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NCCN Guidelines Panel: Colon/Rectal Cancers Panel

The American Society for Radiation Oncology has reviewed the Colon Cancer and Rectal Cancer guidelines for gaps relative to radiation therapy. We offer a total of 13 recommendations supported by evidence-based rationales for your consideration.

Colon Cancer

Recommendation One: On pages COL-2 and 3, add the bolded to include the option of concurrent chemotherapy and radiotherapy in the treatment algorithm for PRIMARY TREATMENT cT4b and ADJUVANT TREATMENT T4, N1-2, T Any, N2.

- “Consider neoadjuvant FOLFOX or CAPEOX or **Concurrent Capecitabine or 5-FU + RT.**”

Rational: Radiotherapy concurrently with chemotherapy has been used for cT4b tumors. It is also stated under “Principles of Radiation Therapy” (Page COL-E). Indications for adjuvant radiation therapy include: T4 with fixation, close or positive margin when a target can be clearly demarcated.

References:

- Pellino G, Warren, O, Mills S, et al. Comparison of Western and Asian Guidelines Concerning the Management of Colon Cancer. *Dis Colon Rectum*. 2018;61(2):250-259.
- Ludmir E, Arya R, Wu Y. et al. Role of Adjuvant Radiotherapy in Locally Advanced Colonic Carcinoma in the Modern Chemotherapy Era. *Ann Surg Oncol*. 2016;23(3):856-62.

Recommendation Two: On page COL-E, we recommend changing the bolded:

1. *Fourth line:* Small bowel dose should be limited to **45-50 Gy, with a max point dose of 55 Gy for conventional fractionation.**
2. *Third bullet:* “If radiation therapy is to be used, conformal external beam radiation should be routinely used and intensity-modulated radiation therapy (IMRT) should be reserved only for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or anatomical situations **where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints.**”
3. To simplify different radiation dose options, consider this format:
 - **Neoadjuvant and adjuvant radiation therapy:** 45-50 Gy in 25-28 fractions
 - **For close or positive margins, 10-20 Gy external beam radiation or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy**
 - **IORT: 10-20 Gy**
 - **Unresectable disease: 54 Gy if technically feasible**
 - **SBRT metastasis: Doses depend on the fractionation and location of tumor. Single fraction treatments: 14-26 Gy, 3 fraction: range 28-60 Gy, 5 fraction: range 50-60 Gy.**
4. In patients with a limited number of ~~liver and lung~~ oligometastases, radiotherapy to the metastatic site can be considered and highly selective cases or in the setting of a clinical trial...The techniques can include 3-D conformal radiation therapy, **image-guided radiotherapy (IGRT), fiducial placement, respiratory-gated radiotherapy**, IMRT or SBRT.

Rational: (1) These are the accepted dose constraints and (2) rationales for the utilization of IMRT in clinical practice. (3) For the information to be easy to read and more concise. (4) SBRT has been used to treat oligometastases in other locations than liver and lung. Additionally, image-guidance and respiratory gating are essential components of highly conformal radiation therapy and widely utilized in practice.

References:

- Bae B, Kang M, Kim J, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J.* 2017;35(3):208-216.
- Brady JT, Crawshaw BP, Murrell B. Influence of intraoperative radiation therapy on locally advanced and recurrent colorectal tumors: A 16-year experience. *Am J Surg.* 2017 Mar;213(3):586-589.
- Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. *World J Gastroenterol.* 2014;20:4220-9
- Kavanagh B, Pan C, Dawson L, et al. Radiation Dose–Volume Effects in the Stomach and Small Bowel. *IJROBP.* 2010;1;76(3, suppl):S101–S107
- Lawton CA, Michalski J, El-Naqa I, et al. RTOG GU Radiation Oncology Specialists Reach Consensus on Pelvic Lymph Node Volumes for High-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys.* 2009;74(2):383–387.

Recommendation Three: In Discussion on page MS-21 (column 1, line 6), we recommend changing the bolded: “If radiation therapy is to be used, conformal beam radiation should be the routine choice; intensity-modulated radiation therapy (IMRT), which uses ~~computer-imaging~~ **computer-assisted inverse treatment planning** to focus radiation to the tumor site and potentially decrease toxicity to normal tissue, should be **considered for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints.**”

Rational: This is a common rationale for the utilization of IMRT in clinical practice.

Reference: Bae B, Kang M, Kim J, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J.* 2017;35(3):208-216.

