台北榮民總醫院
Taipei Veterans General Hospital

Rectal Cancer

大腸直腸癌醫療團隊
2007年9月初版
2007年12月14日修訂
2008年4月11日修訂
2009年7月22日第二版
2010年8月19日修訂
2011年5月27日第三版
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2017年8月04日第8版
2018年7月27日第九版
2019年8月19日第十版
2020年8月21日第十一版
2021年8月20日第十二版
2022年8月26日第十三版

(same with colon , please reference to colon)

Before Guidelines

- This panel is for medical fitted patients, adjustment might be considered for medical unfitted patients(elder..) or for individual considerations under clinical practices.
- Although the guidelines are believed to represent the optimal treatment strategy, the panel believes that, when appropriate, patients should preferentially be included in a clinical trial over standard or accepted therapy.
- Adenocarcinomas of the small bowel or appendix may be treated with systemic chemotherapy according to these guideline.
- The determination of an optimal treatment plan for an individual patient with rectal cancer is a complex process. In addition to decisions relating to the intent of rectal cancer surgery (ie, curative or palliative), consideration must also be given to the likely functional results of treatment, including the probability of maintaining or restoring normal bowel function/anal continence and preserving genitourinary functions.

Contents

- Stage (refer to colon cancer)
- Flowchart and information
- Principle of surgery
- Principles of Radiation Therapy
- Other Modalities (refer to colon cancer)
- Principles of oligometastasectomy (refer to colon cancer)
- Pathology review (Some refer to colon cancer)
- Chemotherapy (advanced/metastatic regimens refer to colon cancer)

