB, Shaheen M, Warneke JA, Ikeguchi A, Najera JE, Chmielowski B, Crompton JG, Floyd JD, Hsueh E, Margolin KA, Chow WA, Grossmann KF, Dietrich E, Prieto VG, Lowe MC, Buchbinder EI, Kirkwood JM, Korde L, Moon J, Sharon E, Sondak VK, Ribas A. Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma. N Engl J Med. 2023 Mar 2;388(9):813-823. doi: 10.1056/NEJMoa2211437. PMID: 36856617.

Yan L, Li Y, Li XY, Xiao J, Tang J, Luo Y. Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma: A retrospective study with more than 5 years of follow-up. Cancer. 2023 Apr 15. doi: 10.1002/cncr.34802. Epub ahead of print. PMID: 37060239.

Literature Update 2023
Head & Neck
Focus on skin and thyroid cancer

MUSC Medical University of South Carolina | Hollings Cancer Center
An NCI-Designated Cancer Center

W. Greer Albergotti, MD
Assistant Professor, Head & Neck Surgery
Medical University of South Carolina
albergot@musc.edu
Cell – 864-934-4682

MUSC Medical University of South Carolina | Hollings Cancer Center
An NCI-Designated Cancer Center

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

N.D. Gross, D.M. Miller, N.I. Khushalani, V. Divi, E.S. Ruiz, E.J. Lipson, F. Meier, Y.B. Su, P.L. Swiecicki, J. Atlas, J.L. Geiger, A. Hauschild, J.H. Choe, B.G.M. Hughes, D. Schadendorf, V.A. Patel, J. Homsi, J.M. Taube, A.M. Lim, R. Ferrarotto, H.L. Kaufman, F. Seebach, I. Lowy, S.-Y. Yoo, M. Mathias, K. Fenech, H. Han, M.G. Fury, and D. Rischin

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Background

- Cutaneous squamous cell carcinoma incidence increasing steadily
  - 200% increase since 1990
- Most curable with minor surgery
- Small percentage develop into larger cancers or with regional disease
  - Treatments potentially disfiguring
  - Adjuvant XRT
  - QOL issues
- Cemiplimab
  - PD-1 inhibitor
  - FDA approved for recurrent or metastatic cutaneous SCC
  - Objective response rates of 44-50%
  - Pilot data in stage III or IV cSCC: pCR 55%

8/26/23

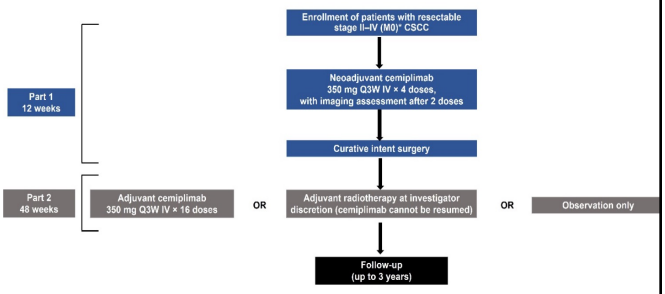
MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Study Design and Treatment

- Phase 2, multicenter, single-group, nonrandomized study
  - Australia, Germany and United States
- 2 parts:
  - Neoadjuvant cemiplimab***
  - Optional adjuvant cemiplimab, XRT or observation
- IV cemiplimab 350mg q3 weeks for 4 doses
  - Or until unacceptable SE, progression, withdrawal of consent

Figure S1. Study design



8/26/23

Inclusion Criteria

- Stage II (at least 3cm), III, IV cSCC
- Resectable and primary surgery would be recommended
  - No metastasis
- 18+
- ECOG 0/1
- No history of radiation for cSCC
- At least one measurable lesion by RECIST 1.1

AJCC8	
T1	Tumor <2 cm
T2	Tumor ≥2 cm but <4 cm
T3	Tumor >4 cm or minor bone erosion or PNI or deep invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
N1	Metastasis in a single ipsilateral lymph node ≤3 cm and ENE (–)
N2a	Metastasis in a single ipsilateral or contralateral lymph node ≤3 cm and ENE (+) or a single ipsilateral node >3 cm but ≤6 cm and ENE (–)
N2b	Metastasis in a multiple ipsilateral lymph nodes ≤6 cm and ENE (–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm and ENE (–)
N3a	Metastasis in a single lymph node >6 cm and ENE (–)
N3b	Metastasis in a single lymph node >3 cm and ENE (+) or multiple ipsilateral, contralateral or bilateral nodes, any with ENE (+)
I	T1, N0, M0
II	T2, N0, M0
III	T3 or N1, M0
IV	T4 or N≥2 or M1

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center
Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

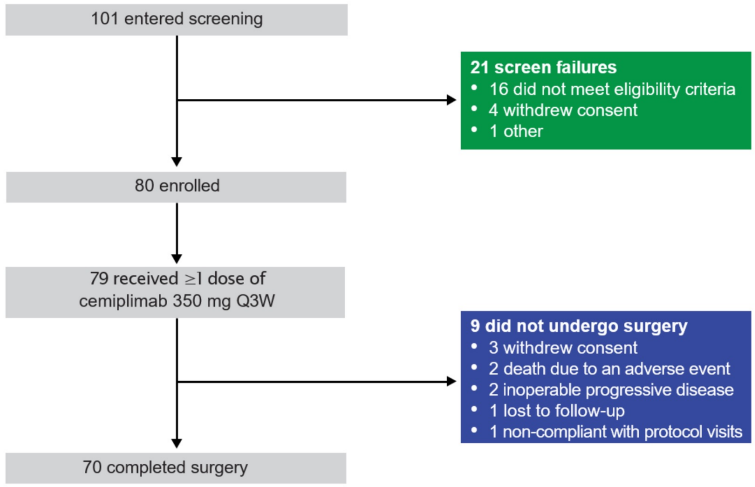
End Points and Statistical Design

- Primary
  - Pathologic CR
- Secondary
  - Pathologic major response
    - Less than 10% of surgical specimen is viable tumor cells
  - Objective response on imaging
  - Adverse events
- Independent review
  - Central lab
  - 2 non-investigator pathologists
  - Adjudicated if needed (10 cases)
- Exploratory analyses
  - PD-L1 expression >1%
  - Tumor Mutational Burden
- Powered for 72 patients to reject null hypothesis
  - pCR in 25% of patients