Recommendation Four: In Discussion on page MS-24 (column 1, line 11), we recommend changing the bolded: “EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of ~~liver or lung~~ oligometastases or the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include **image-guided radiotherapy, respiratory-gated radiotherapy, fiducials**, three-dimensional conformal radiation therapy (CRT), SBRT, and IMRT, which uses **computer-assisted inverse treatment planning** to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.

Rational: Image-guidance and respiratory gating are essential components of highly conformal radiation therapy and widely utilized in practice. There are multiple Phase I/II and retrospective studies for the treatment of liver metastasis with SBRT. Treatments ranged from 1-5 fractions and doses from 14-60 Gy. The local control rates ranged from 57-100%. Similarly, there are multiple retrospective and one Phase I/II study evaluating treatment of pulmonary metastasis with SBRT. Treatments ranged from 1-5 fractions and doses from 26-60 Gy. The local control rates ranged from 53-100%. There was a study with 7 patients who received SBRT to an isolated enlarged lymph node in 3 fractions to 36-51 Gy. There was 1 local recurrence. Spinal metastases treated with SBRT have crude local control rates of 81-94%.

References:

- Bae B, Kang M, Kim J, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J.* 2017;35(3):208-216.

- Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. *World J Gastroenterol*. 2014;20:4220-9.

Recommendation Five: In the Discussion on page MS-29, section *Neoadjuvant and Adjuvant therapy for resectable metastatic disease*, there is no mention of concurrent chemotherapy and radiation in selected patients, as stated on page MS-20, section *Perioperative Chemoradiation*.

Rational: To be consistent for the indications of radiotherapy

Recommendation Six: There are a number of sections that do not have citations attached to the recommendation. Examples include:

1. Page COL-E: There are no citations given on any of these recommendations.
2. Page MS-20 (Perioperative Chemoradiation): There are no citations for the use of RT on T4b tumors or with definitive chemoRT for locally unresectable disease.

Rationale: As an evidence-based guideline, it would be valuable to included citations in these areas.

Reference: Ludmir EB, Arya R, Palta M, Willet CG, Czito BG. Role of Adjuvant Radiotherapy in Locally Advanced Colonic Carcinoma in the Modern Chemotherapy Era. *Ann Surg Oncol*. 2016;23(3):856-62.

Rectal Cancer

Recommendation One:

1. On REC-7, for “Synchronous unresectable metastases of other sites”, consider adding Local Ablative Therapy as an option as well as Systemic Therapy.
2. On REC-10, for “Nonobstructing”, consider adding Local Ablative Therapy as an option as well as Systemic Therapy.

Rationale: Although studies of oligometastatic treatment in rectal cancer have focused on liver and lung ablative techniques, this is primarily due to the common presentation of oligometastatic disease. Therefore, it is feasible to extrapolate that these locally ablative procedures would be effective at other sites, and these sites have been treated safely with radiation therapy in the past.

Reference: Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. *World J Gastroenterol*. 2014; 20:4220-9.

Recommendation Two: On page REC-C (Page 1 of 3) make the bolded edit to be consistent with REC-5 and REC-E recommendations, “Surgery should be 5-12 weeks following conventional dose 5.5-week neoadjuvant chemoradiation. **For short course neoadjuvant radiation therapy, surgery can be considered at 3-7 days or 4-8 weeks.**”

Rationale: Recommendation to remain consistent within the document. Traditional short-course studies had surgery following RT 3-7 days later. This is not the typical timeline for surgery, and it is important to make sure the surgeons are aware of this pattern. Additionally, more recent data has shown efficacy with delayed surgery at 4-8 weeks. The Stockholm III data may encourage considering a delay in timing between short-course radiation and surgery to minimize risk of postoperative complications while also limiting local recurrence risk.

References:

- Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol*. 2012;30:3827-33.
- Erlandsson J, Holm T, Pettersson D, Berglund Å, Cedermark B, Radu C, Johansson H, Machado M, Hjern F, Hallböök O, Syk I, Glimelius B, Martling A. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. *Lancet Oncol*. 2017;18(3):336-346.

