UNIVERSITY OF KRAGUJEVAC
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Radiotherapy of gastrointestinal malignancies
Benign conditions – indications for radiotherapy

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Pancreatic cancer

- 200000 new cases per year in the world
- in Europe, it ranks seventh among tumors
- the third most common gastrointestinal tumor, with a mortality rate of 10.9/100,000 per year
- 5-year survival for unresectable tumors is less than 5%, while for resectable tumors it is 5-20%

Ductal carcinoma
Adenocarcinoma
Giant cell carcinoma
Adenosquamous carcinoma
Microadenocarcinoma
Mucinous
Cystadenocarcinoma
Acinar cell carcinoma
Acinar cell adenocarcinoma
Acinar cell cystadenocarcinoma
Mixed type
Acinar ductal and islet carcinoma
Unspecified type
Papillary-cystic type
Pancreaticoblastoma
Unclassified type
Giant cell carcinoma
Small cell carcinoma
Clear cell carcinoma

TNM classification of pancreatic tumors

8th AJCC staging system	
T1	Maximum tumor diameter $\leq$ 2 cm
T2	Maximum tumor diameter $>$ 2 cm and $\leq$ 4 cm
T3	Maximum tumor diameter $>$ 4 cm
T4	Tumor involves the celiac axis, the superior mesenteric artery, and/or common hepatic artery
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N2	Metastasis in $\geq$ 4 regional lymph nodes

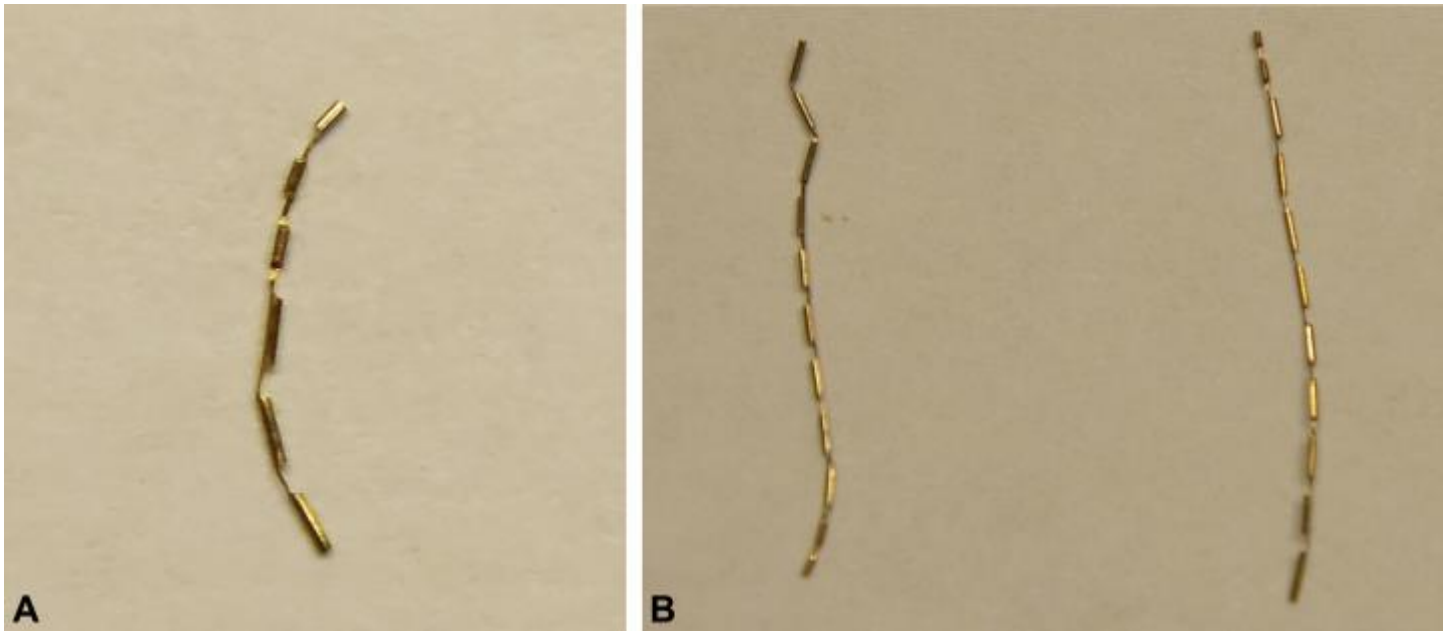
Schouten TJ, et al; Dutch Pancreatic Cancer Group. Nationwide Validation of the 8th American Joint Committee on Cancer TNM Staging System and Five Proposed Modifications for Resected Pancreatic Cancer. Ann Surg Oncol. 2022 Sep;29(9):5988-9.

Radiotherapy of pancreatic tumors

- Minimum standard 3D-CRT, preferred application of complex radiation techniques (IMRT/VMAT, SBRT)
- CT simulation in the supination position, with arms raised above the head and knees slightly bent, under which a suitable pad is placed.
- The patient should be advised not to eat for 3 hours before the CT simulation, so that the stomach is separated from the tumor/target volume as much as possible.
- Sections 2-3 mm thick, perorally and/or intravenously applied contrast is applied.
- To implement the SBRT radiation technique, CT simulation is performed with the application of 4D-CT imaging.

Fiducial marker

Fiducial markers are placed at the site of the tumor, in order to mark the tumor bed and perform quality IGRT procedures.



Coronel E, et al. EUS-guided placement of fiducial markers for the treatment of pancreatic cancer. VideoGIE.2019 ;4(9):403-6.

Indications for radiotherapy in patients with pancreatic cancer

- Resectable or marginally resectable tumors - adjuvant approach
- Locally advanced tumors
- Palliative approach
- Relapse of the disease

Radiotherapy of the pancreas

Preoperative or definitive RT +/- CHT

Place the fiducial marker in the center of the tumor

Adjuvant RT +/- HT

It reduces the rate of local recurrences

CHT+RT doses 45–50.4 Gy, 1.8–2 Gy per fraction to the tumor bed, surgical anastomoses (hepatojejunostomy and gastrojejunostomy can be avoided) and surrounding Ln groups, with the possibility of dose escalation to high-risk regions

Highly sophisticated RT techniques 45 to 54 Gy (daily dose 1.8 Gy)

If the therapeutic response is not satisfactory RT+ HT 36 Gy with 2.4 Gy per fraction

Intraoperative radiotherapy (15 to 20 Gy in one fraction)

Using the SBRT radiation technique, it is possible to apply a "boost" dose to the reduced target volume

RT in locally advanced pancreatic tumor

- The goal is to prevent or delay the local progression of the disease (pain or obstruction), enable local control of the disease, ensure R0 resection in patients who are potential candidates for surgery.
- Induction CHT followed by CHT-RT or SBRT in selected patients
- CHT-RT, SBRT or hypofractionated RT

- Standard regimens: 45-54 Gy 1.8-2 Gy per fraction
- SBRT regimens: 3 fractions (30-45 Gy) or 5 fractions (25-50 Gy)
- Hypofractionated regimens: 67.5 Gy in 15 fractions or 75 Gy in 25 fractions

Defining target volumes for neoadjuvant radiotherapy of pancreatic tumors

Target volumes	Neoadjuvant RT
GTVt: all localizations	The tumor shown on PET-CT imaging
GTVn: all localizations	Macroscopically enlarged Ln (n+) on PET-CT
CTVt	GTV + 3 cm wide margin in the pancreatic tissue
CTVn+	GTVn + 0.5 cm wide margin
CTVn	Levels of Ln depending on anatomical localization that are irradiated prophylactically
CTV 45Gy	CTVt + CTVn + CTVn+
PTV 45 Gy	CTV 45 Gy + margin width 12 mm in the craniocaudal direction, 7 mm in the lateral and anterior direction, 5 mm in the posterior direction
OAR	Small and large intestine, liver, kidneys and spinal cord

Using the SBRT it is possible to apply a boost dose of up to 9 Gy to the reduced target volume

Organ at Risk (OAR)	Neoadjuvant/Definitive/Palliative and Recurrent Recommendations[d]	Adjuvant Recommendations[e]
Kidney (right and left)	Not more than 30% of the total volume can receive ≥18 Gy. If only one kidney is functional, not more than 10% of the volume can receive ≥18 Gy.	For 3D conformal plans in patients with two normally functioning kidneys, at least 50% of the right kidney and at least 65% of the left kidney must receive <18 Gy. For IMRT planning, mean dose to bilateral kidneys must be <18 Gy. If only one kidney is present, not more than 15% of the volume of that kidney can receive ≥18 Gy and not more than 30% can receive ≥14 Gy.
Stomach, duodenum, jejunum	Max dose 55 Gy.	Max dose ≤54 Gy; <10% of each organ volume can receive between 50 and 53.99 Gy; <15% of the volume of each organ can receive between 45 and 49.99 Gy.
Liver	Mean dose cannot exceed 30 Gy.	Mean liver dose must be ≤25 Gy.
Spinal cord	Max dose to a volume of at least 0.03 cc must be ≤45 Gy.	Max dose ≤45 Gy.

Radiotherapy of locally recurrent pancreatic cancer

- Induction CHT followed by CHT-RT or SBRT (if not previously performed)
- CHT-RT or SBRT in selected patients who are not candidates for induction CHT

- Standard regimens: 45-54 Gy 1.8-2 Gy per fraction
- SBRT regimens: 3 fractions (30-45 Gy) or 5 fractions (25-50 Gy)

Palliative radiotherapy in pancreatic cancer

- Reduction of the intensity of pain, bleeding, symptoms of local obstruction in patients with metastatic or non-metastatic disease
- In non-metastatic disease in elderly patients who are not candidates for definitive therapy (comorbidities or poor PS)
- In metastatic disease for irradiation of painful areas (short course RT)

Hepatocellular carcinoma (HCC) radiotherapy

- Not applicable by default
- Highly sophisticated techniques
- SBRT shows promising results for the treatment of smaller primary tumor changes
- Precise application of a high therapeutic radiation dose (BED >100 Gy) to a respiratory mobile target volume in the liver

