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The American Society for Radiation Oncology has reviewed the **2020 NCCN Non-Small Cell Lung Cancer guideline** for gaps relative to radiation therapy and offers **14 key recommendations** supported by evidence-based rationales and 9 additional minor suggestions for your consideration.

We hope you find these recommendations useful to your panel as you review and update the guidelines.

Sincerely,

Laura I. Thevenot
Chief Executive Officer, American Society for Radiation Oncology

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Recommendation 1: DIAG-2 [note the statement on tissue confirmation required also to be modified as in DIAG-2, NSCLC-2, and NSCLC-3]

Rationale: "Patients require tissue confirmation…" is in contradiction to the next sentences about patients for whom a biopsy is too risky or difficult and the discussion on empiric SBRT. Please soften the wording 'require' to something like "Patients should undergo tissue confirmation" or "Tissue confirmation is strongly preferred."

Reference: The lack of absolute need for biopsy has been reported in British Thoracic Society's guidelines and ASTRO's SBRT guidelines [Statement KQ 2E: SBRT can be delivered in patients who refuse a biopsy, have undergone nondiagnostic biopsy, or who are thought to be at prohibitive risk of biopsy. Prior to SBRT in patients lacking tissue confirmation of malignancy, patients are recommended to be discussed in a multidisciplinary manner with a consensus that the lesion is radiographically and clinically consistent with a malignant lung lesion based on tumor, patient, and environmental factors → Recommendation strength: Strong].

Recommendation 2: NSCL-2

Rationale: In footnote m "image guided thermal ablation," we are unaware of high level data that suggest thermal ablation is clearly superior to cryotherapy. Radioablative techniques are referenced later, and given that radiation therapy (RT) is the preferred approach in medically inoperable patients and that there is a lack of definitive data comparing cryotherapy and thermal ablation, please consider reworking footnote m to "Cryo/thermal ablation techniques may be an option for select patients not receiving definitive RT." Also, by writing "Definitive RT including SABR," this might suggest that non-SABR is an acceptable option, when SABR should be delivered instead of conventionally fractionated RT to increase local control, reduce toxicities, and potentially even improve overall survival.

References:

1) Ball D, Mai GT, Vinod S, et al; TROG 09.02 CHISEL investigators. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. Lancet Oncol. 2019 Apr;20(4):494-503.
2) Nyman J, Hallqvist A, Lund JÅ, et al. SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiother Oncol. 2016 Oct;121(1):1-8.

Recommendation 3: NSCL-3

Rationale: Please add a rationale or references for changing the recommendation of adjuvant chemotherapy after SBRT from category 2B to category 2A.

References:

1) Verma V, McMillan MT, Grover S, et al. Stereotactic Body Radiation Therapy and the Influence of Chemotherapy on Overall Survival for Large (≥5 Centimeter) Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017;97(1):146-154.
2) Verma V, Shostrom VK, Kumar SS, et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors. Cancer. 2017;123(4):688-696.

Recommendation 4: NSCL-5 and NSCL-7

Rationale: Currently, there are no scenarios of EBUS or surgically detected N2 disease. NSCL-7 should please lead back to NSCL-4 if EBUS/surgically detected N2 disease. Similarly, on NSCL-5, if EBUS and radiographically occult cN2 disease is identified, it should lead back to the N2 portion of the guidelines. Lastly, on NSLC-7, if surgery is performed and there is N2 disease, regardless of margins, radiation should be considered but the guidelines currently only indicated radiation for positive margins.

Recommendation 5: NSCL-10

Rationale: Any N2-N3 patient with multiple lung cancers is directed to receive systemic therapy alone. However, if a patient has a locally advanced lung cancer with N2 or N3 disease and a separate T1N0 lung cancer in another lobe or lung, the patient should be a candidate for definitive therapy to both separate lung cancers, inclusive of surgery or radiation therapy, and not only assigned to receive systemic therapy.

Recommendation 6: NSCL-14

Rationale: Patients with PS 2-4 are only assigned to receive systemic therapy. However, oligometastatic patients even with PS 2 can benefit from local therapy. These patients are currently allowed in NRG LU002 and have been included in oligometastatic trials showing a survival benefit to local therapy.