Recommendation Three: Consider the following changes to page REC-D:

1. Regarding treatment technique: remove the following statement: ~~Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in a unique clinical situation such as reirradiation of previously treated patients with recurrent disease or unique anatomical situations.~~ And replace with the following: If radiation therapy is to be used, conformal external beam radiation should be routinely used and intensity-modulated radiation therapy (IMRT) should be reserved only for unique clinical situations such as reirradiation of previously treated patients with recurrent disease or anatomical situations where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints.
2. Regarding radiation dose: Make the bolded changes.
 - **Long-course radiation therapy:** 45-50 Gy in 25-28 fractions to the pelvis
 - Small bowel dose should be limited to **45-50 Gy, with max point dose of 55 Gy for conventional fractionation.**
 - Short-course radiation therapy: 25 Gy in 5 fractions **to the pelvis**
 - **IORT: 10-20 Gy**
 - **For close or positive margins, 10-20 Gy external beam radiation or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy**
 - **Unresectable: 54 Gy if technically feasible**
 - **SBRT metastasis: Doses depend on the fractionation and location of tumor. Single fraction treatments 14-26 Gy. 3 fraction range 28-60, 5 fraction range 50-60 Gy.**

Rationale: This is a common rationale for the utilization of IMRT in clinical practice and would make the information easier to read and more concise.

References:

- Bae B, Kang M, Kim J, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J.* 2017;35(3):208-216.
- Brady JT, Crawshaw BP, Murrell B. Influence of intraoperative radiation therapy on locally advanced and recurrent colorectal tumors: A 16-year experience. *Am J Surg.* 2017 ;213(3):586-589.
- Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. *World J Gastroenterol.* 2014; 20:4220-9
- Kavanagh B, Pan C, Dawson L, et al. Radiation Dose–Volume Effects in the Stomach and Small Bowel. *IJROBP.* 2010;76(3, suppl):S101–S107

Recommendation Four: Page REC-2, under “WORKUP,” add: “fertility risk discussion/counseling in appropriate patients.”

Rationale: Although the majority of rectal cancers are diagnosed in patients >60 years old, this should be a consideration for patients who are of child-bearing age.

Recommendation Five: In Discussion on MS-20, 2nd paragraph under *Technical Aspects of Radiation Therapy*, consider making the bolded changes: “Intensity-modulated radiation therapy (IMRT) should only be used in the setting of a clinical trial or in unique clinical situations such as reirradiation of previously treated patients with recurrent disease or anatomical situations **where IMRT facilitates the delivery of recommended target volume doses while respecting accepted normal tissue dose-volume constraints.**”

Rationale: These are common rationales for the utilization of IMRT in clinical practice and to be consistent with requested colon cancer changes.

Reference: Bae B, Kang M, Kim J, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J.* 2017;35(3):208-216.

Recommendation Six: In Discussion on MS-29, 2nd paragraph under *Liver- or Lung- Directed Radiation*, consider the bolded edits, “EBRT to the metastatic site can be considered in highly selected cases in which the patient has a limited number of ~~liver or lung~~ **oligometastases** or the patient is symptomatic or in the setting of a clinical trial. It should be delivered in a highly conformal manner and should not be used in place of surgical resection. The possible techniques include **image-guided radiotherapy, respiratory-gated radiotherapy, fiducials**, three-dimensional conformal radiation therapy, SBRT, and IMRT, which uses computer-assisted inverse treatment planning to focus radiation to the tumor site and potentially decrease toxicity to normal tissue.”

Rationale: Image-guidance and respiratory gating are essential components of highly conformal radiation therapy and widely utilized in practice and to be consistent with requested colon cancer changes. There are multiple Phase I/II and retrospective studies for the treatment of liver metastasis with SBRT. Treatments ranged from 1-5 fractions and doses from 14-60 Gy. The local control rates ranged from 57-100%. Similarly, there are multiple retrospective and one Phase I/II study evaluating the treatment of pulmonary metastasis with SBRT. Treatments ranged from 1-5 fractions and doses from 26-60 Gy. The local control rates ranged from 53-100%. There was a study with 7 patients who received SBRT to an isolated enlarged lymph node in 3 fractions to 36-51 Gy. There was 1 local recurrence. Spinal metastases treated with SBRT have crude local control rates of 81-94%.

References:

- Bae B, Kang M, Kim J, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol J*. 2017 Sep;35(3):208-216.
- Takeda A, Sanuki N, Kunieda E. Role of stereotactic body radiotherapy for oligometastasis from colorectal cancer. *World J Gastroenterol*. 2014; 20:4220-9.

Recommendation Seven: On pages REC-3, REC-4, REC-6, consider being consistent with the headings by providing descriptors under the different treatment algorithms such as “Sandwich therapy” and “Concurrent therapy” and Chemo→ChemoRT and Chemo (similar to organization on REC 5).

Rationale: It is very confusing on these pages to distinguish the recommendations. It would be helpful to break down some of these suggestions, or to have titling of sections. Distinguishing indications for each may also be helpful.

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

Sincerely,



Laura I. Thevenot
Chief Executive Officer