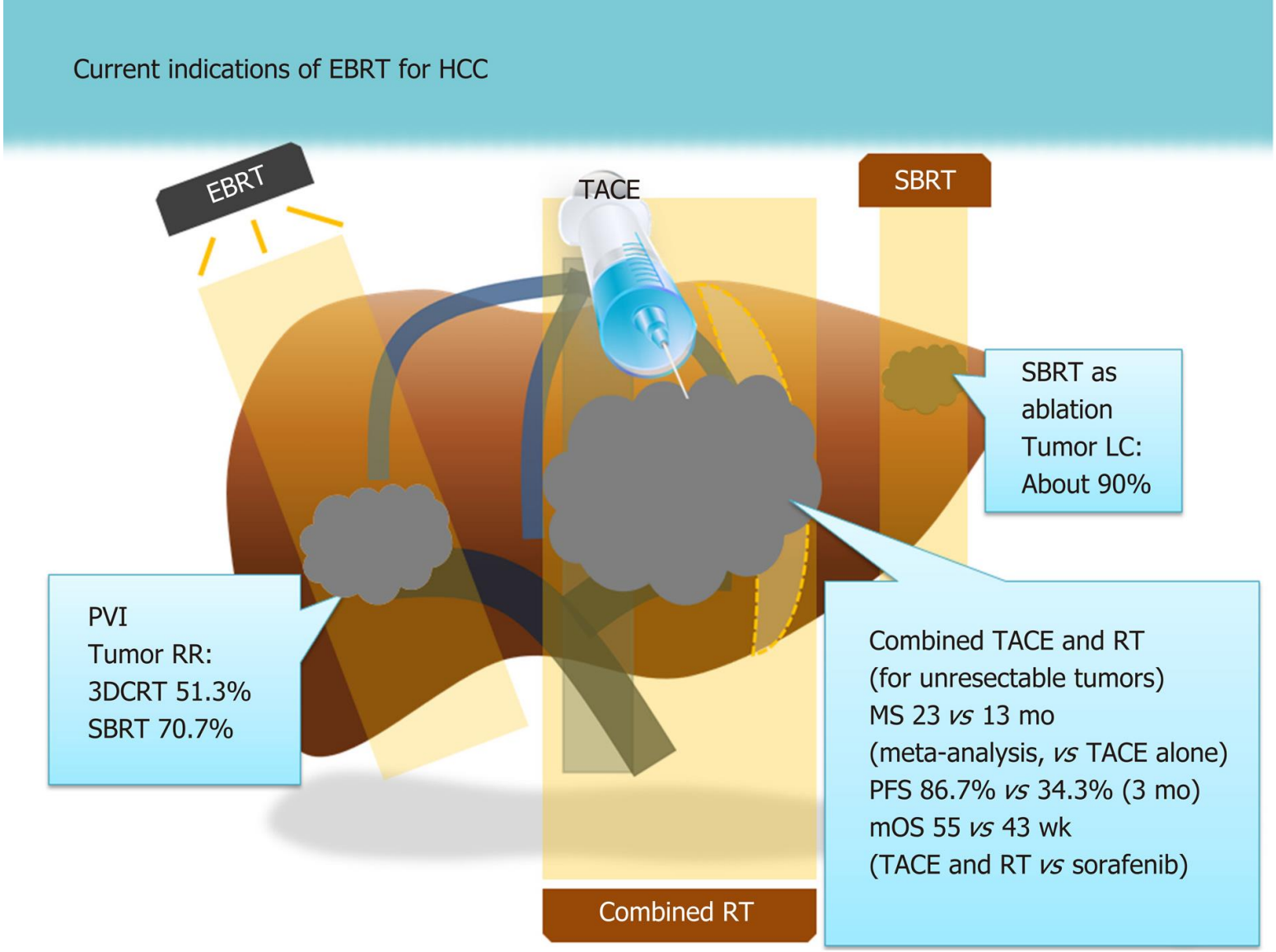
SBRT of liver metastases indications:

- up to 3 (metachronous) metastases
- not larger than 6 cm (best up to 3 cm)
- ECOG status 0-2
- CHT before and after SBRT

HCC indications for RT

- In limited cases, as a therapeutic option for unresectable HCC in patients with existing comorbidities that do not allow extensive surgery
- RT combined with transcatheter arterial chemotherapy in the treatment of unresectable hepatocellular carcinoma

- Challenges in RT planning:
- Radiosensitivity of the surrounding liver parenchyma and other OARs
- functional activity of the liver, i.e. the degree of damage to the remaining liver parenchyma due to associated diseases (cirrhosis, inflammation)

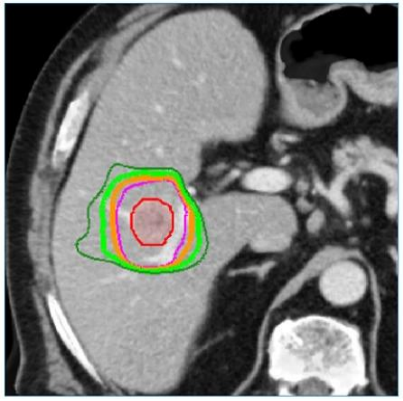


Park S, et al. Indications of external radiotherapy for hepatocellular carcinoma from updated clinical guidelines: Diverse global viewpoints. World J Gastroenterol 2020; 26(4): 393-403.

Barcelona Clinic Liver Cancer stage

Stage 0

Not a resection candidate
Location not suitable for thermal ablation

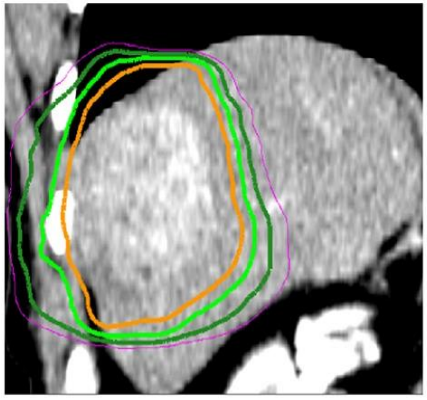


Consider SABR if abutting major vessels or bile ducts.
Non-invasive option for subphrenic or exophytic HCC.

Stage A

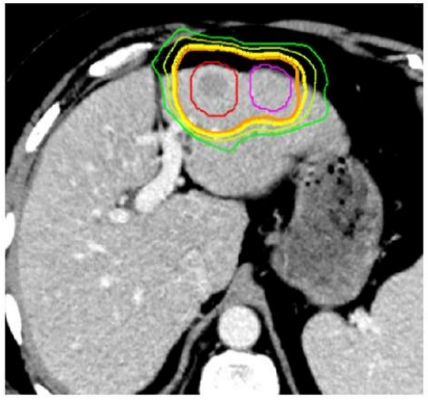
Single lesion

Not for resection/OLT
Location not suitable or too large for thermal ablation



Multifocal
≤ 3 lesions ≤ 3cm

Not for resection/OLT
Not suitable for or recurred following ablation or TACE

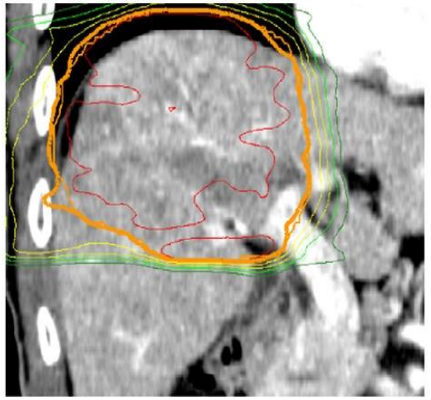


Potential first-line ablative therapy or adjunctive therapy for residual or recurrent disease following TACE.
Potential option for bridge to OLT in patients unsuitable for thermal ablation or TACE.

Stage C

Dominant lesion with MVI
Liver confined disease

Systemic therapy
TACE + RT or TARE
SABR



RT or SABR can be effective in controlling tumor thrombus.
Consider combining with TACE.

Shanker MD, et al. Stereotactic radiotherapy for hepatocellular carcinoma: Expanding the multidisciplinary armamentarium. J Gastroenterol Hepatol 2021;36(4):873-84.

What's new?

- HCC is a radiosensitive tumor
- The application of SBRT has shown a high rate of local control in patients with different stages of HCC
- The prognosis depends on tumor factors, functional capacity of the liver and patient characteristics
- Necessary modern imaging for planning
- High degree of local control
- Minimally invasive method of treatment
- Ability to overcome anatomical limitations
- Does not depend on location (near major blood vessels, including portal vein, inferior vena cava, and bile duct)
- Possible treatment of complicated forms of tumors
- Short treatment period (usually within 2 weeks)
- Improving the patient's quality of life
- Reduction of treatment costs
- The possibility of improving the immune response to tumors

With the standard regimen of fractionation using a conventional technique, a therapeutic dose of 30-40 Gy provided a <30% response rate.

Challenges in planning

- Uncertain outcome of treatment
- The possibility of pronounced toxicity in large tumors
- Treatment of tumors near critical organs
- Unclear effects of re-irradiation
- Mobility of the target due to breathing and the presence of ascites

SBRT of liver metastases

- SBRT most effective in patients with up to 3 (metachronous) metastases, no larger than 6 cm (best up to 3 cm), ECOG status 0-2, and in those who received HT before and after SBRT.
- If dose-volume limitations are observed, SBRT of liver metastases is a safe ablative method, where mortality is 0.5%.

Esophageal cancer

- Sixth place in the number of deaths
- One-year survival of these patients is about 33%, and five-year survival is between 10% and 20%.
- Every year in the world, about 480,000 people fall ill with esophageal tumors, and about 400,000 sufferers die from this disease.
- Men get sick almost twice as often as women

TNM classification

8th stage	T	N	M
0	Is	0	0
I	1	0–1	0
II	2	0–1	0
	3	0	0
III	3	1	0
	1–3	2	0
IVA	4	0–2	0
	Any	3	0
IVB	Any	Any	1

Esophageal carcinoma radiotherapy

- **Neoadjuvant CHT-RT** (stages cT1b-T2N+; cT/cT and any cN+)
- Phase I TD of 41.4 Gy applied in 23 fractions
- Phase II TD 9 Gy in 5 fractions (only tumor and PET+ Ln)

- **Definitive CHT-RT** - cT4b stage (potentially curative approach in patients with SCC)

- **Palliative RT**

Recommendations for the treatment of squamous carcinoma (SCC) of the esophagus according to the stage

Stage 0 and Ia (T1a and T1b)	Esophagectomy Endoscopic mucosal resection or submucosal dissection with/without photodynamic therapy or radiofrequency ablation
Stage IB (T2-3N0), II and III (including patients with positive LN) – inoperabins	The general approach for these stages is: preoperative chemotherapy (5-FU + cisplatin) + radiotherapy -» surgery
Stage IV - palliative therapy	Palliative chemotherapy Palliative chemoradiotherapy Palliative radiotherapy Palliative surgery Palliative symptomatic and supportive therapy.