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Figure S2. CONSORT diagram



8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Table 1. Characteristics of the 79 Patients at Baseline.*

Characteristic	Value
Median age (range) — yr	73 (24–93)
Male sex — no. (%)	67 (85)
Race — no. (%)†	
White	69 (87)
Other	2 (3)
Not reported	8 (10)
Not Hispanic or Latinx — no. (%)†	74 (94)
Primary tumor site — no. (%)	
Head and neck	72 (91)
Trunk, arms, and legs	7 (9)
Stage group — no. (%)‡	
II	5 (6)
III	38 (48)
IV (M0)	36 (46)
Tumor stage at screening — no. (%)‡	
TX	23 (29)
Tis	1 (1)
T1	4 (5)
T2	10 (13)
T3	39 (49)
T4a	2 (3)
Node stage at screening — no. (%)‡	
NX	1 (1)
N0	31 (39)
N1	13 (16)
N2§	11 (14)
N2b	9 (11)
N2c	1 (1)
N3¶	1 (1)
N3a	1 (1)
N3b	11 (14)
ECOG performance-status score — no. (%)‖	
0	60 (76)
1	19 (24)

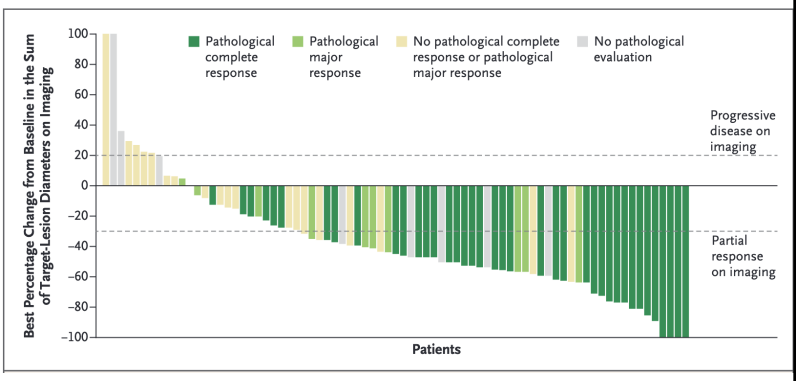
8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Results

- 17 (22%) patients did not receive all 4 planned doses of cemiplimab
  - Progression on imaging (8)
  - Clinical progression (3)
  - Presumably remainder were AE's
- 9 (11%) did not undergo surgery
  - 5 partial response
    - 3 declined surgery
    - 1 lost to follow-up
    - 1 died from MI
  - 3 disease progression
  - 1 died of AE
- pCR in 40/79 (50.6%) patients
- Major pathologic response 10/79 (13%) patients

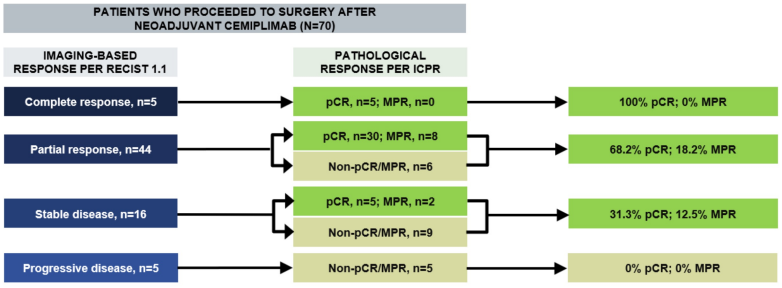


MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Results

- Imaging criteria
  - Complete response 5/79 (6.3%)
  - Partial response 49/79 (62%)
  - Stable disease 16/79 (20.2%)
  - Progressive disease 8/79 (10.1%)
  - No imaging 1/79 (1.3%)
- 9 months average follow-up
  - No recurrence noted
- PD-L1 >1% in 51% of patients
  - 20% pCR in PD-L1 negative
  - 54% pCR in PD-L1 positive
- TMB not associated with efficacy
  - Trend toward higher TMB with better pCR



8/26/23

Safety

- 87% AE (13% grade 3 or higher)
  - Fatigue, diarrhea, nausea, rash
  - 72% related to treatment
- Grade 3: 8 patients
- Grade 4: 2 patients
- Grade 5: 4 patients
  - CHF exacerbation 93y/o (2 doses cemiplimab) – possibly related
  - MI 85y/o (3 doses)
  - MI 73 y/o (7 weeks after one dose, progressive disease)
  - COVID pneumonia 82 y/o (postop)

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center
Neoadjuvant Cemiplimab for Stage II to IV Cutaneous Squamous-Cell Carcinoma

Limitations

- Absence of a control group
- Lack of randomization
- Short follow-up
- Homogenous group
- Lack of reporting of extent of surgery
  - Any changes based on neoadjuvant treatment?