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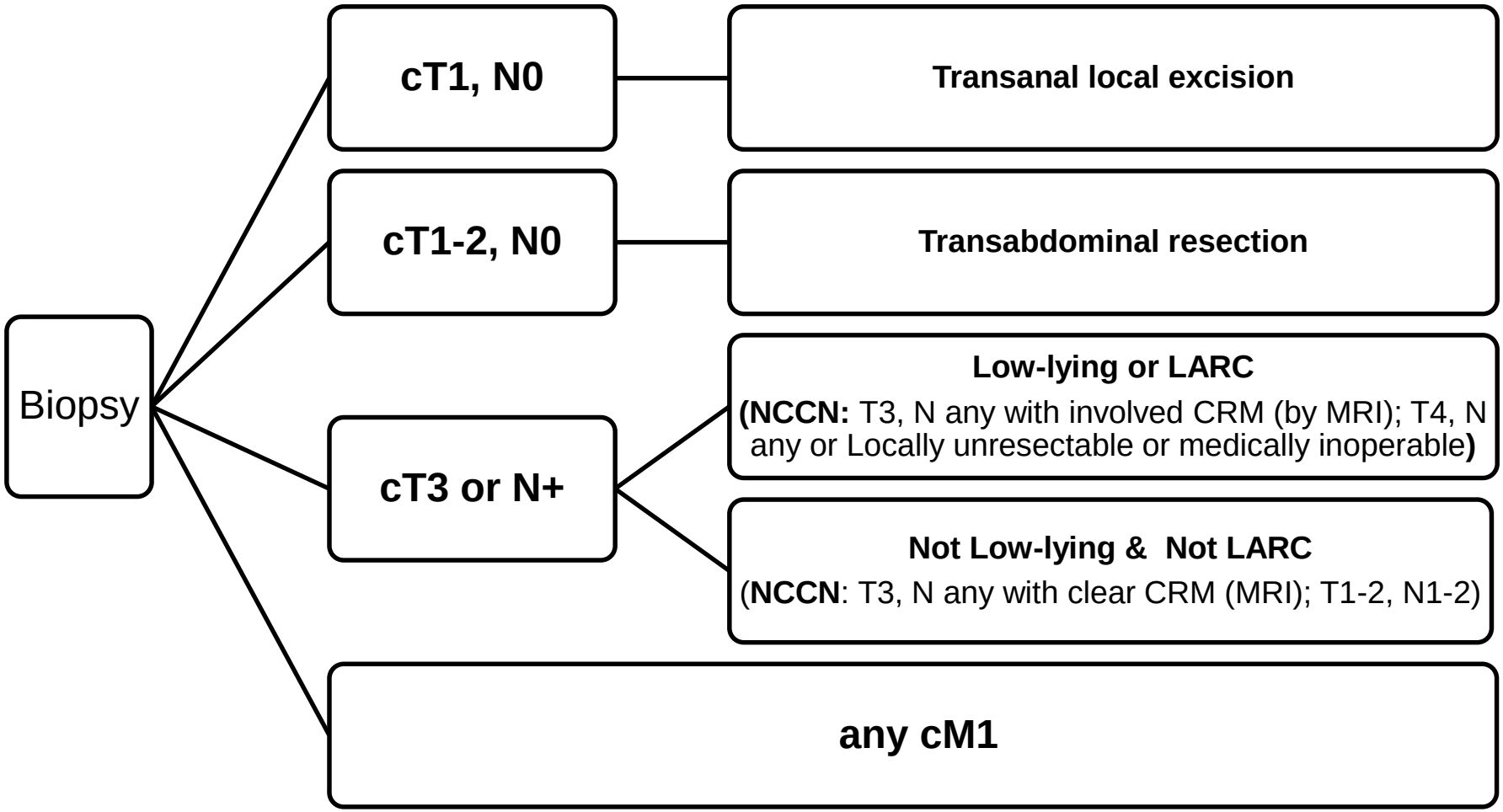
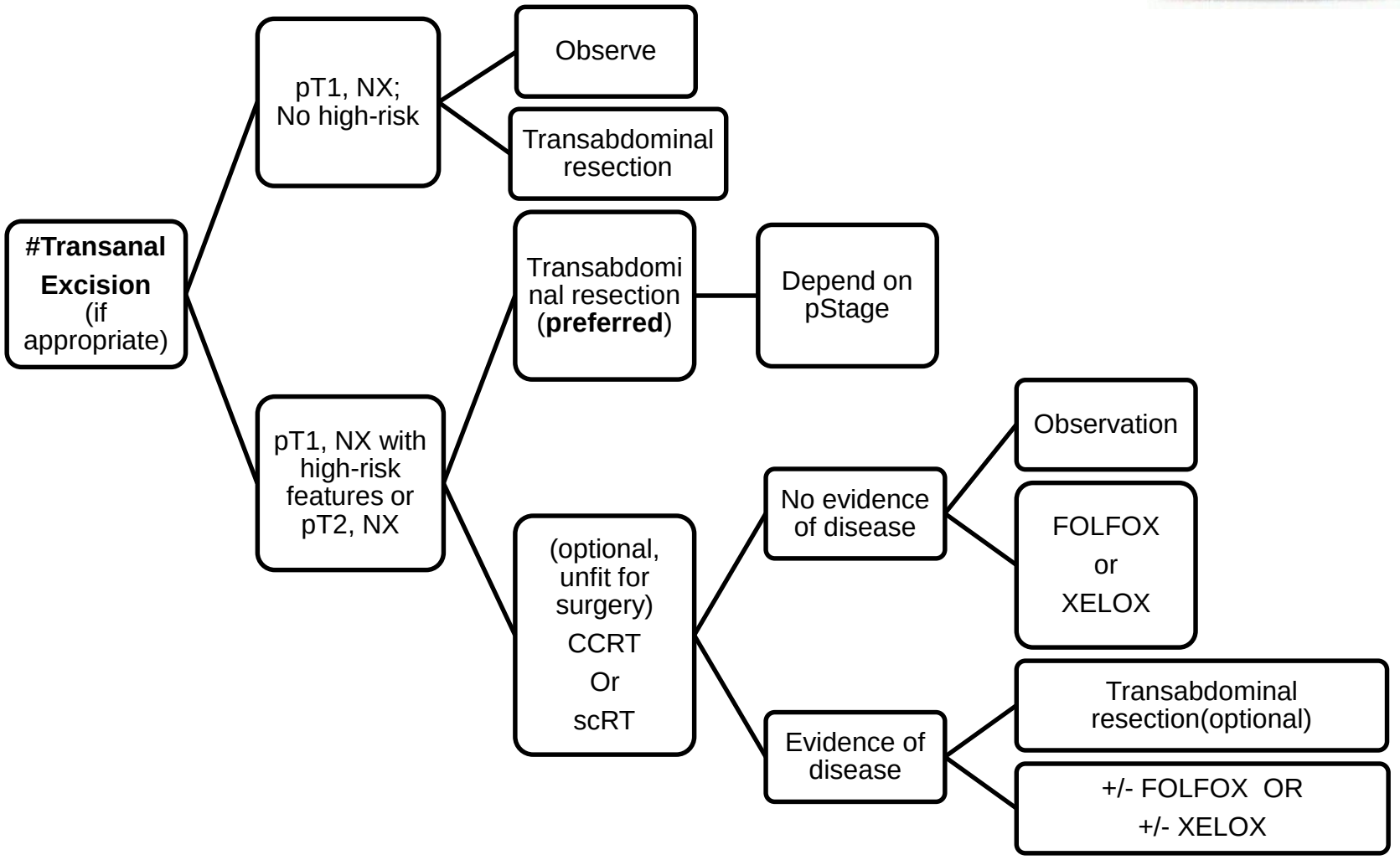
Flowchart