Recommendations for the treatment of adenocarcinoma of the esophagus according to the stage

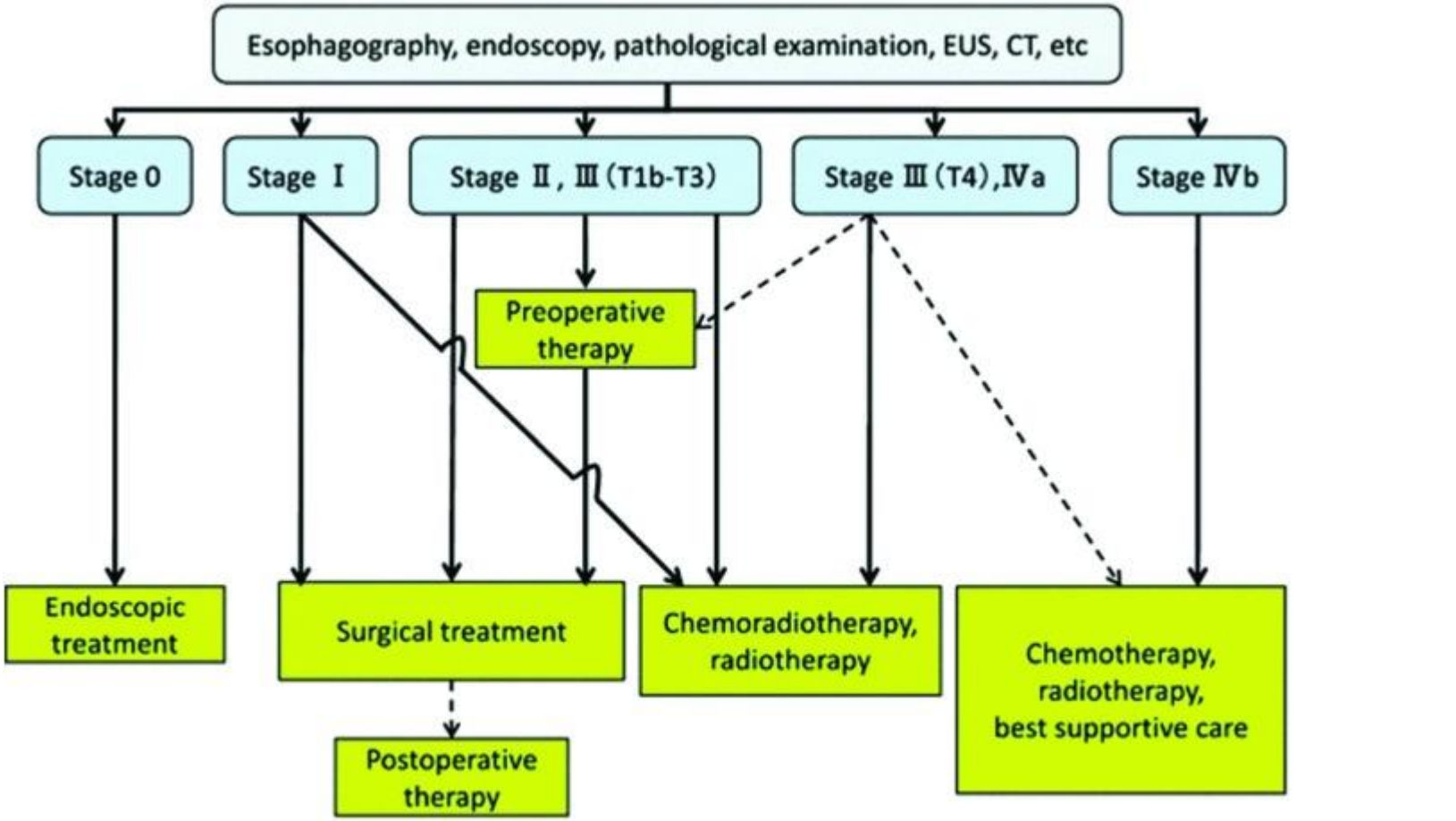
Stage 0 and Ia (T1a and T1b)	Esophagectomy Endoscopic mucosal resection or submucosal dissection with/without photodynamic therapy or radiofrequency ablation
Stage IB (T2-3N0), II and III (including patients with positive LN) – inoperable	Preoperative chemoradiotherapy (5-FU + cisplatin, 50 Gy), followed by diagnostics to assess operability
Stage III and IVA (operable), for patients with ECOG PS 0 or 1	Preoperative chemotherapy (5-FU + cisplatin) + radiotherapy -* surgery
Stage IV - palliative therapy	Cocurrent chemotherapy (5-FU + cisplatin) and radiotherapy Monotherapy such as: radiotherapy, chemotherapy Palliative surgery Palliative symptomatic, supportive and roborant therapy Placement of stents, dilators, endoscopic laser therapy

Radiotherapy of esophageal cancer

- X-radiation (energy 6-16 MV)
- Application of complex radiation techniques (IMRT and VMAT), whose planning is based on 4D-CT simulation and CT-PET imaging and whose implementation is controlled by IGRT procedures
- Delineation of OAR and compliance with tolerance limits

CT simulation

- In a supinated position, with the arms raised above the head, a thermoplastic mask for the head and neck with the arms resting against the body. A suitable pad is placed under the knee. Lateral lasers are projected at the level of the intermamillary line at half the AP diameter, and the sagittal laser at the level of the medial line of the body.
- CT imaging is performed with the use of intravenous contrast, and if necessary, oral contrast is also used.
- In the case of carcinoma of the lower third of the esophagus or gastroesophageal junction, the patient should be advised not to eat for three hours before CT simulation and before each radiation fraction.



Sohda M, Kuwano H. Current Status and Future Prospects for Esophageal Cancer Treatment. Ann Thorac Cardiovasc Surg 2017;23(1):1-11.

Delineation of target volumes and dose prescription

Target volume	Structures and margins
	Phase 1 (23 x 1,8 Gy)
GTVt	Tumor involving the entire circumference of the esophagus (use EGDS/CT/PET)
GTVn	Macroscopically enlarged lymph node (n+).
CTVt: SCC	A margin of size 1 cm radially, and 3 cm proximal and distal to the GTVt
CTVt: AC	A margin of size 1 cm radially, and 3 cm proximally and 5 cm distally from the GTVt
CTVn+	GTVn + margin size 0.5 cm
CTVn	Levels of lymph nodes depending on the anatomical localization of the tumor
PTV 41,4 Gy	CTV 41,4 Gy (CTVt + CTVn + CTVn+) + 5 mm
	Optional: Phase 2 (5 x 1,8 Gy)
PTV 50,4 Gy	CTV 50,4 Gy (CTVt + CTVn+) + 5 mm
OAR	Lungs, heart, spinal cord, larynx, liver, kidneys

3D-CRT tehnika

Brachytherapy of esophageal cancer

- Intraluminal, alone or in combination with laser ablation or EBRT
- The dose is prescribed at 1 cm lateral to the axis of the catheter
- Simple palliative regimens 1x 15Gy
- Local boost combined with EBRT 1 x 7.5 Gy at the beginning and end of EBRT
- Metastatic esophageal cancer with dysphagic complaints 1-2 x 6-10 Gy

Stomach cancer

- Intestinal or diffuse type
- **The cardia/GEJ area** is much more common in men than in women (5:1), tumors that arise in the upper parts and spread to the GEJ are classified as esophageal carcinomas.
- **Cancer of the lower parts of the stomach** is more common in men, it is more common in blacks than in whites with the highest incidence in older age (from 50 to 70 years).

WHO (2010)	Lauren (1965)
Papillary adenocarcinoma Tubular adenocarcinoma Mucinous adenocarcinoma	Intestinal type
Signet-ring cell carcinoma And other poorly cohesive carcinoma	Diffuse type
Mixed carcinoma	Indeterminate type
Adenosquamous carcinoma	
Squamous cell carcinoma	
Hepatoid adenocarcinoma	
Carcinoma with lymphoid stroma	
Choriocarcinoma	
Carcinosarcoma	
Parietal cell carcinoma	
Malignant rhabdoid tumor	
Mucoepidermoid carcinoma	
Paneth cell carcinoma	
Undifferentiated carcinoma	
Mixed adeno-neuroendocrine carcinoma	
Endodermal sinus tumor	
Embryonal carcinoma	
Pure gastric yolk sac tumor	
Oncocytic adenocarcinoma	

CA CANCER J CLIN 2021;71:209–249

Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries

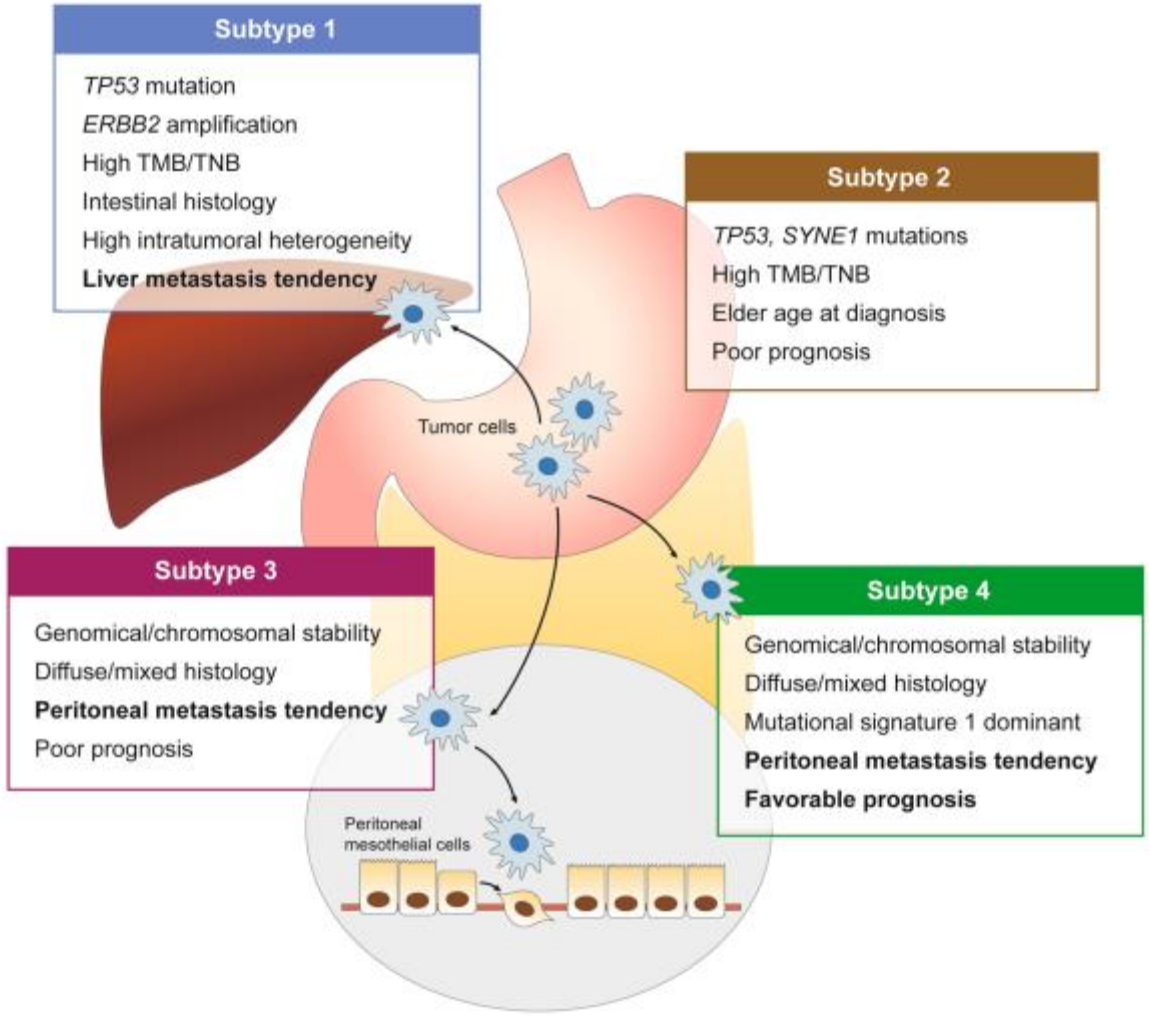
Hyuna Sung, PhD [1]; Jacques Ferlay, MSc, ME[2]; Rebecca L. Siegel, MPH [1]; Mathieu Laversanne, MSc[2]; Isabelle Soerjomataram, MD, MSc, PhD[2]; Ahmedin Jemal, DMV, PhD[1]; Freddie Bray, BSc, MSc, PhD[2]

CANCER SITE	NO. OF NEW CASES (% OF ALL SITES)		NO. OF NEW DEATHS (% OF ALL SITES)	
Female breast	2,261,419	(11.7)	684,996	(6.9)
Lung	2,206,771	(11.4)	1,796,144	(18.0)
Prostate	1,414,259	(7.3)	375,304	(3.8)
Nonmelanoma of skin[a]	1,198,073	(6.2)	63,731	(0.6)
Colon	1,148,515	(6.0)	576,858	(5.8)
Stomach	1,089,103	(5.6)	768,793	(7.7)
Liver	905,677	(4.7)	830,180	(8.3)
Rectum	732,210	(3.8)	339,022	(3.4)

Stomach cancer

- In terms of morbidity, it is in sixth place, and in terms of mortality, it is in third place among all malignancies

Gastric carcinoma - classification integrates multidimensional genetic features



Wang H, et al. A novel genomic classification system of gastric cancer via integrating multidimensional genomic characteristics. Gastric Cancer 2021;24(6):1227-41.