Reference: Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J Clin Oncol. 2019;37(18):1558-1565.

Recommendation 7: NSCL-15

Rationale: Definitive chemoradiation is recommended for T3-T4N2 but definitive RT or chemoradiation are recommended for T3N1. These patients should, when inoperable, be treated with concurrent chemoradiation and not definitive RT alone to improve overall survival.

Reference: Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol. 2010;28(13):2181-2190.

Recommendation 8: NSCL-20

Rationale: SABR and surgery are only considered in scenarios of 'isolated' metastasis (oligoprogression), but they should also be considered for oligometastasis at diagnosis. This population should similarly be considered in the EGFR/ALK sections. In prior slides, oligometastasis was defined loosely as <3 or <5 lesions,

so for oligoprogression, the same definition should be used and not limit it to just 1 progressive lesion; please reword or give an asterisk after "isolated."

Reference: Lievens Y, Guckenberger M, Gomez D, et al. Defining oligometastatic disease from a radiation oncology perspective: An ESTRO-ASTRO consensus document [published online ahead of print, 2020 Apr 22]. Radiother Oncol. 2020;148:157-166.

Recommendation 9: NSCL-B 1 of 4

Rationale: While it is certainly reasonable to say that for medically operable disease resection is the preferred local treatment modality," please qualify this to be in patients who are candidates for anatomic pulmonary resection (as opposed to patients who can only medically tolerate a wedge resection). More appropriate language may be "For patients who can tolerate an anatomic resection, surgery is the preferred…" Also, the sentence "Surgery provides the predominant opportunity for prolonged survival in patients with early-stage lung cancer" is very misleading, as there are numerous 5-year reports of SABR at this point showing continued durable local control and drop in survival predominantly related to comorbidities related to inherent biases in who is undergoing surgery versus who is undergoing SABR. Please consider improving this text and minimizing bias by deleting the word "predominant" or by not mentioning survival here, as the focus is on not denying active smokers the option of surgery.

Reference: Videtic GMM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol. 2017;7(5):295-301.

Recommendation 10: NSCL-C 3 of 10 and NSCL-C 7 of 10

Rationale: On NSCL-C 3 of 10, please update the sentence "preliminary results demonstrate no high-grade toxicities at 50 Gy in 5 fractions" now that the RTOG 0813 trial has been published and doses up to 60 Gy in 5 fractions did not have appreciably higher toxicities. On NSCL-C 7 of 10, For 5-fraction regimens, please change the dose range to 50-60 Gy, not 50-55 Gy.

Reference: Bezjak A, Paulus R, Gaspar LE, et al. Safety and Efficacy of a Five-Fraction Stereotactic Body Radiotherapy Schedule for Centrally Located Non-Small-Cell Lung Cancer: NRG Oncology/RTOG 0813 Trial. J Clin Oncol. 2019;37(15):1316-1325.

Recommendation 11: NSCL-C 4 of 10

Rationale: Postoperative radiation therapy should please be listed as a recommendation or at least consideration for pN1 patients who cannot tolerate chemotherapy, as this population can achieve a survival benefit with adjuvant radiation therapy.

Reference: Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys. 2008;72(3):695-701.

Recommendation 12: NSCL-C 7 of 10 and NSCL-C 8 of 10

Rationale: Dose constraints are listed for conventional fractionation and for SABR. Please consider adding dose constraints for hypofractionated regimens like 60 Gy in 12-15 fractions.

Recommendation 13: NSCL-C 8 of 10

Rationale: The brachial plexus constraint should be maximum dose instead of median dose, as it is a serial and not parallel structure.

Recommendation 14: MS-28

Rationale: Please add a discussion of hippocampal avoidance for whole brain radiation therapy and the use of memantine, ideally as a footnote on this algorithm slide or otherwise in the discussion section.

References:

1) Brown PD, Gondi V, Pugh S, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. J Clin Oncol. 2020;38(10):1019-1029.
2) Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol. 2013;15(10):1429-1437.