Takeaways

- Strong but small study
- Already changed and/or reinforce practice patterns
  - However better phase 3 data needed
- Questions remain unanswered
  - Does the extent of surgery change?
  - How does adjuvant therapy change?
  - Are there patients who can avoid surgery altogether?
  - How is prognosis affected?
    - 42 month follow-up of smaller pilot study
      - Of 15 responders, no recurrences; of 5 non-responders 3 recurrences despite adjuvant therapy

Ferrarotto R, JAMA Oto Aug 2023

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

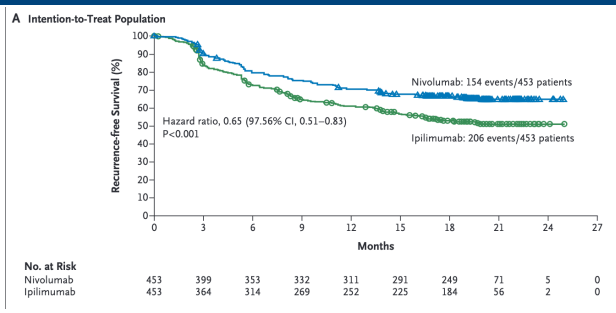
S.P. Patel, M. Othus, Y. Chen, G.P. Wright, Jr., K.J. Yost, J.R. Hyngstrom, S. Hu-Lieskovan, C.D. Lao, L.A. Fecher, T.-G. Truong, J.L. Eisenstein, S. Chandra, J.A. Sosman, K.L. Kendra, R.C. Wu, C.E. Devoe, G.B. Deutsch, A. Hegde, M. Khalil, A. Mangla, A.M. Reese, M.I. Ross, A.S. Poklepovic, G.Q. Phan, A.A. Onitilo, D.G. Yasar, B.C. Powers, G.C. Doolittle, G.K. In, N. Kokot, G.T. Gibney, M.B. Atkins, M. Shaheen, J.A. Warneke, A. Ikeguchi, J.E. Najera, B. Chmielowski, J.G. Crompton, J.D. Floyd, E. Hsueh, K.A. Margolin, W.A. Chow, K.F. Grossmann, E. Dietrich, V.G. Prieto, M.C. Lowe, E.I. Buchbinder, J.M. Kirkwood, L. Korde, J. Moon, E. Sharon, V.K. Sondak, and A. Ribas

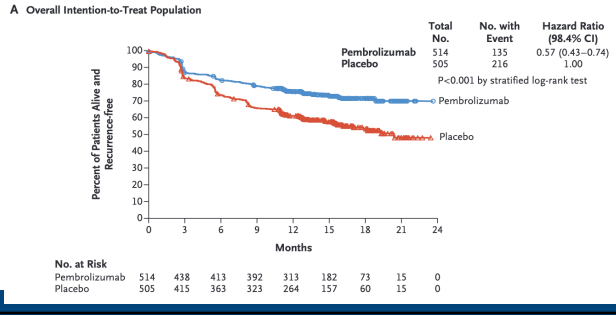
MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Background

- Standard of care for melanoma has long been surgery
  - Followed by risk-adapted adjuvant therapy
  - PD-1 blocking antibody therapy adjuvant considered standard for stage 2b and above





Weber J, NEJM 2017
Eggermont AMM, NEJM 2018

8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Background

- Anti PD-1 therapy success in adjuvant setting suggests blocking immune checkpoint generates a systemic immune response
- Tumor infiltrating T-cells would be removed by surgery
- Hypothesis that neoadjuvant may activate more antitumor T-cells than if same drug administered adjuvantly
- SWOG S1801: clinically detected, resectable stage III or IV melanoma

8/26/23

Methods

Inclusion criteria

18 or older

Cutaneous, acral or mucosal melanoma

Stage IIIB – IVD or oligometastatic stage IV

Measurable disease by RECIST

Non-recurrent

Trial design

Open-label phase 2 trial

Randomized

- 200mg pembrolizumab IV q3 weeks x 3 doses pre-operatively followed by surgery and 15 adjuvant doses
- Surgery followed by 200mg pembrolizumab IV q3 weeks x 18 doses

Primary outcome: event-free survival (disease progression, toxic effects of treatment that precluded surgery, inability to resect all gross disease, disease progression, recurrence of melanoma after surgery or any death)

8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Statistics

- Final analysis after 104 events
  - 81% power to detect HR of 0.64
- Randomly assigned in a 1:1 ratio

8/26/23

Patient characteristics

- 313 patients from 90 sites
  - 154 neoadjuvant-adjuvant
    - 2 withdrew
  - 159 adjuvant
    - 7 withdrew
- 14.7 months of follow-up

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Neoadjuvant–Adjuvant Group (N=154)	Adjuvant-Only Group (N=159)
Median age (range) — yr	64 (19–90)	62 (22–88)
Sex — no. (%)		
Female	62 (40)	48 (30)
Male	92 (60)	111 (70)
Zubrod's performance-status score — no. (%)†‡		
0	113 (73)	125 (79)
1	39 (25)	33 (21)
2	1 (<1)	0
LDH level — no. (%)		
Low or normal	132 (86)	138 (87)
High	22 (14)	21 (13)
Disease stage — no. (%)§		
IIIB	62 (40)	64 (40)
IIIC	69 (45)	74 (47)
IIID	9 (6)	10 (6)
IV	14 (9)	11 (7)
Primary melanoma subtype — no. (%)†		
Cutaneous or unknown	143 (93)	153 (96)
Acral	4 (3)	5 (3)
Mucosal	4 (3)	0
Ulceration — no. (%)†		
Yes	56 (36)	46 (29)
No	50 (32)	58 (36)
Unknown	46 (30)	55 (35)
BRAF mutation status — no. (%)		
Mutated	41 (27)	38 (24)
Wild-type	62 (40)	64 (40)
Unknown	51 (33)	57 (36)
Previous BRAF and MEK adjuvant therapy — no. (%)		
Yes	3 (2)	1 (1)
No	151 (98)	158 (99)
Previous radiotherapy — no. (%)		
Yes	2 (1)	1 (1)
No	152 (99)	158 (99)