Tumors of GEJ division according to Siewert

- **Type I** - the center of the tumor is located > 1 cm above the anatomical border of the GEJ
- **Type II** - the center of the tumor is located up to 1 cm above and 2 cm below the anatomical border of the GEJ
- **Type III** - the center of the tumor is located > 2 cm, but not > 5 cm below the anatomical border of the GEJ

TNM classification

Table 4 Stage grouping of stomach tumors, 7th edition[9]

Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0, N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4a	N3	M0
	T4b	N2, N3	M0
Stage IV	Any T	Any N	M1

Gastric cancer radiotherapy

- **RT combined with sequential and concomitant CHT** (Cisplatin/5-fluorouracil/leucovorin)
- **Preoperative RT** - 45 Gy in 25 fractions (tumors of the GEJ region, enables R0 resection)
- **Postoperative RT+/- CHT** - TD- 45 Gy in 25 fractions (stages II and III, suboptimal surgery, R1)
- **Metastatic disease** hypofractionated RT: symptomatic locally advanced or recurrent disease, bleeding, obstruction or pain

CT simulation

- Oral barium contrast is used to visualize the anastomosis site of the esophagus and the rest of the stomach, as well as the small intestine.
- Sections from the roof of the diaphragm to L4, while for tumors of the gastroesophageal transition, the upper limit of the CT volume should be at the level of the trachea carina
- It is performed in a supinated position, with the arms raised above the head and the knees slightly bent
- The lateral lasers are projected at the level of the xiphoid at half the AP diameter, and the sagittal laser at the level of the medial line of the body.
- The patient should be advised not to eat for 3 hours before the CT simulation and before each radiation fraction
- If necessary, CT simulation can be performed with the application of oral and intravenous contrast (e.g. when planning postoperative radiotherapy)

Target volumes in the application of neoadjuvant radiotherapy for gastric cancer

GTVt: all localizations - tumor (use EGDS/CT/PET)
GTVn: all localizations - macroscopically enlarged lymph nodes (n+)
CTVt: GEJ GTVt + margin width 1 cm radially, 3 cm cranially and 5 cm caudally
CTVt: tumor of the upper 1/3 of the stomach - stomach without pylorus and antrum; minimum 5 cm wide margin from the edges of the GTV
CTVt: tumor of the middle 1/3 of the stomach - the whole stomach
CTVt: tumor of the lower 1/3 of the stomach - stomach without cardia and fundus; minimum 5 cm wide cranial margin from the edges of the GTV; in case of infiltration of the duodenum and pylorus, the CTVt should be expanded around the duodenum with a 3 cm wide margin from the edges of the GTV
CTVn+ - macroscopically enlarged lymph nodes (n+) + 0.5 cm
CTVn - levels of LN that, depending on the anatomical localization of the tumor, are irradiated prophylactically; CTVn is defined as a margin of 7 mm around associated blood vessels
CTV 45 Gy CTVt + CTVn + CTVn+
PTV 45 Gy - CTV 45 Gy + 3D 1.5 cm wide margin (for 3D conformal RT + NAL protocol)
OAR - small and large intestine, liver, heart, lungs, kidneys, spinal cord

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Radiotherapy of colon and rectal cancer

Neoadjuvant RT + CHT (5-Fu +/- oxaliplatin): stage II and III rectal cancer

- Primary aim: downsizing, downstaging, devitalization of tumor cells, increasing the efficiency of surgery, local disease control and long-term survival.
- Surgery follows 10-12 weeks after completion of RT
- In the case of complete responce (CR), with frequent controls, the application of operative treatment can be delayed until a possible relapse of the disease (the so-called "watch and wait" approach)

Preoperative RT as monotherapy in a hypofractionated regimen, and surgery is performed within seven days of RT ("short course")

- Hypofractionated radiation (without chemotherapy), for the same PTV prescribes a dose of 25 Gy in 5 fractions.

Radiotherapy of colon and rectal cancer

- **Adjuvant (postoperative) RT +/- CHT** (5-Fu) 4-6 weeks after surgery: pT3> pT4, pN+ stage, tumor infiltration of perirectal tissue and surrounding organs, resection margins <3 mm, tumor >3 cm, LVI positive LN or R1/2 resection in pT2N0 stage disease.
- Positive resection margins (R1) after performed preoperative HT-RT and operative treatment - consider postoperative application of a boost dose to the tumor bed of 25 Gy in 5 fractions using the SBRT technique, before performing adjuvant HT

OAR	Dose/volume	Max dose
Large intestine	V45<20 cc	55 Gy
Small intestine	V45<195 cc	
Bowel bag	V30<450 cc	
Femoral head	V50<5%	
Wings of the iliac bone	V30<50%; V40<35%; V50<5%	
External genitalia	V20<50%; V30<35%; V40<5%	
Bladder	V35<50%; V40<35%; V50<5%	

- Chemo-reirradiation in non-metastatic disease
- If, after the preoperative CHT-RT and operative treatment, the histopathological findings indicate R1, it is indicated postoperatively, before performing adjuvant CHT, to apply a boost dose of 25 Gy in 5 fractions to the tumor bed, using the SBRT radiation technique
- Palliative RT and reirradiation of rectal cancer.
- Re-irradiation after the appearance of a local recurrence, with a hyperfractionated accelerated radiation regimen, a dose of 36 Gy in 30 fractions, 1.2 Gy per fraction, two fractions per day with an interval of 6 hours, for 15 working days is prescribed to the PTV

Benefits of neoadjuvant CHT/RT

- T down-staging and T-down-sizing
- Increase in % of complete resections, as well as sphincter-preserving surgeries
- Reducing the percentage of local recurrences
- Reducing the malignant potential of dissemination
- Tumor cells during surgery
- Sterilization of peripheral clinically undetectable malignant foci as well as deposits in lymph nodes;
- Less toxicity compared to postoperative RT (smaller air volume - less irradiation of the small intestines and less frequent inclusion of the perineum in the air field)

SHORT COURSE vs. LONG COURSE

SHORT COURSE

- Less acute toxicity
- Lower percentage of tumor regression
- Greater number of late complications (urinary, intestinal and sexual dysfunctions)
- Short lasting, cheaper

LONG COURSE – standard

- Greater acute toxicity
- Higher percentage of tumor regression (down-staging and down-sizing-40-60%)
- Complete tumor regression (CR) is achieved in 9-30% of patients
- A higher percentage of sphincter-preserving surgeries (about 60%)
- Long lasting, significantly more expensive
- Tumor regression partly depends on factors: total dose of radiation, applied cytostatic, time between preoperative treatment and surgery

Indications for neoadjuvant radiotherapy

- The stage of the disease
- Tumor localization
- Status lgl
- Status of the mesorectal fascia

- Tumors in the middle and lower third of the rectum benefit more from neoadjuvant radiotherapy compared to high rectal cancer

Delineation of target structures and volumes

- GTV includes the primary tumor and macroscopically enlarged lymph nodes on a based on the findings of endoscopy and MRI of the pelvis
- CTV 4500 (CTV1 + CTVLN)

- CTV1 - Tumor of the rectum + mesorectum + presacral space + 2 cm each
- cranial - caudal direction
- In the case of tumors localized within 6 cm of the anal line (in sphincter-sparing operations) and patients with sphincter infiltration, the perineum must be included in CTV 1
- CTVLN - iliac (internal and external) lymph nodes with a cranial border from the bifurcation of the aorta and obturator lymph nodes
- Inguinal lymph nodes are involved in the CTVLN in low-lying tumors (distal rectum) and/or with infiltration of the dentate line and vagina

Delineation of target structures and volumes

- PTV 4500
- A margin of 0.5 cm to 1 cm around CTV 45 in all directions.
- In the case of tumors located in the middle and upper third of the rectum (up to the lower edge of the mesorectum), the lower part of the anal canal, which is usually 2 cm long, should be spared

- PTV 5040 (Boost) - covers CTV1 (tumor bed) with a margin of 1 to 2 cm

Delineation of target structures and volumes

Delineation of the 7 topographic regions that may be included in the CTV:

- Mesorectum (M),
- Presacral lgl (PS/PN),
- Lateral lymph nodes (LLN),
- External lymph nodes (EIN),
- Ischiorectal fossa (IRF),
- Inguinal lymph nodes and
- Sphincter complex

Mileusnić i sar. Radijaciona onkologija, 2020.