Clinical Approach

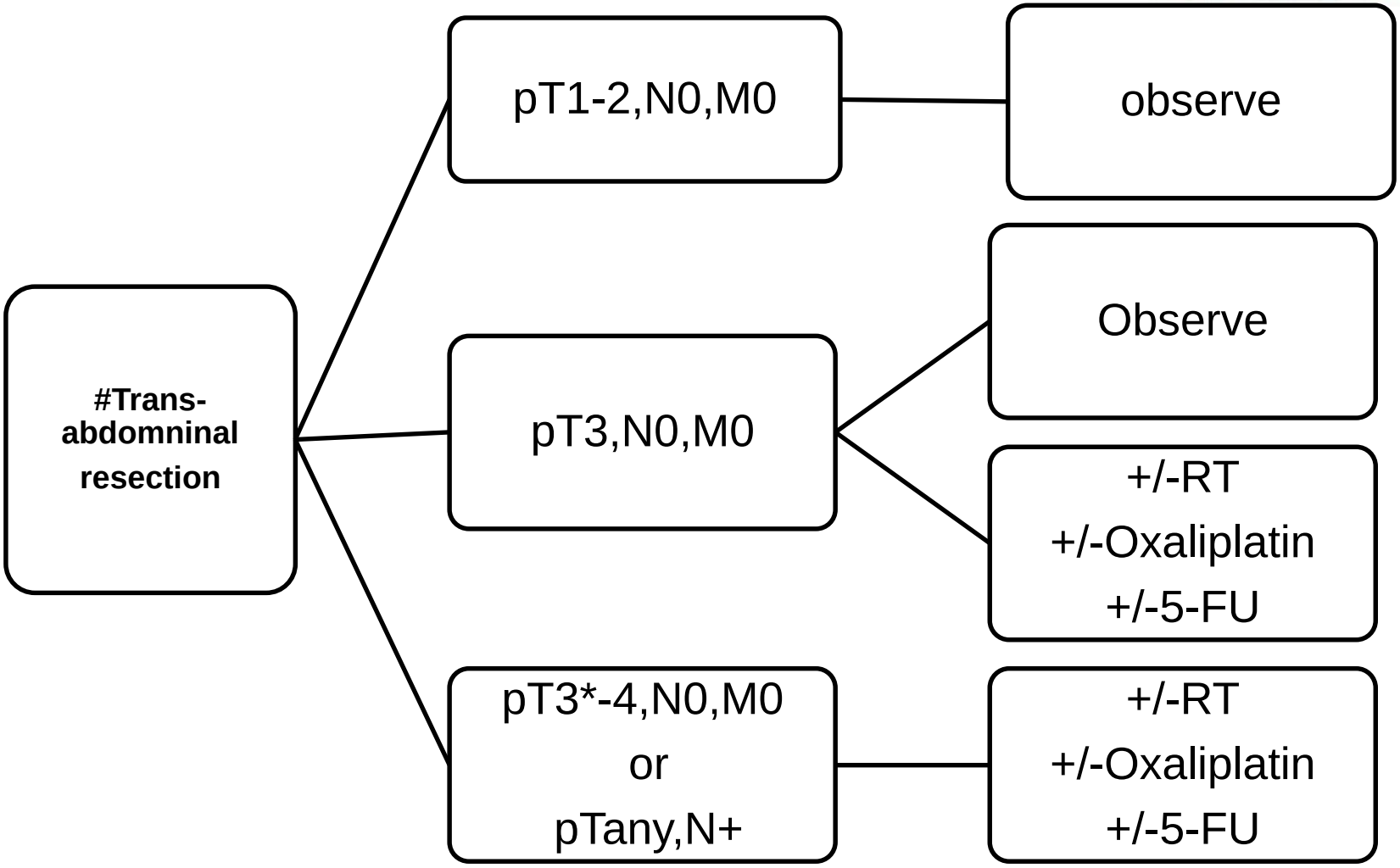


Transanal excision



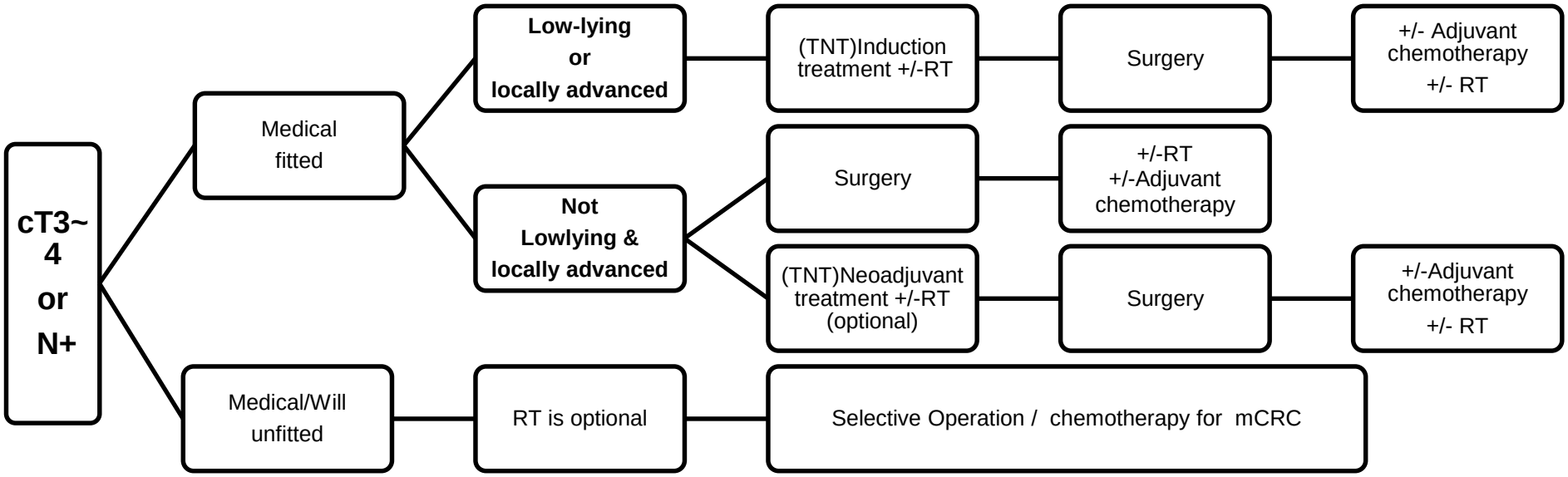
High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion (submucosal invasion to the lower third of the submucosal level). ; *: T3N0: observation is a alternative choice

Transabdominal resection



High-risk features include positive margins, lymphovascular invasion, poorly differentiated tumors, or sm3 invasion (submucosal invasion to the lower third of the submucosal level). ; *: T3N0: observation is a alternative choice; local advanced RC (LARC)

cT3~4/N+



- Low-lying: below peritoneal reflection; locally advanced: like T4;
- RT : radiation
- **Either of induction or neoadjuvant treatment(including TNT) with or without RT: individual consideration**

cT3-4/N+

- RT should be either pre- or post- surgery.
- Neoadjuvant therapy (eg: Total Neoadjuvant Therapy) or induction therapy
  - Chemotherapy (oxaliplatin preferred)
  - Radiation (CCRT/scRT)
  - Schema by physicians
  - Immune check point inhibitors (benefit at MSI-H subtype)

- Surgery first is optional
- LCRT would be chosen for sphincter preservation and complete resection of tumor, although enough supporting evidence is unavailable.
- NCCN panel does not endorse the use of bevacizumab, cetuximab, panitumumab, irinotecan, or oxaliplatin with concurrent radiotherapy for rectal cancer.
- Watch-and-Wait Nonoperative Approach for Clinical Complete Responders (highly education and selection and well explanation)
  - In those patients who achieve a complete clinical response with no evidence of residual disease on digital rectal examination, rectal MRI, and direct endoscopic evaluation, a “watch and wait,” nonoperative (chemotherapy and/or RT) management approach may be considered in centers with experienced multidisciplinary teams. The degree to which risk of local and/or distant failure may be increased relative to standard surgical resection has not yet been adequately characterized. Decisions for nonoperative management should involve a careful discussion with the patient of his/her risk tolerance. 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

References for RT scRT not with C/T

Table 2. Comparison of short-course radiotherapy (5 × 5 Gy) and long-course chemoradiotherapy

