AMERICAN SOCIETY FOR RADIATION ONCOLOGY
251 18th St. South, 8th Floor
Arlington, VA 22202

Main: 703.502.1550 · Fax: 703.502.7852
www.astro.org · www.rtanswers.org

Email: Submissions@nccn.org

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The American Society for Radiation Oncology has reviewed the **2021 NCCN esophageal guideline** for gaps relative to radiation therapy. We offer **two recommendations** supported by evidence-based rationales for your consideration.

We hope these recommendations are useful to your panel as they review and update the guidelines.

Sincerely,

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

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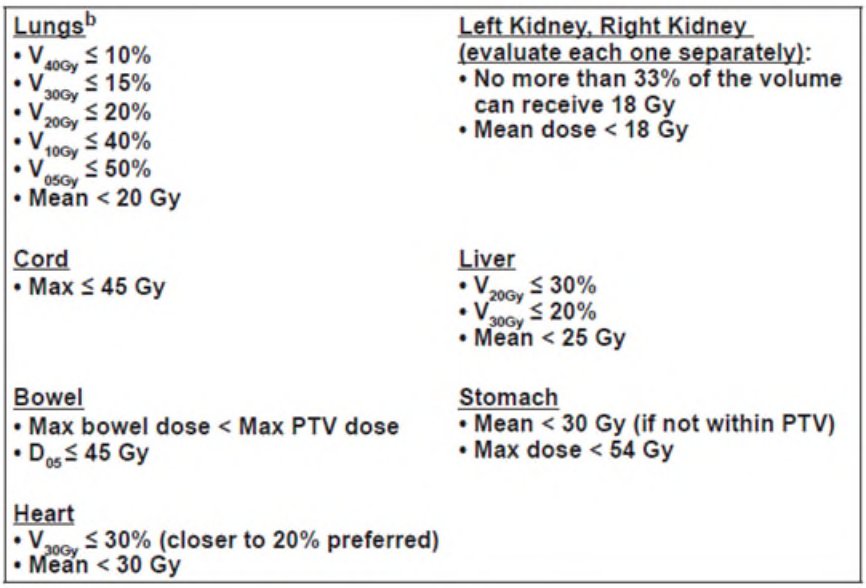
Recommendation 1:
We recommend updating the dosimetric constraints for the liver to V30 Gy <30%-40%, and also the stomach mean dose to 40-45 Gy (without a PTV-overlapping requirement). For heart, a mean dose <26 Gy should be considered (by adding "closer to 26 Gy preferred").

Rationale: Currently, the NCCN Guidelines showed the following constraints [ESOPH-G, Page 3 OF 5 (Page 63)]:



Lungs[b]
- V_{40Gy} ≤ 10%
- V_{30Gy} ≤ 15%
- V_{20Gy} ≤ 20%
- V_{10Gy} ≤ 40%
- V_{05Gy} ≤ 50%
- Mean < 20 Gy

Cord
- Max ≤ 45 Gy

Bowel
- Max bowel dose < Max PTV dose
- D_{05} ≤ 45 Gy

Heart
- V_{30Gy} ≤ 30% (closer to 20% preferred)
- Mean < 30 Gy

Left Kidney, Right Kidney (evaluate each one separately):
- No more than 33% of the volume can receive 18 Gy
- Mean dose < 18 Gy

Liver
- V_{20Gy} ≤ 30%
- V_{30Gy} ≤ 20%
- Mean < 25 Gy

Stomach
- Mean < 30 Gy (if not within PTV)
- Max dose < 54 Gy

However, the heart and liver constraints are not currently used on the 2 modern RT trials (NRG-GI006 and RTOG 1010) for preoperative chemoradiation. The QUANTEC publication supported the preferred heart dose/constraint cited above.

References:

- NRG-GI006 (ClinicalTrials.gov NCT 03801876) (05-NOV-2020), PHASE III RANDOMIZED TRIAL OF PROTON BEAM THERAPY (PBT) VERSUS INTENSITY MODULATED PHOTON RADIOTHERAPY (IMRT) FOR THE TREATMENT OF ESOPHAGEAL CANCER.
- RTOG 1010, A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of HER2-Overexpressing Esophageal Adenocarcinoma NCI/Local Protocol #: RTOG 1010. NCI Protocol Version Date: November 15, 2018
- Gagliardi G., Constine L., et al. Radiation Dose-Volume Effects in the Heart. Int J Rad Onc Biol Phys, Vol 76, No 3, Supplement, pp. S77-S85, 2010.

Recommendation 2:

We recommend listing both "3-D techniques" and "IMRT" as options for radiation planning techniques. We also recommend patients to be treated with proton beam radiation therapy within the context of a clinical trial or their outcomes tracked on a prospective registry per ASTRO PBT guidelines.

Rationale: Currently, on Esoph-G, page 1 of 5, page 61, "IMRT or proton beam therapy is appropriate in clinical settings where reduction in dose to organs at risk (e.g., heart, lungs) is required that cannot be achieved by 3-D techniques." However, IMRT is a well-established radiation technique to provide highly conformal dose to target while minimizing dose to adjacent organs at risk. We recommend that the use of IMRT be considered a standard option, as in practicality, it will meet the dose reduction criterion specified above. Use of IMRT is supported by a number of references (selected representative studies are cited below).

Furthermore, IMRT can help limit the high-dose areas to normal lungs and heart. There are evolving data on the impact of radiation to the heart/coronary vasculature and major acute coronary events in patients with NSCLC. An NRG/RTOG 0617 secondary analysis (Chun SG, 2017) showed that, compared to 3-D conformal radiation therapy, IMRT was associated with a lower rate of grade 3 or high radiation pneumonitis. A propensity score-based analysis (Lan K, 2020) also supported this finding, and along with another study (Lin SH, 2012), even suggested a possible survival benefit for IMRT than 3-D CRT in patients with esophageal cancer.

Comparing to 3-D conformal radiation therapy, the use of radiation modalities (IMRT, protons) was strongly associated with less postoperative complications after neoadjuvant chemoradiation in a group of 444 and 580 patients with esophageal cancer by MD Anderson Cancer Center and also multi-institutional analyses, respectively (Wang J, 2013; Lin SH, 2017).

There is phase II study which compared toxicity between IMRT and protons. And currently, there is an ongoing national NRG GI-006 trial (protons vs. IMRT) to evaluate these two techniques. We encourage institutions with proton beam capabilities to put patients on clinical trials and/or tracking their outcome by using prospective registries.

References:

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