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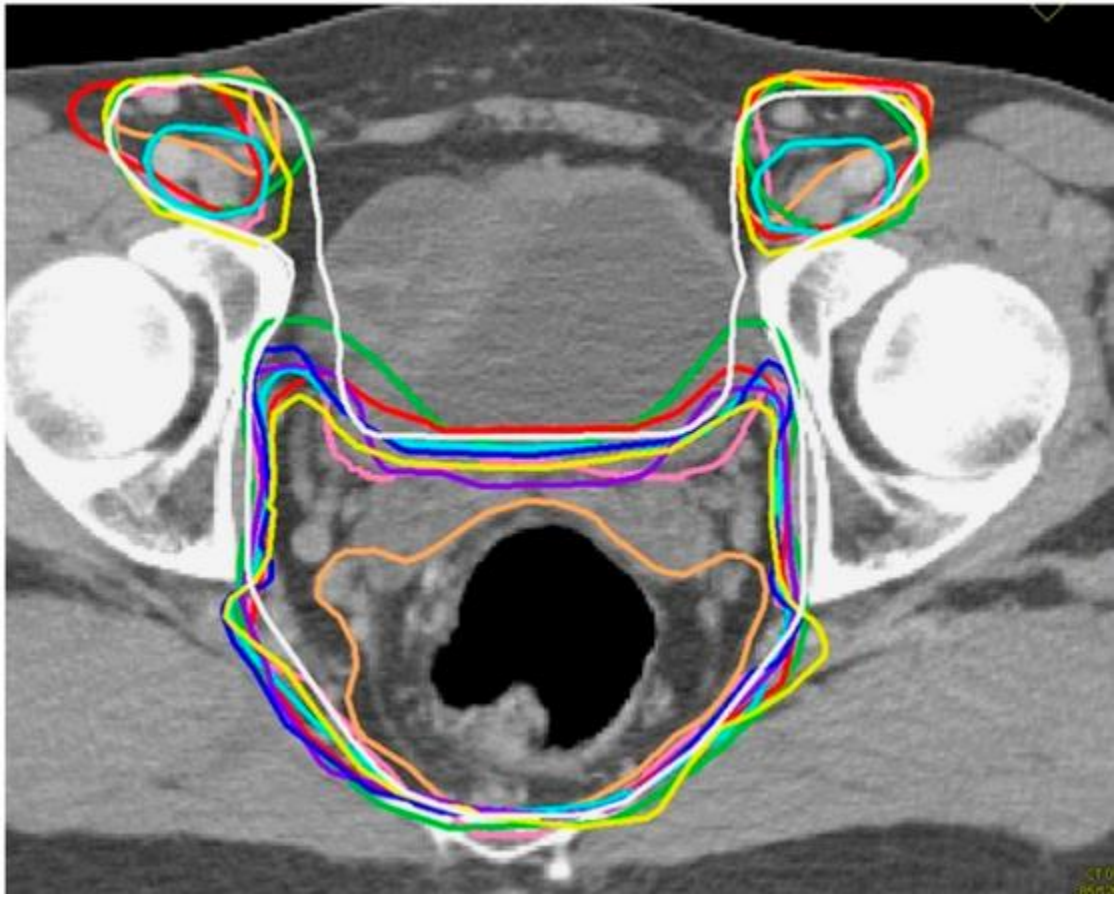
Rectal cancer guidelines

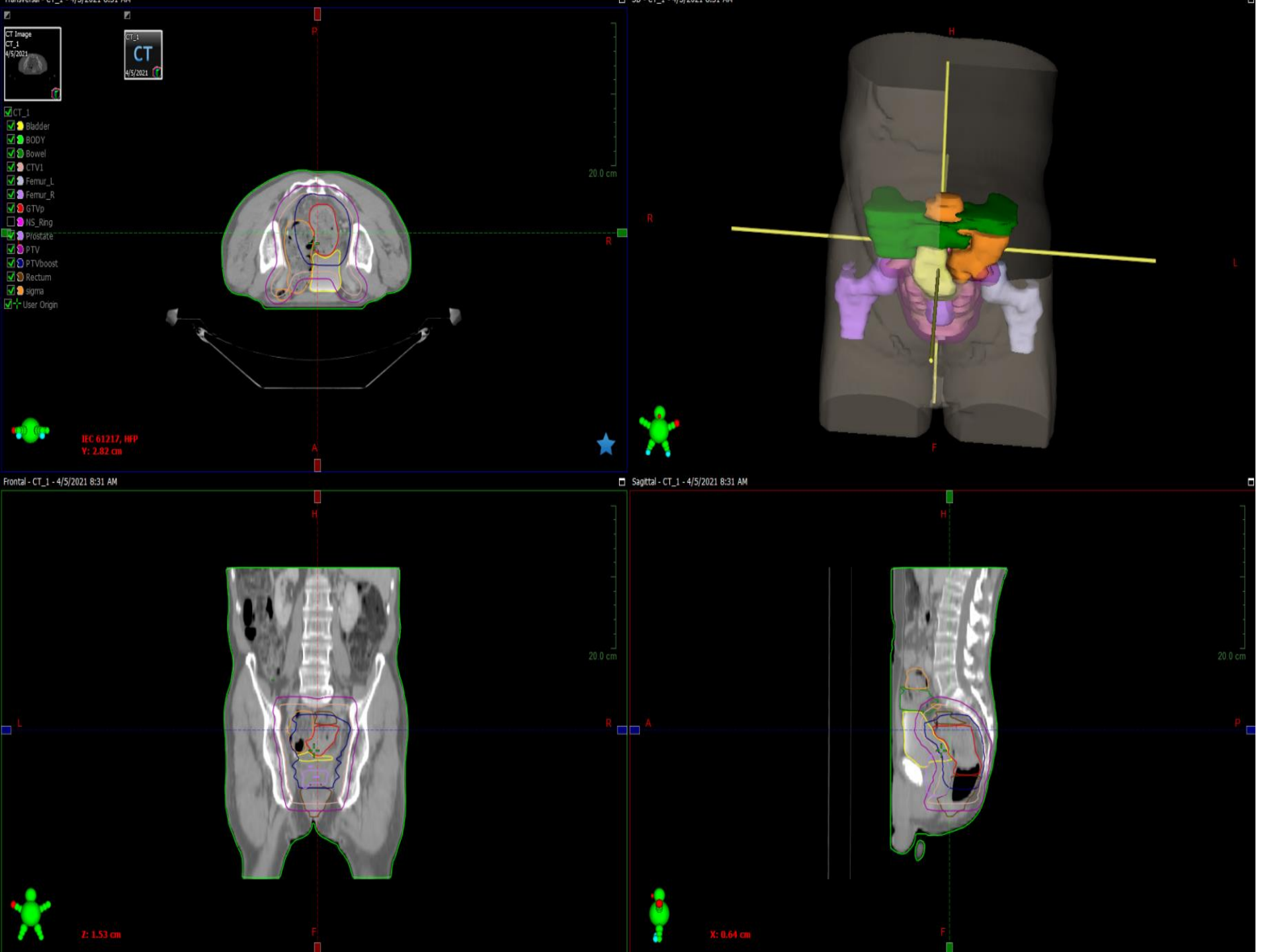
International consensus guidelines on Clinical Target Volume delineation in rectal cancer

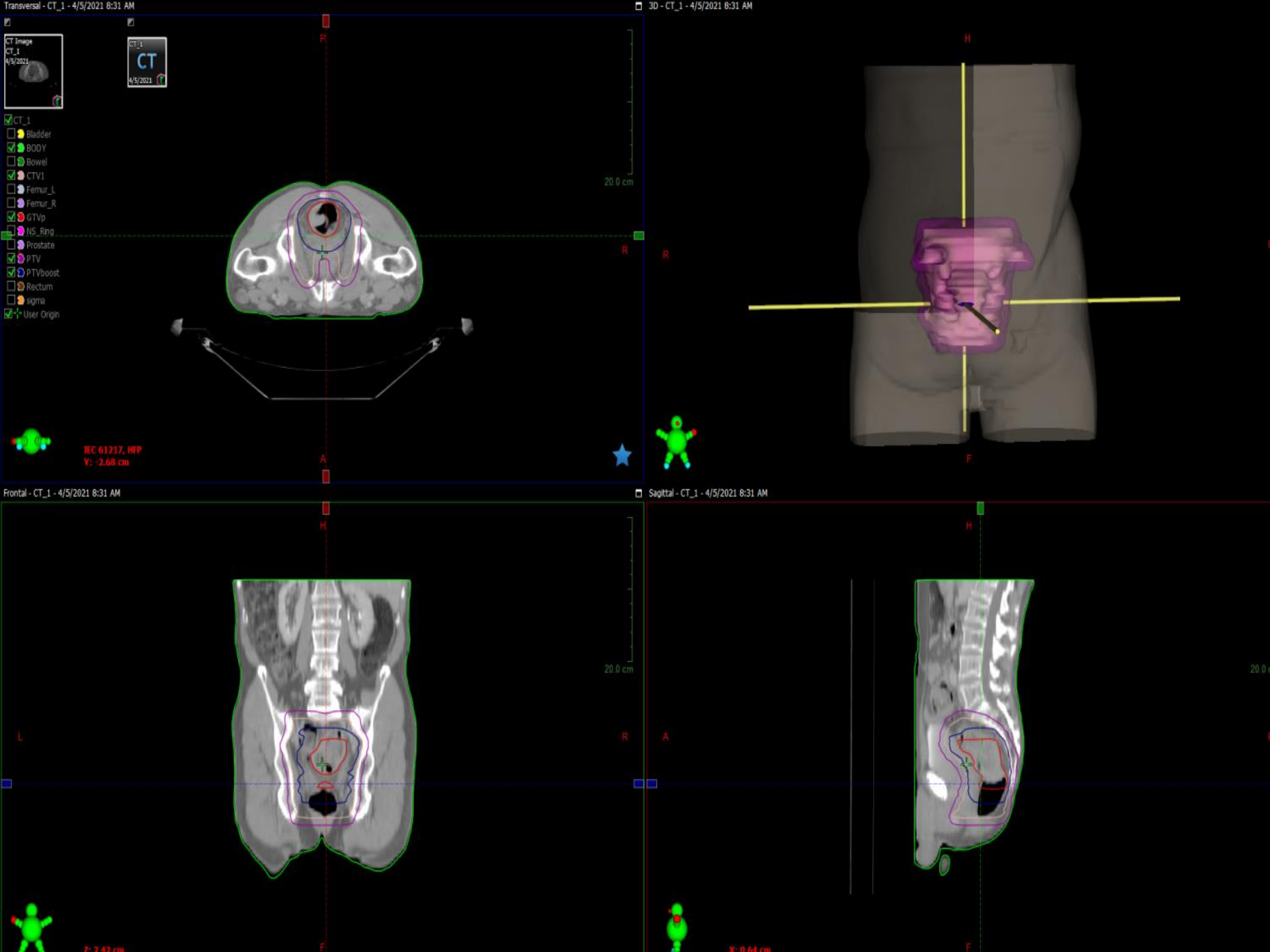
Vincenzo Valentini [a], Maria Antonietta Gambacorta [a,*], Brunella Barbaro [b], Giuditta Chiloiro [a], Claudio Coco [c], Prajnan Das [d], Francesco Fanfani [e], Ines Joye [f], Lisa Kachnic [g], Philippe Maingon [h], Corrie Marijnen [i], Samuel Ngan [j], Karin Haustermans [f]



Delineation

- GTVt + CTVt+ PS/PN+IRF+SC- usually one volume
- PTVt - 1cm, PTVn - 7 mm
- PTVt + PTVn = PTV