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Methods

- Inclusion criteria
  - 18 or older
  - Cutaneous, acral or mucosal melanoma
  - Stage IIIB – IVD or oligometastatic stage IV
  - Measurable disease by RECIST
  - Non-recurrent
- Trial design
  - Open-label phase 2 trial
  - Randomized
    - 200mg pembrolizumab IV q3 weeks x 3 doses pre-operatively followed by surgery and 15 adjuvant doses
    - Surgery followed by 200mg pembrolizumab IV q3 weeks x 18 doses
  - Primary outcome: event-free survival (disease progression, toxic effects of treatment that precluded surgery, inability to resect all gross disease, disease progression, recurrence of melanoma after surgery or any death)

Statistics

- Final analysis after 104 events
  - 81% power to detect HR of 0.64
- Randomly assigned in a 1:1 ratio

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Results

- 105 events
  - 38 neoadjuvant-adjuvant, 67 adjuvant-only
- 2-year event free survival
  - 72% neoadjuvant-adjuvant (14 deaths)
  - 49% adjuvant (22 deaths)
  - No differences in subgroup analysis
- 127/144 (88%) in neoadjuvant group underwent surgery
  - 2 withdrawal of consent
  - 1 toxic effects
  - 12 disease progression
  - 1 coexisting conditions
  - 1 CR who declined surgery

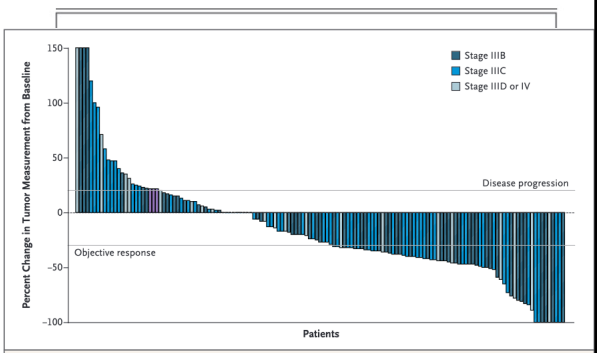


Figure 3. Overall Response in the Neoadjuvant–Adjuvant Group.
The waterfall plot shows the maximum percentage change in the size of target lesions from baseline in patients who were assigned to receive both neoadjuvant and adjuvant therapy. Each bar represents 1 patient, and the dark green, blue, and light green bars indicate the disease stage at the time of enrollment in patients who underwent imaging assessment after completing neoadjuvant therapy. The thresholds for objective response (≥30% decrease) and disease progression (>20% increase) according to Response Evaluation Criteria in Solid Tumors, version 1.1, are shown. The purple bars indicate 3 patients (1 in each disease-stage subgroup) who had clinical disease progression without a follow-up tumor imaging assessment (1 patient) or discontinued neoadjuvant therapy early because of toxic effects (2 patients; 1 underwent surgery without imaging and 1 did not undergo surgery). Data from 10 patients who were still receiving neoadjuvant therapy and 2 patients who withdrew consent immediately after randomization are excluded from this figure.

Toxicity

- Grade 3 or 4 events
  - Neoadjuvant-adjuvant
    - 11/152 (7%) related to neoadjuvant pembrolizumab
    - 9/127 (7%) related to surgery
    - 12% related to adjuvant pembrolizumab
  - Adjuvant
    - 5/141 (4%) related to surgery
    - 14% related to adjuvant pembrolizumab
- No deaths related to pembrolizumab in either group

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center
Neoadjuvant-Adjuvant or Adjuvant-Only Pembrolizumab in Advanced Melanoma

Takeaways

- 23% improvement event-free survival with neoadjuvant + adjuvant pembrolizumab in resectable stage III or IV melanoma
- <10% disease progression with inability to undergo surgery
- Reasonable toxicity profile
- Standard of care changed based on phase II data

MUSC Medical University of South Carolina | Hollings Cancer Center
An NCI-Designated Cancer Center

Surgery 173 (2023) 252–259

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Association of comprehensive thyroid cancer molecular profiling with tumor phenotype and cancer-specific outcomes

Jason B. Liu, MD, MS[a], Kimberly M. Ramonell, MD[a], Sally E. Carty, MD[a], Kelly L. McCoy, MD[a], Barry M. Schaitkin, MD[b], Esra Karslioglu-French, MD[c], Elena M. Morariu, MD[c], N. Paul Ohori, MD[d], Raja R. Seethala, MD[d], Simion I. Chiosea, MD[d], Marina N. Nikiforova, MD[d], Yuri E. Nikiforov, MD, PhD[d], Linwah Yip, MD[a,*]

[a] Division of Endocrine Surgery, Department of Surgery, University of Pittsburgh, PA
[b] Department of Otolaryngology, University of Pittsburgh, PA
[c] Division of Endocrinology and Metabolism, Department of Medicine, University of Pittsburgh, PA
[d] Division of Molecular and Genomic Pathology, Department of Pathology, University of Pittsburgh, PA

