Taipei Veterans General Hospital Practices Guidelines Radiation Oncology

Rectal Cancer

2022.6.3

修正

All updates in 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Rectal Cancer

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Discussion

Updates in Version 1.2022 of the NCCN Guidelines for Rectal Cancer from Version 2.2021 include:

General -- FOLFOXIRI replaced with FOLFIRINOX

REC-3
- **pT1, NX with high-risk features or pT2, NX: Short-course RT removed as a treatment option.**

REC-5
- **Total Neoadjuvant Therapy specified as preferred**
  - **FOLFOX or CAPEOX: 12–16 wk added**
- **Adjuvant Treatment**
  - **Up to 6 mo perioperative treatment removed**
  - **FOLFOX or CAPEOX: 12–16 wk added**
- **Footnote v modified with addition of last sentence: Surveillance recommendations include DRE, proctoscopy every 3-4 months for 2 years, then every 6 months for a total of 5 years. MRI rectum is recommended every 6 months for at least 3 years to monitor for extraluminal local recurrence. (also applies to REC-6)**

REC-7
- **Workup**
  - **Bullet 5 modified: NGS Panel clarified as tissue- or blood-based (also applies to footnote z) (also added to foonote mm on REC-12)**

REC-9
- **Reassess response**
  - **Unresectable**
    - **Systemic therapy *and consider local therapy for select patients* (also applies to REC-14)**

REC-12
- **Footnote kk added: If previous RT given (short course or chemoradiation), see Principles of Radiation Therapy (REC-E) for further guidance.**

REC-14
- **Re-evaluate for conversion**
  - **Resectable**
    - **Resection noted as preferred and local therapy added as an additional or alternate option to resection.**
    - **Footnote ee added: Resection is preferred over locally ablative procedures (eg, image-guided ablation or SBRT). However, these local techniques can be considered for liver or lung oligometastases (REC-C and REC-E).**

Principles of Imaging

REC-A 2 of 4
- **Follow-up/Surveillance**
  - **Bullet 4 modified: PET/CT is not indicated with the exception of selected patients who are considered for image-guided liver-directed therapies for hepatic metastases (ie, ablation, radioembolization) *or serial CEA elevation during follow-up.***

Principles of Pathologic *and Molecular* Review

REC-B 5 of 9
- **Methods for Testing added**
  - **Bullet moved from under *KRAS, NRAS, BRAF* Mutation Testing: The testing can be performed on formalin-fixed paraffin-embedded tissue (preferred) *or blood-based assay*.**

REC-B 6 of 9
- ***NTRK* Fusions**
  - **Bullet 1 modified: ~~These data support limiting the subpopulation of colorectal cancers that should be tested for NTRK fusions to those with wild type KRAS, NRAS, BRAF, and arguably to those that are MMR deficient (dMMR)/MSI-H~~ *NTRK fusions are more frequently found among patients with dMMR.***

Continued
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Updates in Version 1.2022 of the NCCN Guidelines for Rectal Cancer from Version 2.2021 include:

Principles of Surgery

REC-C 1 of 3

- Transabdominal Resection
  - Bullet 1, sub-bullet removed: Surgery should be 5–12 weeks following full-dose 5.5-week neoadjuvant chemoradiation. For short-course neoadjuvant radiation therapy, surgery can be considered at 3–7 days or 4–8 weeks

REC-C 2 of 3

- Liver
  - Bullet 8 modified: ~~Conformal~~ *Ablative* external beam radiation therapy (EBRT) ~~(category 3)~~ may be considered in highly selected cases or in the setting of a clinical trial and should not be used indiscriminately in patients who are potentially surgically resectable. (also applies to lung section)

Principles of Perioperative Therapy

REC-D 1 of 2

- Dosing added for FOLFIRINOX and modified FOLFIRINOX (references added on REC-D 2 of 2)
- Regimens removed: Simplified biweekly infusional 5-FU/LV (sLV5FU2); Capecitabine; 5-FU
- Footnote d added: FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 mg/m² over 48 hours). Patients in the United States (U.S.) have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.