CT Image
CT_1
4/5/2021
CT_1
CT
4/5/2021
CT_1
Bladder
BODY
Bowel
CTV1
Femur_L
Femur_R
GTVp
NS_Ring
Prostate
PTV
PTVboost
Rectum
sigma
User Origin
20.0 cm
IEC 61217, HFP
Y: 2.82 cm
Frontal - CT_1 - 4/5/2021 8:31 AM
Z: 1.53 cm
Sagittal - CT_1 - 4/5/2021 8:31 AM
X: 0.64 cm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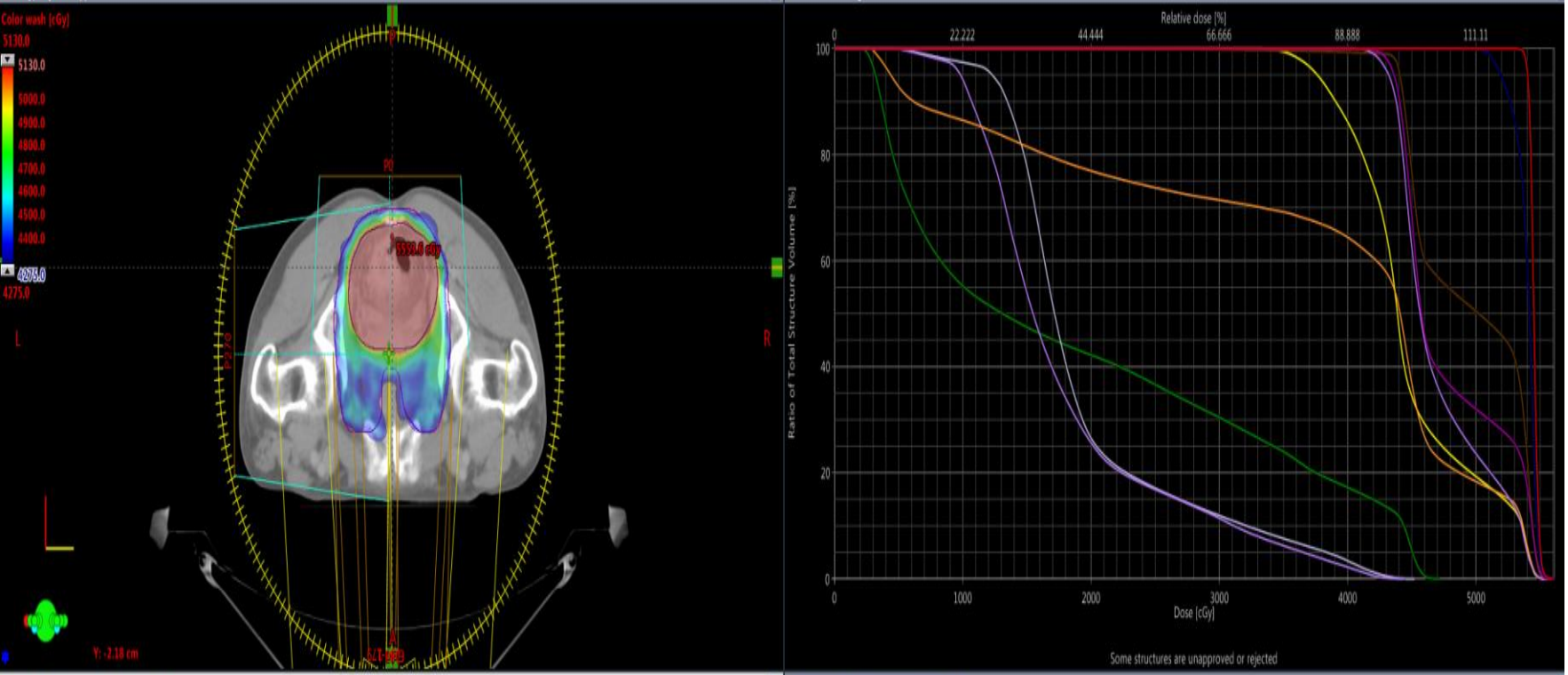
3D - CT_1 - 4/5/2021 8:31 AM
Frontal - CT_1 - 4/5/2021 8:31 AM
Sagittal - CT_1 - 4/5/2021 8:31 AM
CT Image
CT_1
4/5/2021
CT
CT_1
Bladder
BODY
Bowel
CTV1
Femur_L
Femur_R
GTVp
NS_Ring
Prostate
PTV
PTVboost
Rectum
sigma
User Origin
20.0 cm
IEC 61217, HFP
Y: -2.68 cm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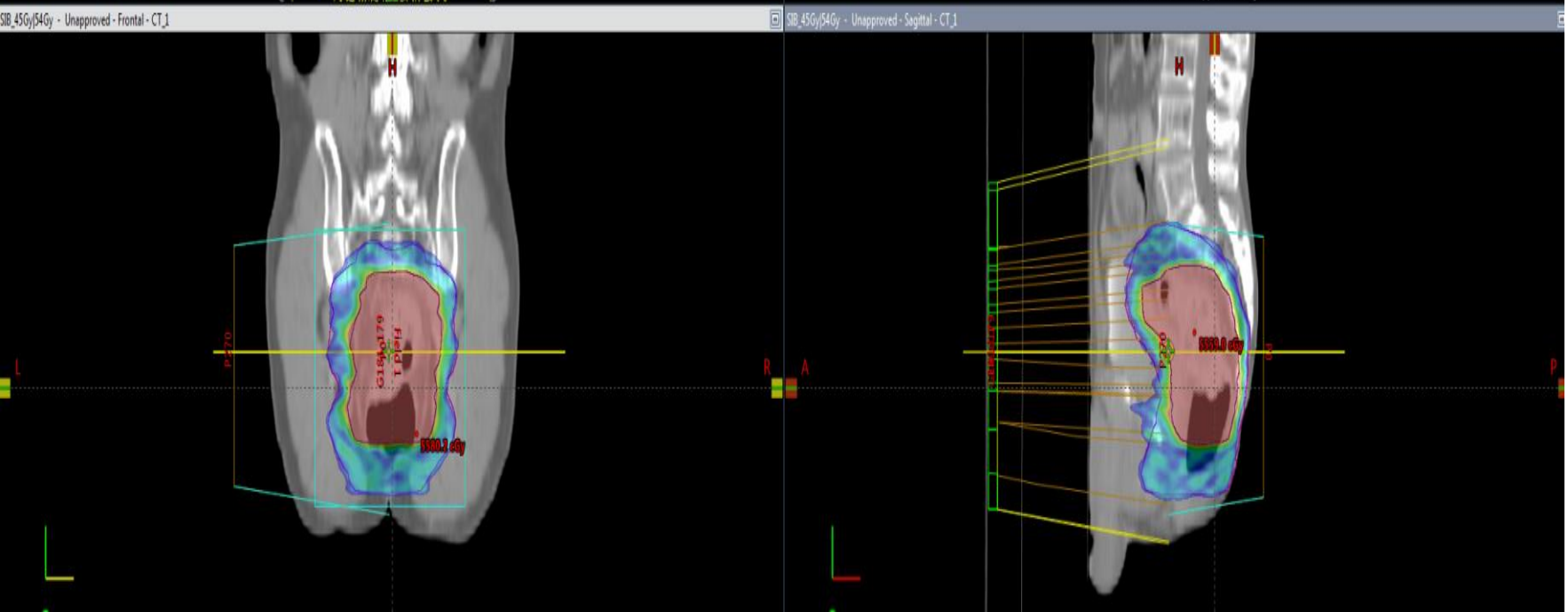
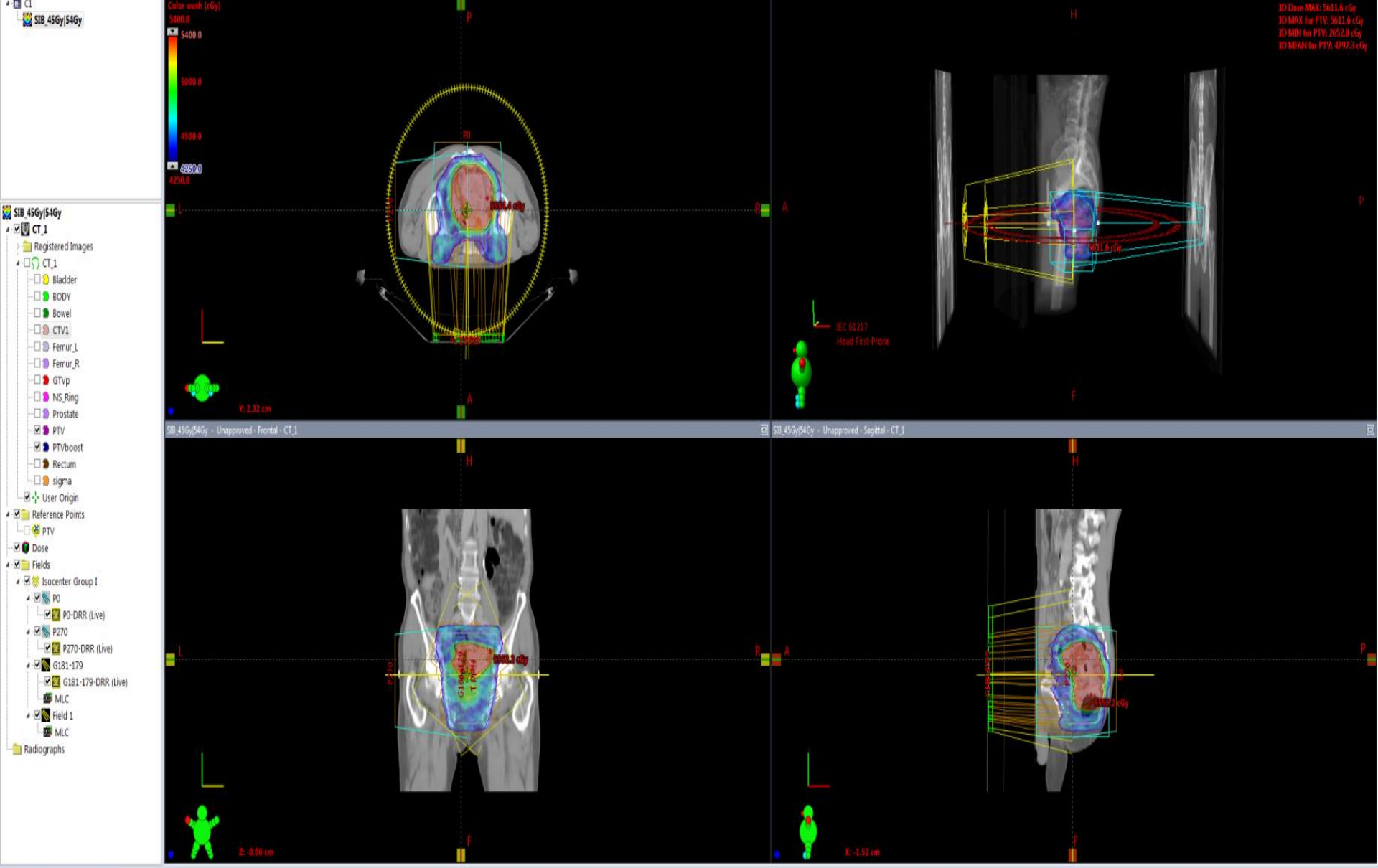
5130.0
5130.0
5000.0
4900.0
4800.0
4700.0
4600.0
4500.0
4400.0
4275.0
4275.0
P2
P270
5338.0 cGy
L
R
A
Y: -2.18 cm
Relative dose [%]
0
22.222
44.444
66.666
88.888
111.11
100
80
60
40
20
0
Ratio of Total Structure Volume [%]
0
1000
2000
3000
4000
5000
Dose [cGy]
Some structures are unapproved or rejected