MUSC Medical University of South Carolina | Hollings Cancer Center
An NCI-Designated Cancer Center

Association of comprehensive thyroid cancer marker profiling with tumor phenotype and cancer-specific outcomes

Background

- Molecular testing (MT) has been used for nearly 10 years to risk-stratify indeterminate thyroid nodules on cytology
- Knowledge of mutational patterns in thyroid cancer has advanced
  - RAS/RAF – less aggressive
  - BRAF – more aggressive
  - TERT – more aggressive
  - NTRK/RET – targetable
- Unclear whether preop MT can predict histopathologic features and cancer-specific outcomes

2017 Bethesda System for Reporting Thyroid Cytopathology

Diagnostic Category	ROM if NIFTP not cancer	ROM if NIFTP is cancer	Management
Nondiagnostic/unsatisfactory Cyst fluid only Acellular specimen Other: Obscuring factors	5–10%	5–10%	Repeat fine needle aspiration under ultrasound guidance
Benign Benign follicular nodule Chronic lymphocytic (Hashimoto) thyroiditis, in proper clinical setting Granulomatous (subacute) thyroiditis	0–3%	0–3%	Clinical and US follow-up until two negative
Atypia of undetermined significance/ follicular lesion of undetermined significance	6–18%	10–30%	Repeat FNA, molecular testing, or lobectomy
Follicular neoplasm/ suspicious for a follicular neoplasm (Specify if Hürthle cell type)	10–40%	25–40%	Molecular testing, lobectomy
Suspicious for malignancy	45–60%	50–75%	Lobectomy or near-total thyroidectomy
Malignant Papillary thyroid carcinoma Medullary thyroid carcinoma Poorly differentiated carcinoma Undifferentiated (anaplastic) carcinoma Squamous cell carcinoma Carcinoma with mixed features Metastatic malignancy Non-Hodgkin lymphoma Other	94–96%	97–99%	Lobectomy or near-total thyroidectomy

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Association of comprehensive thyroid cancer marker profiling with tumor phenotype and cancer-specific outcomes

Methods

- Retrospective cohort
- TT or HT for thyroid ca
- Preop MT as part of routine clinical care
- Exclusion:
  - Recurrent disease
  - Medullary thyroid cancer
  - NIFTP
  - Distant metastasis at presentation
- Stratified by Thyroseq v.3.0
  - Low-risk
    - RAS and RAS-like alterations (BRAF K601E, PAX8/PPARG)
  - Intermediate risk
    - BRAF V600E, BRAF-like alterations, BRAF-like GEAs
  - High risk
    - TERT, TP53, PIK3CAfDICER1 with high-level CNA's

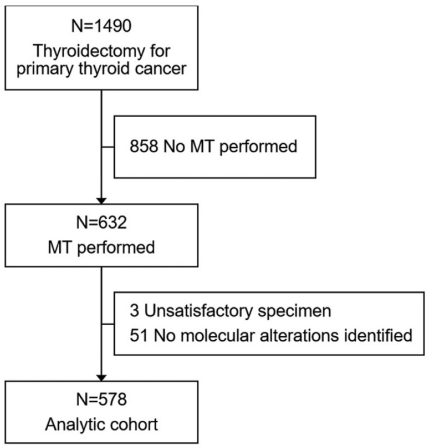


Figure 1. Patient selection schema. MT, molecular testing.

8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Association of comprehensive thyroid cancer marker profiling with tumor phenotype and cancer-specific outcomes

Methods

- Stratified by Thyroseq v.3.0
  - Low-risk
    - RAS and RAS-like alterations (BRAF K601E, PAX8/PPARG)
  - Intermediate risk
    - BRAF V600E, BRAF-like alterations (ETV6/NTRK fusion), BRAF-like GEAs
  - High risk
    - TERT, TP53, PIK3CA, DICER1 with high-level CNA's
- Primary outcome
  - Thyroid cancer recurrence
    - Structural or biochemical

8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center — An NCI-Designated Cancer Center

Association of comprehensive thyroid cancer marker profiling with tumor phenotype and cancer-specific outcomes

Results

- 578 patients included
- Most with indeterminate thyroid nodules
- 86.5% PTC on histology
- Most had total thyroidectomy (69.9%)
- 9.1% recurrence rate
- Average follow-up of 19 months

8/26/23

Table I
Patient and perioperative characteristics of the entire cohort and by molecular risk group