Principles of Radiation Therapy

REC-E 1 of 2

- General Principles
  - Bullet 1 modified: ~~Fluoropyrimidine-based~~ Chemotherapy *with a fluoropyrimidine in oral or continuous venous infusion form* should be delivered concurrently with *conventionally fractionated* radiation therapy
- Treatment Information
  - Bullet 2 modified: IMRT ~~should only be used in the setting of a clinical trial, in unique clinical situations such as~~ *is preferred for* reirradiation of previously treated patients with recurrent disease, *patients treated postoperatively due to increased acute or later toxicity* or in unique anatomical situations (eg, coverage of external iliac or inguinal lymph nodes or avoidance of small bowel).
  - Bullet 3 added: In patients with locally recurrent disease after prior pelvic radiation therapy, consider use of hyperfractionated pelvic re-irradiation if re-treatment is planned.
  - Bullet removed: Consider SBRT for patients with oligometastatic disease.
  - References added:
    Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731-1740.
    Tao R, Tsai CJ, Jensen G, et al. Hyperfractionated accelerated reirradiation for rectal cancer: an analysis of outcomes and toxicity. Radiother Oncol 2017;122:146-151.

REC-E 2 of 2

- Target Volumes
  - Sub-bullet 1 added: Target volume definition should be performed per ICRU 50 recommendations.
  - Sub-bullet 2 added: Gross tumor volume (GTV) should include all primary tumor and involved lymph nodes, using information from physical examination, endoscopic findings, diagnostic imaging, and the simulation planning study for delineation. Clinical target volume (CTV) should include the GTV plus areas at risk for microscopic spread from the primary tumor and at-risk nodal areas. A consensus atlas may be helpful to review when defining elective nodal CTVs.
  - Sub-bullet 3 added: At-risk nodal regions include mesorectal, presacral, internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.

Continued

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Updates in Version 1.2022 of the NCCN Guidelines for Rectal Cancer from Version 2.2021 include:

REC-E 2 of 2
- Target Volumes
  - Sub-bullet 4 modified: ~~Radiation therapy fields should include the tumor or tumor bed, with a 2- to 5-cm margin, the mesorectum, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures.~~ Fusion of the pelvic MRI is strongly recommended to optimally define gross disease.
  - Sub-bullet 5 modified: *If using 3D conformal radiation,* multiple radiation therapy fields should be used (generally a 3- or 4-field technique). *Prone* positioning, *full bladder*, and other techniques to minimize the volume of small bowel in the fields ~~is~~*are* encouraged.
- RT Dosing
  - Sub-bullet 1; diamond 2 modified: Small bowel dose should be limited to ~~45~~*50* Gy.
  - Sub-bullet 2 modified: Short-course radiation therapy (25 Gy in 5 fractions) can also be considered for patients *for preoperative radiation.*
  - Sub-bullet removed: If IORT is not available, 10–20 Gy EBRT and/or brachytherapy to a limited volume could be considered soon after surgery, prior to adjuvant chemotherapy.
- Supportive Care
  - Terminologies modified to be more inclusive of all sexual and gender identities.
  - Bullet 2 added: Patients of child bearing potential should be counseled about the effects of premature menopause and consideration should be given to referral for discussion of hormone replacement strategies.
  - Bullet 3 added: Patients of child bearing potential should be counseled that an irradiated uterus cannot carry a fetus to term.
  - Bullet 4 modified: Patients should be counseled on sexual dysfunction, *potential for future low testosterone levels*, and infertility risks and given information regarding sperm banking *or oocyte, egg, or ovarian tissue banking, as appropriate, prior to treatment.*
- Reference added: Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring atlas. Int J Radiation Oncology Biol Phys 2009;74:824-830.

Systemic Therapy for Advanced or Metastatic Disease

REC-F 1 of 13
- ~~Patient appropriate for~~ Intensive therapy *recommended*
  - Footnote d added to all FOLFOX, CAPEOX, and FOLFIRINOX regimens (applies to REC-F 2 of 13 through REC-F 6 of 13)
- ~~Patient NOT appropriate for~~ Intensive therapy *NOT recommended*
  - The following Initial Therapy options removed: Fam-trastuzumab deruxtecan-nxki (HER2-amplified and *RAS* and *BRAF* WT)

REC-F 7 of 13
- Footnote d added: Discontinuation of oxaliplatin should be strongly considered after 3 to 4 months of therapy (or sooner for unacceptable neurotoxicity) while maintaining other agents until time of progression. Oxaliplatin may be reintroduced if it was discontinued for neurotoxicity rather than for disease progression.