SIB_45Gy|54Gy - Unapproved - Frontal - CT_1
H
P270
G180
L
R
5380.1 cGy
SIB_45Gy|54Gy - Unapproved - Sagittal - CT_1
H
P270
5338.0 cGy
A
P



Fields | Dose | Reference Points | Dose Statistics

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☑	BODY	Unapproved	SIB_45Gy|54Gy	C1	21408.6	100.0	100.1	0.3	5611.6	1343.0
☑	Bladder	Unapproved	SIB_45Gy|54Gy	C1	244.1	100.0	100.0	3251.9	5530.9	4488.1
☑	Bowel	Unapproved	SIB_45Gy|54Gy	C1	381.8	100.0	100.0	198.9	4713.9	1942.1
☑	Femur_L	Unapproved	SIB_45Gy|54Gy	C1	177.5	100.0	100.0	449.9	4521.4	1953.4
☑	Femur_R	Unapproved	SIB_45Gy|54Gy	C1	178.1	100.0	100.0	434.7	4433.9	1799.6
☑	Rectum	Unapproved	SIB_45Gy|54Gy	C1	151.4	100.0	100.0	1995.1	5611.6	4949.4
☑	sigma	Unapproved	SIB_45Gy|54Gy	C1	349.2	100.0	100.0	274.2	5565.1	3642.4
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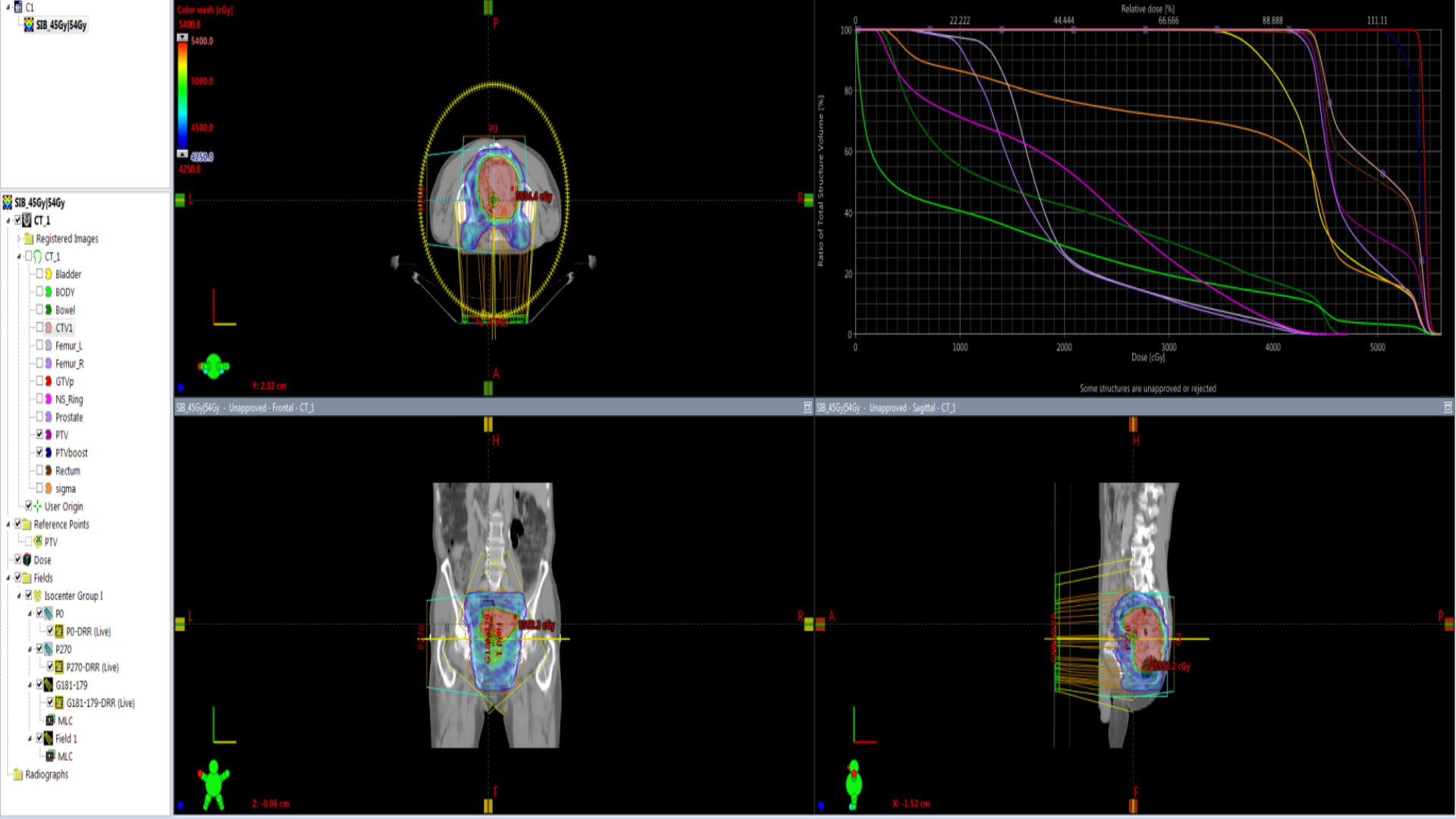

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☑	PTV	Unapproved	SIB_45Gy/54Gy	C1	2245.5	100.0	100.0	2652.0	5611.6	4797.3
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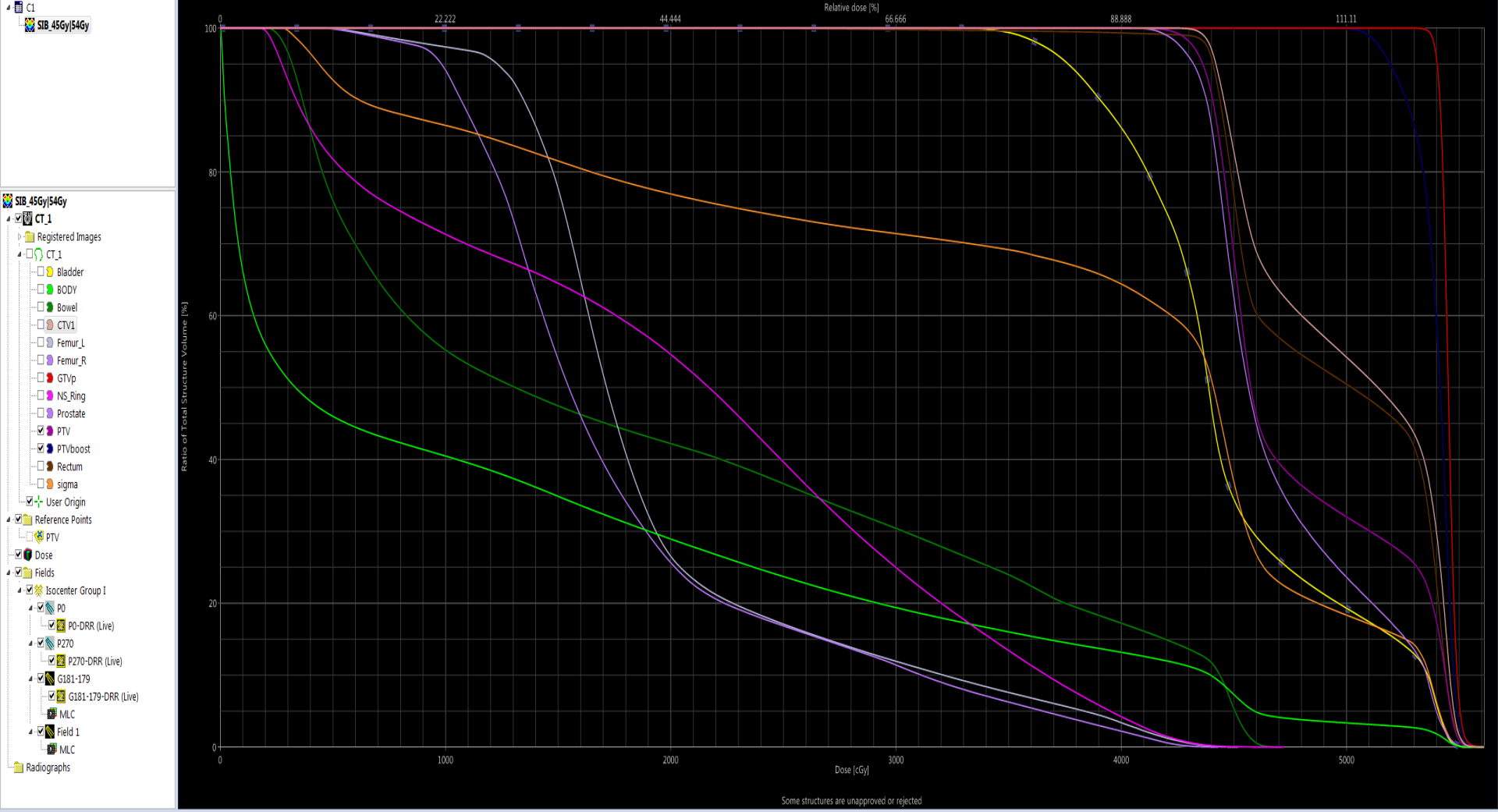

SIB_45Gy|54Gy
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  - Registered Images
  - CT_1
    - Bladder
    - BODY
    - Bowel
    - CTV1
    - Femur_L
    - Femur_R
    - GTVp
    - NS_Ring
    - Prostate
    - PTV
    - PTVboost
    - Rectum
    - sigma
    - User Origin
  - Reference Points
    - PTV
  - Dose
  - Fields
    - Isocenter Group I
      - P0
        - P0-DRR (Live)
      - P270
        - P270-DRR (Live)
      - G181-179
        - G181-179-DRR (Live)
        - MLC
      - Field 1
        - MLC
  - Radiographs

Dose | Reference Points | Dose Statistics

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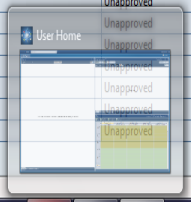