	Polish [15]	TROG [16]
No. of patients	312	326
CCRT regimen	50.4 Gy + FL	50.4 Gy + 5-FU CI
RM+ (%)	12.9 vs. 4.4	5 vs. 4
pCR (%)	0.7 vs. 16.1	-
	(p=0.017)	-
LR (%)	10.6 vs. 15.6 (at 4 years)	7.5 vs. 5.7 (at 5 years)
	-	(p=0.51)
DFS (%)	58.4 vs. 55.6 (at 4 years)	-
	-	(p=0.47)
OS (%)	67.2 vs. 66.2 (at 4 years)	74 vs. 70 (at 5 years)
	-	(p=0.62)
Acute toxicity ≥3 (%)	3.2 vs. 18.2	-
	(p<0.001)	-
Late toxicity ≥3 (%)	10.1 vs. 7.1	-
	-	(p=0.53)
Sphincter preservation (%)	47 vs. 42	63 vs. 69

CCRT, concurrent chemoradiation; FL, 5-fluorouracil and leucovorin; 5-FU CI, 5-fluorouracil continuous infusion; RM+, positive resection margin; pCR, pathological complete response; LR, local recurrence; DFS, disease-free survival; OS, overall survival.

Metastatic/recurrence rectal cancer

- Refer to colon cancer.

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Principles of surgery

Principle of surgery

- Transanal resection
  - Criteria
    - < 30% circumference of bowel
    - < 3 cm in size
    - Margin clear (> 3 mm)
    - Mobile, non-fixed
    - Within 8 cm of anal verge
    - T1 only
    - Endoscopically removed polyp with cancer or indeterminate pathology
    - Well to moderately differentiated
    - No lymphovascular (LVI) or perineural invasion
    - No evidence of lymphadenopathy on pretreatment imaging
    - Full thickness excision must be feasible
  - When the lesion can be adequately identified in the rectum, transanal microsurgery may be used.

- **Transabdominal Resection: Abdominoperineal resection or low anterior resection or coloanal anastomosis using total mesorectal excision.**
  - Management Principles
    - The treating surgeon should perform an endoscopy before initiating treatment
    - Removal of primary tumor with adequate margins
    - Laparoscopic surgery: optional
    - Treatment of draining lymphatics by total mesorectal excision
    - Restoration of organ integrity, if possible
  - Total mesorectal excision
    - Reduces positive radial margin rate.
    - Extend 4-5 cm below distal edge of tumors for an adequate mesorectal excision. In distal rectal cancers (ie, < 5cm from anal verge), negative distal bowel wall margin of 1-2 cm may be acceptable, this must be confirmed to be tumor free by frozen section.
    - Full rectal mobilization allows for a negative distal margin and adequate mesorectal excision.
  - Lymph node dissection
    - Biopsy or remove clinically suspicious nodes beyond the field of resection if possible.
    - Extended resection not indicated in the absence of clinically suspected nodes.

- Taipei Veterans General Hospital Practices Guidelines Radiation Oncology

Rectal Cancer

2022.6.3

修正

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Rectal Cancer

NCCN Guidelines Index
Table of Contents
Discussion

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

UPDATES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Rectal Cancer

NCCN Guidelines Index
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Discussion

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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- Makishima H et al. Single fraction carbon ion radiotherapy for colorectal cancer liver metastasis: A dose escalation study. Cancer Sci. 2019 Jan; 110(1): 303–309.
- Takahashi W, Nakajima M, Yamamoto N, et al. Carbon ion radiotherapy for oligo-recurrent lung metastases from colorectal cancer: a feasibility study. Radiat Oncol. 2014 Dec; 9(1): 68.
- **NCCN guideline for rectal cancer, version 1, 2022.**

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Pathology Reviews

Principles of Pathologic Review

- TRG
  - Grade 0
    - Complete response
  - Grade 1
    - Moderate response
    - Single cells or small groups of cancer cells
  - Grade 2
    - Minimal response
    - Residual cancer outgrown by fibrosis
  - Grade 3
    - Poor response
    - Minimal or no tumor kill; extensive residual cancer

- Ref. CAP Cancer Protocol 2011

Chemotherapy

- The following regimen is specific for rectal cancer .
- For metastatic rectal cancer, refer to colon cancer.