REC-F 8 of 13
- Cetuximab every 2 week dosing noted as preferred (also applies to REC-F 9 of 13, REC-F 10 of 13)

REC-F 9 of 13
- Dosing added for FOLFIRINOX and modified FOLFIRINOX (references added to REC-F 12 of 13)
- Footnote dd added: FOLFIRINOX is recommended instead of FOLFOXIRI because FOLFOXIRI uses a high dose of fluorouracil (3,200 mg/m² over 48 hours). Patients in the United States (U.S.) have been shown to have greater toxicity with fluorouracil. The dose of fluorouracil (2,400 mg/m² over 46 hours) is a starting dose consistent with the dose recommended in FOLFOX or FOLFIRI and should be strongly considered for U.S. patients.

Update in RT principles (major points)

- **In patients with locally recurrent disease after prior pelvic radiation therapy, consider use of hyperfractionated pelvic re-irradiation if re-treatment is planned.**
- **Intraoperative radiation therapy (IORT), if available, may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers.**
- **Arterially directed catheter therapy, and in particular yttrium-90 microsphere selective internal radiation, is an option in highly selected patients with chemotherapy-resistant/-refractory disease and with predominant hepatic metastases.**

ROLE OF RADIOTHERAPY IN RECTAL CANCER

- **Pelvic RT**
  - –Pre-operative RT (long or short course):
    - Downstaging locally advanced (stage II, III) disease.
    - Increased resectability (R0 resection) and local control.
    - Possible sphincter preservation for lower seated tumors.
  - –Post-operative RT:
    - To obtain better local/regional control for:
    - Locally advanced disease(pT3-4, N+) or positive margin after transabdominal resection.
    - Early disease (pT1-2N0) after transanal resection.
- **Definitive treatment for locally recurrent /metastatic disease (palliation or radical).**

PRINCIPLES OF RADIATION THERAPY

- **For pelvic disease, radiation therapy fields should include the tumor or tumor bed, with a 2-5 cm margin, the presacral nodes, and the internal iliac nodes. The external iliac nodes should also be included for T4 tumors involving anterior structures. Consider inguinal nodes for tumors invading into the distal anal canal.**
- **Multiple radiation therapy fields should be used (generally a 3 or 4 field technique with 3 D CRT or 5 to 7 fields with IMRT or 2 or more arcs with VMAT).**
- **For postoperative patients treated by abdominoperineal resection, the perineal wound should be included within the fields.**
- **Radiation doses (combined with chemotherapy):**
  - 45-50 Gy in (25-28) fractions to the pelvis.
  - For resectable cancers, after 45 Gy a tumor bed boost with a 2 cm margin of 9.0 Gy in 3 fractions could be considered for preoperative radiation and 5.4-9.0 Gy in 3-5 fractions for postoperative radiation.
  - Small bowel dose should be limited to 45 Gy.
  - For unresectable cancers, doses higher than 54 Gy may be required.
  - 5-fluorouracil based chemotherapy should be delivered as continuous infusion or as a bolus daily with radiation.
  - Oral chemotherapy with UFUR (200 mg/m2/d) + folic acid (45 mg/d) is an alternative when combined with RT.

Principles of patient simulation

- **Before simulation, oral contrast media (barium meal) can be given for visualization of small intestine.**
- **Prone position (preoperative mid-to-high rectum or postoperative Rx): use of belly board with full bladder is encouraged for bowel displacement out of RT field. The lower border of the hole on the board is coincided with upper margin of fields.**
- **Supine position: for tumors invading anal region, patients may have an immobilization device (e.g., vacuum bag for thighs and legs) made prior to treatment planning CT scan.**
- **Air enema should be done during simulation if possible for easier contouring of GTV. Radio-opaque markers should be put in the perineal area after APR.**
- **The treatment planning CT scan may be performed with *IV contrast so that the major vessels* of the pelvis are easily visualized. The treatment planning CT scan must be performed with the immobilization device (if made) and in the treatment position.**

Prescription and technique of Radiation Therapy

- **Radiation dose**
  - Preoperative radiotherapy: 25 Gy/ 5 fractions (short-course) or 45 to 54 Gy/ 25 to 28 fractions (long-course), .
  - Postoperative radiotherapy: 50.4 Gy/ 28 fractions. Further boost can be given for positive margins and unresectable lesions.
- **Radiation technique:**
  - **3 D conformal Radiotherapy (3 D CRT): "box" technique with AP-PA and bilateral fields.**
  - **Intensity-Modulated Radiotherapy (IMRT)**

    For lower seated rectal cancer invading the anus, IMRT has been shown to be useful in reducing acute toxicities by reducing the dose to small intestine, urinary bladder, external genitalia, and femoral heads. The application of IMRT to other sites (mid or higher rectum) is evolving and may be used at the discretion of treating physicians.
  - **IMRT and Fractionation**

    A number of ways exist to integrate IMRT, target volume dosing, and fractionation. The Simultaneous Integrated Boost (SIB) technique uses differential "dose painting" (56 to 60 Gy to gross disease; 39.1-45 Gy to subclinical disease) for each fraction of treatment throughout the entire course of radiation.