	Total ($n = 578$)	Molecular risk groups			P
		Low ($n = 288$)	Intermediate ($n = 217$)	High ($n = 73$)	
Age, mean (SD)	50.7 (17.0)	51.4 (16.0)	44.8 (16.1)	65.1 (14.2)	< .001
Female, *n* (%)	430 (74.4)	229 (79.5)	157 (72.4)	44 (60.3)	.002
Preoperative levothyroxine use, *n* (%)	64 (11.1)	32 (11.1)	24 (11.1)	8 (11.0)	1.00
Surgeon specialty, *n* (%)					.19
Endocrine	396 (68.5)	197 (68.4)	156 (71.9)	43 (58.9)	
Otorhinolaryngology	175 (30.3)	86 (29.9)	59 (27.2)	30 (41.1)	
Other	7 (1.2)	5 (1.7)	2 (0.9)	0 (0.0)	
Bethesda category, *n* (%)					< .001
VI	117 (20.2)	2 (0.7)	91 (41.9)	24 (32.9)	
V	58 (10.0)	8 (2.8)	44 (20.3)	6 (8.2)	
IV	155 (26.8)	101 (35.1)	31 (14.3)	23 (31.5)	
III	225 (38.9)	172 (59.7)	42 (19.4)	11 (15.1)	
I/II/not performed	23 (4.0)	5 (1.7)	9 (4.2)	9 (12.3)	
Total thyroidectomy, *n* (%)	404 (69.9)	149 (51.7)	191 (88.0)	64 (87.7)	< .001
Central neck dissection, *n* (%)					< .001
Prophylactic	90 (15.6)	15 (5.2)	59 (27.2)	16 (21.9)	
Therapeutic	48 (8.3)	2 (0.7)	30 (13.8)	16 (21.9)	
Lateral neck dissection, *n* (%)	48 (8.3)	1 (0.4)	31 (14.3)	16 (21.9)	< .001
Median tumor size (IQR), cm	1.9 (1.1–3.0)	2.0 (1.0–3.0)	1.6 (1.1–2.5)	3.5 (2.0–5.3)	< .001
Tumor <1 cm, *n* (%)	110 (19.0)	69 (24.0)	37 (17.1)	4 (5.5)	.001
Metastatic disease at presentation, *n* (%)	15 (2.6)	0 (0.0)	3 (1.4)	12 (16.4)	< .001
Postoperative radioiodine, *n* (%)	195 (33.7)	40 (13.9)	107 (49.3)	48 (65.8)	< .001
Postoperative complications, *n* (%)					.08
Emergency room visit	4 (0.7)	2 (0.7)	1 (0.5)	1 (1.4)	
Hematoma	5 (0.9)	2 (0.7)	1 (0.5)	2 (2.7)	
Hypocalcemia	24 (4.2)	6 (2.1)	12 (5.5)	6 (8.2)	
Recurrent laryngeal nerve paresis	27 (4.7)	8 (2.8)	13 (6.0)	6 (8.2)	
Surgical site infection	5 (0.9)	4 (1.4)	1 (0.5)	0 (0.0)	
Urinary tract infection	1 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	
Other	8 (1.4)	2 (0.7)	4 (1.8)	2 (2.7)	
Long-term complications, *n* (%)					.03
Hypocalcemia	4 (0.7)	0 (0.0)	3 (1.4)	1 (1.4)	
Recurrent laryngeal nerve paresis	9 (1.6)	1 (0.4)	5 (2.3)	3 (4.1)	
Other	3 (0.5)	0 (0.0)	2 (0.9)	1 (1.4)	

Bethesda, Bethesda System for Reporting Thyroid Cytopathology.

Table II
Histopathologic characteristics and outcomes of the entire cohort and by molecular risk group

	Total ($n = 578$)	Molecular risk groups			P
		Low ($n = 288$)	Intermediate ($n = 217$)	High ($n = 73$)	
Histologic type, *n* (%)					< .001
Papillary, classic	255 (44.1)	78 (27.1)	157 (72.4)	20 (27.4)	
Papillary, follicular variant	188 (32.5)	171 (59.4)	15 (6.9)	2 (2.7)	
Papillary, high risk*	57 (9.9)	9 (3.1)	33 (15.2)	15 (20.6)	
Oncocytic/Hürthle cell	37 (6.4)	16 (5.6)	11 (5.1)	10 (13.7)	
Follicular	15 (2.6)	12 (4.2)	0 (0.0)	3 (4.1)	
Poorly differentiated	18 (3.1)	2 (0.7)	1 (0.5)	15 (20.6)	
Anaplastic	8 (1.4)	0 (0.0)	0 (0.0)	8 (11.0)	
Bilobar, *n* (%)	110 (19.0)	36 (12.5)	57 (26.3)	17 (23.3)	< .001
Multifocal, *n* (%)	209 (36.2)	103 (35.8)	82 (37.8)	24 (32.9)	.74
Extrathyroidal extension, *n* (%)					< .001
Microscopic	73 (12.6)	6 (2.1)	56 (25.8)	11 (15.1)	
Gross	41 (7.1)	1 (0.4)	17 (7.8)	23 (31.5)	
Involved margins, *n* (%)	74 (12.8)	6 (2.1)	44 (20.3)	24 (32.9)	< .001
Vascular invasion, *n* (%)	74 (12.8)	18 (6.3)	26 (12.0)	30 (41.1)	< .001
Lymphatic invasion, *n* (%)	145 (25.1)	16 (5.6)	96 (44.2)	33 (45.2)	< .001
Central nodal disease, *n* (%)	102 (17.7)	5 (1.7)	75 (34.6)	22 (30.1)	< .001
Lateral nodal disease, *n* (%)	43 (7.4)	1 (0.4)	31 (14.3)	11 (15.1)	< .001
AJCC prognostic stage, *n* (%)					< .001
I	499 (86.3)	275 (95.5)	194 (89.4)	30 (41.1)	
II	62 (10.7)	13 (4.5)	21 (9.7)	28 (38.4)	
III	8 (1.4)	0 (0.0)	2 (0.9)	6 (8.2)	
IV	9 (1.6)	0 (0.0)	0 (0.0)	9 (12.3)	
ATA risk stratification, *n* (%)†					< .001
Low	400 (71.1)	264 (91.7)	119 (55.6)	17 (27.9)	
Intermediate	115 (20.4)	22 (7.6)	77 (36.0)	16 (26.2)	
High	48 (8.5)	2 (0.7)	18 (8.4)	28 (45.9)	
Median follow-up (IQR), mo	19 (10–31)	18 (11–31)	20 (10–31)	18 (8–31)	0.60
Recurrence, *n* (%)†	51 (9.1)	6 (2.1)	25 (11.7)	20 (32.8)	< .001
Death, *n* (%)	7 (1.2)	1 (0.4)	1 (0.5)	5 (6.9)	< .001