ADDITIONAL MINOR SUGGESTIONS

Recommendation 1: DIAG-2

Rationale: Guidelines on the treatment of patients receiving nonsurgical therapy without tissue confirmation have recently been published and should please be discussed/cited.

Reference: Berman AT, Jabbour SK, Vachani A, et al. Empiric Radiotherapy for Lung Cancer Collaborative Group multi-institutional evidence-based guidelines for the use of empiric stereotactic body radiation therapy for non-small cell lung cancer without pathologic confirmation. Transl Lung Cancer Res. 2019;8(1):5-14.

Recommendation 2: NSCL-6

Rationale: It is currently not clear here or in Principles of Chemotherapy section how many cycles of chemotherapy should be given for patients with superior sulcus tumors. Is the recommendation, 2 cycles concurrent with radiation therapy and 2 more cycles after surgery (per the SWOG trial), 4 cycles before surgery, or just 2 total cycles given concurrently with radiation therapy? Similarly, a footmark should be considered for superior sulcus tumors on NCLC-D.

Reference: Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol. 2007;25(3):313-318.

Recommendation 3: NSCL-25 - Rationale: "TKI inhibitor" in footnote fff should be "TKI"

Recommendation 4: NSCL-27-30

Rationale: Avastin is contained in several strategies, some of which can lead to SABR. Please add an acknowledgement, perhaps in the Principles of Radiation Therapy or in the text after the principles, about the increased risks of VEGF agents and SABR for central/ultracentral lesions.

Reference: Haseltine JM, Rimner A, Gelblum DY, et al. Fatal complications after stereotactic body radiation therapy for central lung tumors abutting the proximal bronchial tree. Pract Radiat Oncol. 2016;6(2):e27-e33.

Recommendation 5: NSCL-30

Rationale: For TKI patients receiving chemotherapy after initial progression, consider adding rechallenge with TKI as an option.

Recommendation 6: NSCL-C 3 of 10

Rationale: The cited references (#39 and #40) pertaining to tumors >5 cm, do not relate to this patient population. Alternative references should please be listed.

References:

1) Verma V, McMillan MT, Grover S, et al. Stereotactic Body Radiation Therapy and the Influence of Chemotherapy on Overall Survival for Large (≥5 Centimeter) Non-Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys. 2017;97(1):146-154.
2) Verma V, Shostrom VK, Kumar SS, et al. Multi-institutional experience of stereotactic body radiotherapy for large (≥5 centimeters) non-small cell lung tumors. Cancer. 2017;123(4):688-696.
3) Verma V, Shostrom VK, Zhen W, et al. Influence of Fractionation Scheme and Tumor Location on Toxicities After Stereotactic Body Radiation Therapy for Large (≥5 cm) Non-Small Cell Lung Cancer: A Multi-institutional Analysis. Int J Radiat Oncol Biol Phys. 2017;97(4):778-785.

Recommendation 7: NSCL-C 3 of 10

Rationale: The sentence "For institutions without an established SABR program, more modestly hypofractionation or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives" is unclear as worded and can be read to indicate that centers without a program should not be doing these alternatives. Alternative wording for consideration, "For institutions without an established SABR program, more modestly hypofractionation or dose-intensified conventionally fractionated 3D-CRT regimens are alternative approaches. "

Recommendation 8: NSCL-C 4 of 10

Rationale: A few minor grammar issues to update: a) "Two randomized trials found improved survival" is written but only one trial reference is listed; b) "IFI is reasonable in order to optimize definitive dosing to the tumor" is written twice; c) RTOG 1106 has long been closed to accrual so "is now being evaluated" should be rephrased "has been evaluated".

Recommendation 9: NSCL-E

Rationale: On the top section of cytotoxic chemotherapy agents, the heading is "concurrent chemotherapy/RT regimens" but on the bottom section for durvalumab, the heading is "definitive chemoradiation." As durvalumab is only approved for use after definitive concurrent chemoradiation, this heading should be updated to add the word 'concurrent.'

Reference:

Antonia SJ, Villegas A, Daniel D, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;379(24):2342-2350.