Contouring guideline

- Image registration of CT and MRI/PET (if available) should be done for GTV delineation.
- **Gross Target Volume (GTV) delineation for primary disease and pelvic LAP**
  - defined as tumor detected on physical examination or imaging studies. In postoperative cases, the GTV was defined as the preoperative gross tumor volume.
- **Clinical Target Volume (CTV) delineation (pelvis)**
  - included all potential areas at risk for microscopic tumor involvement by either direct extension or nodal spread (including inguinal for tumors invading the anal canal).
  - Including volumes 5 mm around GTV.
- **Planning Target Volume (PTV) delineation**
  - including a margin for patient motion and setup errors.
  - Five (with fixation) to 7 mm or larger margin is usually added to CTV (with belly board and no fixation).

Consensus for preoperative RT or CCRT

- **Staging with MRI of pelvis and CT scan of chest. PET scan can be arranged before RT to R/O IMA root lymph node or other distant metastasis or to evaluate tumor response after CCRT.**
- **Two RT regimens (short vs long).**
  - Short course RT: 5 Gy x 5 to gross tumor and mesorectal lymphadenopathy. Followed by chemotherapy with FOLFOX delayed surgery or no treatment.
  - Long course RT: 1.8 Gy x 25 for pelvis, boost with 1.8 or 3 Gy x 3 for T4 or lower seated (≦ 5 cm) tumor to increase the pCR or sphincter preservation rate. Followed by delayed surgery (6 to 8 weeks later).
- **Chemo regimen with long course: UFUR(200mg/m2/d)+ folinate (45 mg qd, D1-33, and D41-68) + mitomycin-C (6 mg/m^2 on D1) or FOLFOX or capecitabine.**

Short-course preoperative or palliative radiotherapy

- **Indications:**
  - For palliative treatment for poor-performance patients with locally advanced rectal cancer. May be followed by delayed surgery or no surgery.
  - For downstaging tumors of cT3-4N anyM0 or T2N1-2M0. No concurrent chemotherapy. Followed by chemotherapy and delayed surgery.
  - For downstaging of primary tumors in patients with potentially resectable metastatic disease (sequential with chemotherapy).

SBRT for liver metastases

- For oligometastases(1-4 in number) from colorectum to the liver, stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) can be given for the largest tumor size < 6 cm. Not used in the place of surgical resection.
- KPS>60 % and adequate liver function are required.
- 36 to 50 Gy/ 4 to 6 fractions may be given to the metastases under image guide to limit >=700 cc of normal liver with < 15 Gy.
- Prescription dose can be adjusted to protect adjacent normal tissue like the heart, kidney, esophagus, stomach, small intestine, spinal cord, rib and skin.

SBRT for lung metastases

- For oligometastases(1-4 in number) from colorectum to the lung, stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) can be given for the medical inoperable cases.
- KPS>60 % and adequate lung function are required.
- 24 to 50 Gy/ 1 to 5 fractions may be given to the metastases under image guide to limit mean total lung dose< 6 Gy and V20<12 %.
- Prescription dose can be adjusted to protect adjacent normal tissue like the heart, major vessels, esophagus, main bronchus, spinal cord, brachial plexus, rib and skin.

Role of carbon ion therapy in rectal cancer

- **In patients with locally recurrent disease, carbon ion can be used in partial pelvic re-irradiation.**
  - Prescription dose/fractions: 70.4 GyE/16 fx (with prior RT) or 73.6 GyE/16 fx (without prior RT)
- **Carbon ion therapy can also be delivered for patients with oligo liver or lung metastases.**
  - Prescription dose/fractions for liver mets: 36 to 58 GyE in a single fraction.
  - Prescription dose/fractions for lung mets: 44 to 64.8 GyE in 4 fractions.

References

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