8/26/23

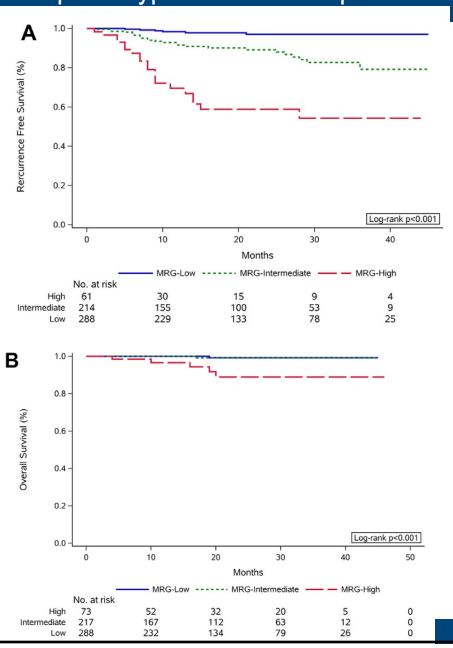
Liu J, *Surgery* 2023

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Association of comprehensive thyroid cancer marker profiling with tumor phenotype and cancer-specific outcomes

Results

- MRG grouping significantly associated with recurrence free survival
  - MRG-high 3.7x more likely to recur than intermediate
  - MRG-intermediate 5.8x more likely to recur than low
    - Maintained after controlling for age, sex, tumor size
- All-cause mortality more frequent in patients with MRG-high (6.9%) than intermediate (0.5%) or low (0.4%)



MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Association of comprehensive thyroid cancer marker profiling with tumor phenotype and cancer-specific outcomes

Implications

- Moving toward routine molecular testing on all thyroid cancers to guide extent of surgery, need for radioactive iodine, and provide prognosis
- MRG-low
  - Hemithyroidectomy may be appropriate
  - Avoidance of RAI
  - Active surveillance option for those with comorbidities
- MRG-high
  - Potential escalation of care
    - Total thyroidectomy
    - Prophylactic CND

MUSC Medical University of South Carolina | Hollings Cancer Center
An NCI-Designated Cancer Center

ORIGINAL ARTICLE

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma: A retrospective study with more than 5 years of follow-up

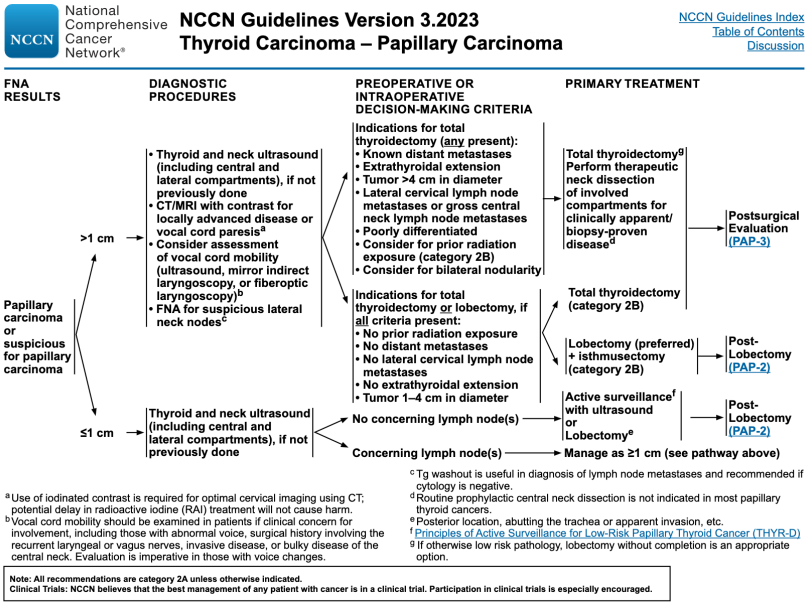
Lin Yan MD | Yingying Li MD | Xin Yang Li MD | Jing Xiao MD | Jie Tang MD | Yukun Luo MD

Cancer. 2023;1–10.

MUSC Medical University of South Carolina | Hollings Cancer Center
An NCI-Designated Cancer Center

Background

- Incidence of well-differentiated papillary thyroid cancer (PTC) has been increasing
- Prognosis is excellent (>99% survival)
- Trend in thyroid cancer management has been toward de-escalation of care:
  - Active surveillance
  - Extent of surgery
    - Hemithyroidectomy
- Ultrasound-guided thermal ablation technology has been used for treatment of early stage PTC
  - Long-term data lacking



8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center, An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Methods

- Retrospective review (China)
- All patients who underwent RFA for solitary T1 (<2cm) PTC
- Refused or unsuitable for surgery
- At least 5 years of follow-up
- Exclusion criteria:
  - Extrathyroidal extension
  - Lymphadenopathy
  - Distant metastasis
  - History of neck radiation
  - Histology other than PTC
  - Incomplete data

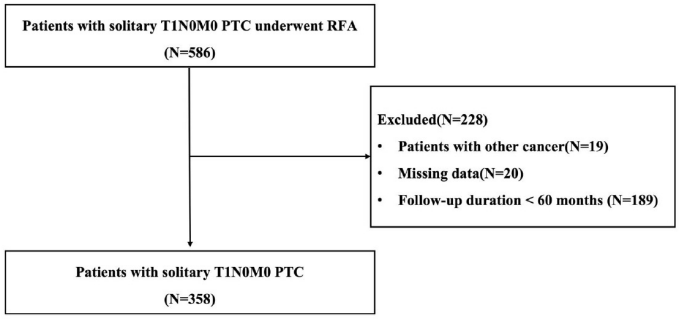
8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Methods