Adjuvant Therapy for Rectal Cancer

- NOTE:
  - Adjuvant therapy for rectal cancer consists of regimens that include both concurrent chemotherapy/RT and adjuvant chemotherapy.
  - A total of approximately **6 months** of perioperative treatment is preferred.
- **Peri-operative Chemotherapy:**
- **5-FU based regimens**
  - **De Gramont:**
    Leucovorin 200 mg/m^2 IV (2h inf), day 1,2 5-FU 400 mg/m^2 IV(bolus) x 2 days then 600 mg/m^2 (22h inf)day x 2 days to be repeated every 2 weeks. (1-3)

- **Simplified biweekly infusional 5-FU/LV (sLV5FU2) :**
  Leucovorin 400 mg/m^2 IV day 1, followed by 5-FU bolus 400 mg/m^2 and then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46–48 hours)continuous infusion. Repeat every 2 weeks to a total of 6 month perioperative therapy. (4)
- **Xeloda(Capecitabine) :**
  Capecitabine 1250 mg/m^2 twice daily days 1–14 every 3 weeks to a total of 6 months perioperative therapy. (5)
- **5-FU** :
  500 mg/m^2 IV bolus weekly x 6 + leucovorin 500 mg/m^2 IV weekly x 6each 8-week cycle. Repeat every 8 weeks to a total of 6 months perioperative therapy. (6)
- **UFUR :**
  400 mg/m^2 tegafur per day in the form of 100 mg units was given orally twice daily for 5 consecutive days every weekday for 1 year, starting 6 weeks postoperatively. The dose was rounded up or down to the nearest 100 mg.

- **Oxaliplatin-5FU based regimens**
  - **mFOLFOX6 :**
    Oxaliplatin 85 mg/m^2 IV, day 1,* .leucovorin 400 mg/m^2 IV day 1,** 5-FU 400 mg/m^2 IV bolus on day 1, then 1200 mg/m^2/day x 2 days (total 2400 mg/m^2 over 46-48 hours) continuous infusion. Repeat every 2 weeks to a total of 6 month perioperative therapy. (8-10)

  - **FOLFOX4** : Leucovorin 200(or 100) mg/m^2 IV(2h inf), day 1,2 .Oxaliplatin 85 mg/m^2 IV(2h inf), day 1 concurrent with folonic acid . 5-FU 400 mg/m^2 IV(bolus) x 2 days then 600 mg/m^2(22h inf)day x 2 days .To be repeated every 2 weeks.(8-10)
  - **mFOLFOX7 :** Oxaliplatin 130 mg/m^2 IV , day 1* . Leucovorin** 400 mg/m^2 IV, day 1** . 5-FU 2400 mg/m^2/2day iv 46 hrs . Repeat every 2 weeks (15) (

- **CapeOx :** Oxaliplatin 130 mg/m^2 over 2 hours, day 1. Capecitabine 1000 mg/m^2 twice daily days 1–14 every 3 weeks. Repeat every 3 weeks to a total of 6 months perioperative therapy. (12, 13).

- **Concurrent Chemotherapy with RT (CCRT):**
  - **XRT + continuous infusion 5-FU** : 5-FU 225 mg/m^2 over 24 hours 5 or 7 days/week during XRT(14)
  - **XRT + Capecitabine :** Capecitabine 825 mg/m^2 twice daily 5 days/week + XRT x 5 weeks (15, 16)
  - **XRT + 5-FU/leucovorin :** 5-FU 400 mg/m^2 IV bolus + leucovorin 20 mg/m^2 IV bolus for 4 days during week 1 and 5 of XRT (17)
  - **XRT + UFUR :** UFUR (200 mg/m^2/day) and LV (45 mg/day) on day 1–28. UFUR (250 mg/m^2/day) and LV were continued on day 36–63.(18) or a single course of oral LV 12.5 mg twice daily and oral UFT 300 mg/m^2/day in three divided doses on Days 8–36 of the RT course. The UFT doses were rounded up or down to the nearest 100 mg.(19)

- **XRT +Mitomycin C-UFUR ：** Mitomycin C 6mg/sqM in 100 ml NS iva for 30 min (6 mg/m2 on D1) UFUR (C1: 200 mg/m2/d, D1-35，C2:250 mg/m2/d, D43 to 70) + folinic acid (45 mg/d) (VGHTPE trail)(20)
- **XRT + XELOX ：** capecitabine 825 mg/m^2 twice daily on days 1 to 5 for 5 weeks .Oxaliplatin IV 2-hour infusion on days 1, 8, 15, 22, and 29 at a dose of 50 mg/m^2 (21)

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