- Pretreatment evaluation
  - CBC, TFT's, coagulation tests
  - US
  - Chest CT
- RFA procedure
  - Local anesthesia
  - Experienced provider (20y)
  - 18-gauge bipolar RF applicator
  - Extended 3mm beyond capsule of tumor
  - CEUS after with re-ablation as needed



8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Methods

- Follow-up
  - 1, 3, 6, 12, 18 months then yearly after
  - US, CEUS, yearly chest CT and physical exam
  - Core needle biopsy performed
  - Volume reduction rate (VRR) calculated at each follow-up
- Primary outcome
  - Disease progression
    - Pathologically-confirmed LNM
    - Recurrent tumor (second primary)
    - Persistent tumor at site of ablation confirmed by biopsy
    - Distant metastasis
- Secondary outcome
  - VRR
  - Rate of complete disappearance
  - Complications
  - Need for surgery (recurrence or patient request)

8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Results

- 358 patients
  - 276 female / 82 male
- Mean age 43y
- T1a – 303 (mean size 7mm)
- T1b – 55 (mean size 15 mm)
- Average volume 194mm^3
- Average follow-up 75.5 mo

TABLE 1 Baseline characteristics of patients before treatments.

Characteristics	Data
Age, year	43.0 ± 10.0
Sex	
Female	276 (77.1)
Male	82 (22.9)
No. of tumors	358
T1a (≤1 cm)	303 (84.6)
T1b (>1 and ≤2 cm)	55 (15.4)
Largest diameter, mm	7.1 ± 3.3
T1a (≤1 cm)	5.9 ± 1.8
T1b (>1 cm and ≤2 cm)	13.4 ± 2.3
Tumor volume, mm^3	194.4 ± 310.0
Location	
Right lobe	201 (56.1)
Left lobe	148 (41.3)
Isthmus	9 (2.5)
Thyroid function	
Hashimoto thyroiditis	86 (24.0)
Normal	272 (76.0)

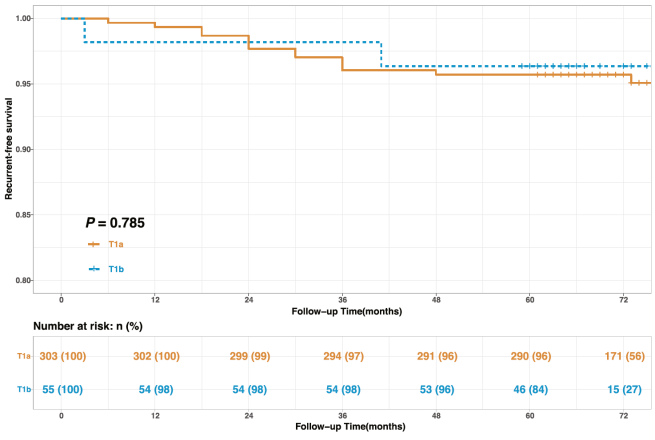
Note: Data are expressed as mean ± SD or number of tumors (percentages).

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Results

- 18 patients showed disease progression (5.0%)
  - 5 LNM (1.4%)
    - Additional RFA
  - 11 recurrent tumors (3.1%)
    - 1 active surveillance
    - 10 additional RFA
  - 2 persistent tumor (0.6%)
    - Additional RFA
  - No DM
  - No cancer-related mortality
  - No difference between T1a and T1b
  - 5-year RFS 95.5%



8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Results

- No complications
- No conversion to surgery for patient preference
- VRR 100% with 96.9% disappearing

TABLE 3 Changes of the volume and VRR after RFA at each follow-up.

Time	Volume (mm^3)	VRR (%)	*p* (vs. initial volume)
After RFA	1121.3 ± 969.6	-	
1 month	490.9 ± 467.0	−460.8 ± 536.4	<.001
3 months	209.7 ± 288.6	−80.3 ± 217.3	<.001
6 months	77.8 ± 158.1	15.7 ± 220.8	<.001
12 months	21.8 ± 74.8	89.4 ± 24.7	<.001
18 months	7.6 ± 38.0	96.9 ± 10.9	<.001
24 months	5.9 ± 43.4	98.4 ± 7.2	<.001
36 months	1.3 ± 11.6	99.6 ± 5.0	<.001
48 months	1.3 ± 11.7	99.6 ± 3.7	<.001
60 months	0.3 ± 2.0	100.0 ± 0.3	<.001

Note: Data are expressed as mean ± SD.

Abbreviations: RFA indicates radiofrequency ablation; VRR, volume reduction rate.

8/26/23

MUSC Medical University of South Carolina | Hollings Cancer Center An NCI-Designated Cancer Center

Clinical outcomes of ultrasound-guided radiofrequency ablation for solitary T1N0M0 papillary thyroid carcinoma

Takeaways

- Favorable recurrence free survival in a cohort with excellent prognosis
- RFA is a reasonable treatment option for early-stage, low-risk thyroid cancer
  - For those who do not wish to undergo surgery
- Long-term data still lacking

8/26/23

Discuss!

W. Greer Albergotti, MD
Assistant Professor, Head & Neck Surgery
Medical University of South Carolina
Cell – 864-934-4682

MUSC
Medical University of South Carolina

Hollings Cancer Center
An NCI-Designated Cancer Center