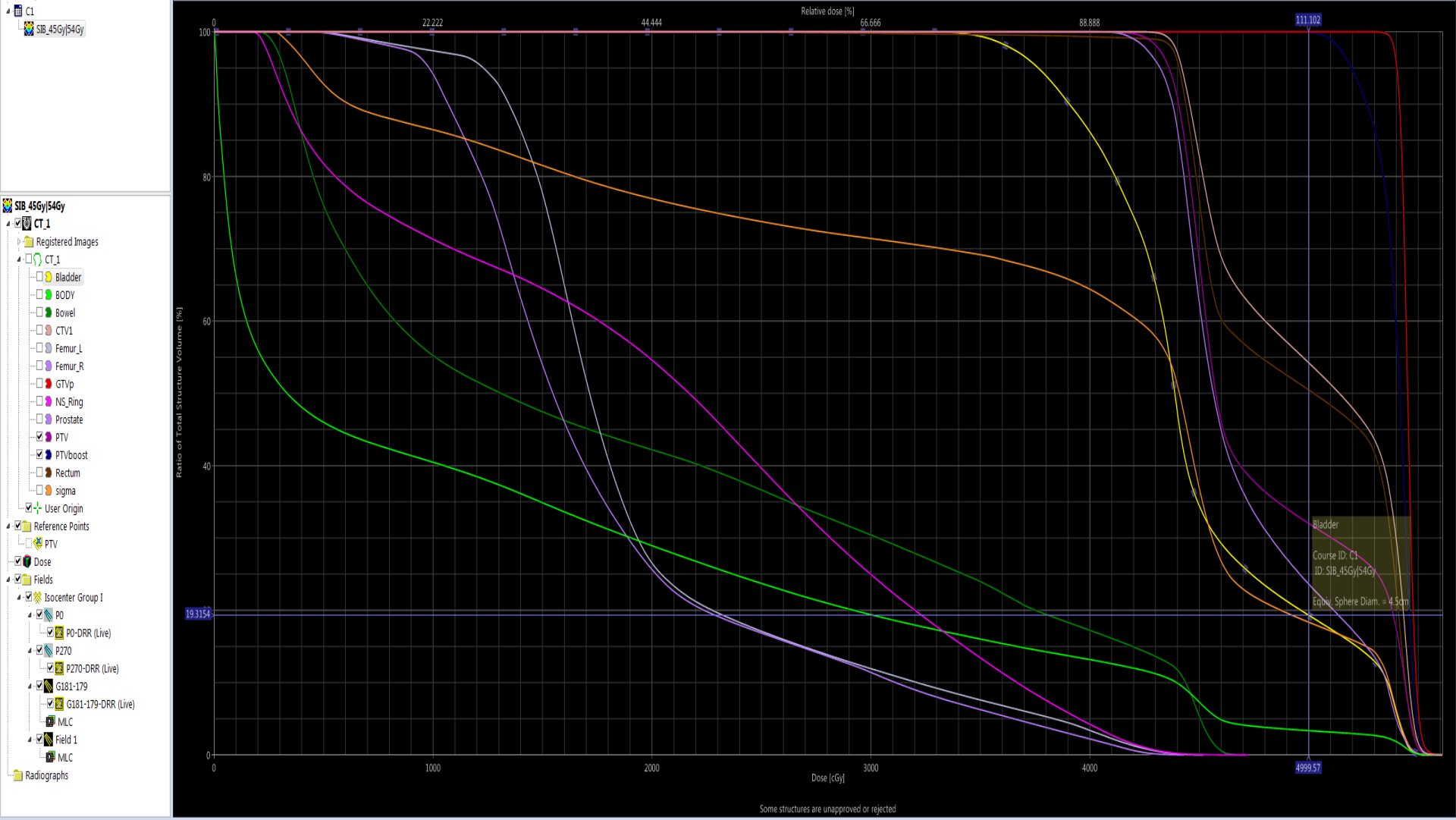

Dose | Reference Points | Dose Statistics

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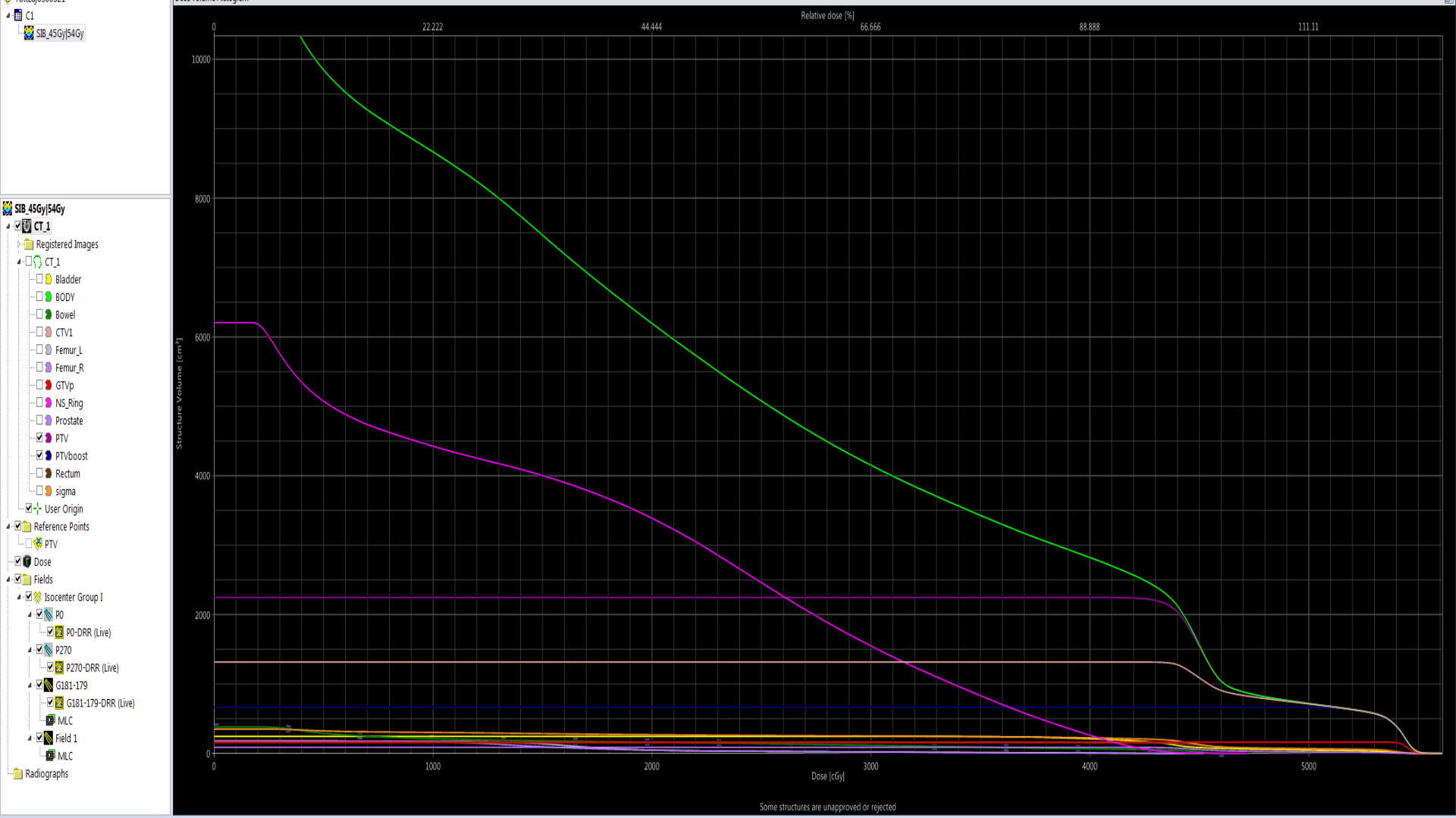

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Dose | Reference Points | Dose Statistics

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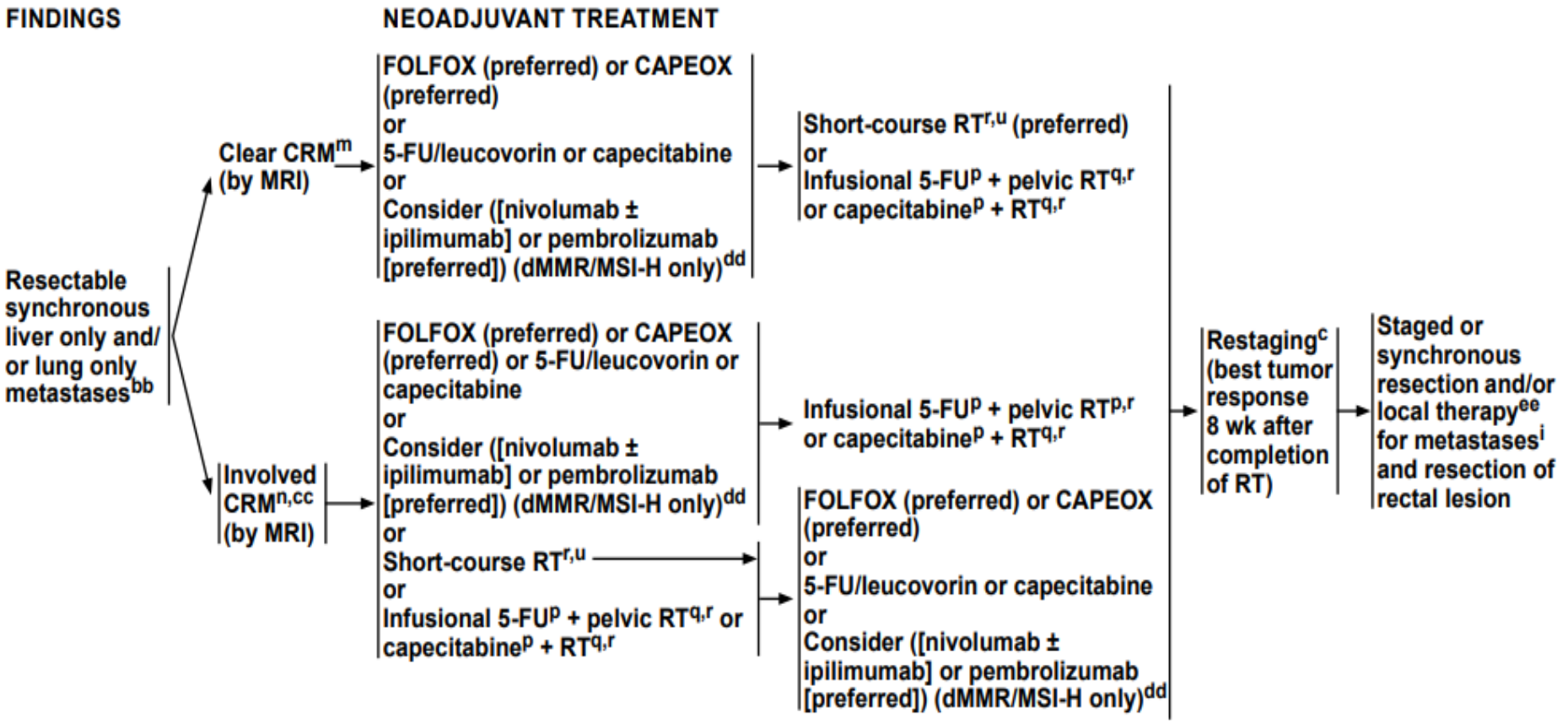
☐	sigma	Unapproved	SIB_45Gy|54Gy	C1	349.2	100.0	100.0	274.2	5565.1	3642.4

Dose escalation

- SIB

– 45 Gy to the mesorectum and lgl+ SIB to the tumor and 2 cm in all directions to a total dose of 52.5-57.5 Gy



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2022
Rectal Cancer

NCCN Guidelines Index
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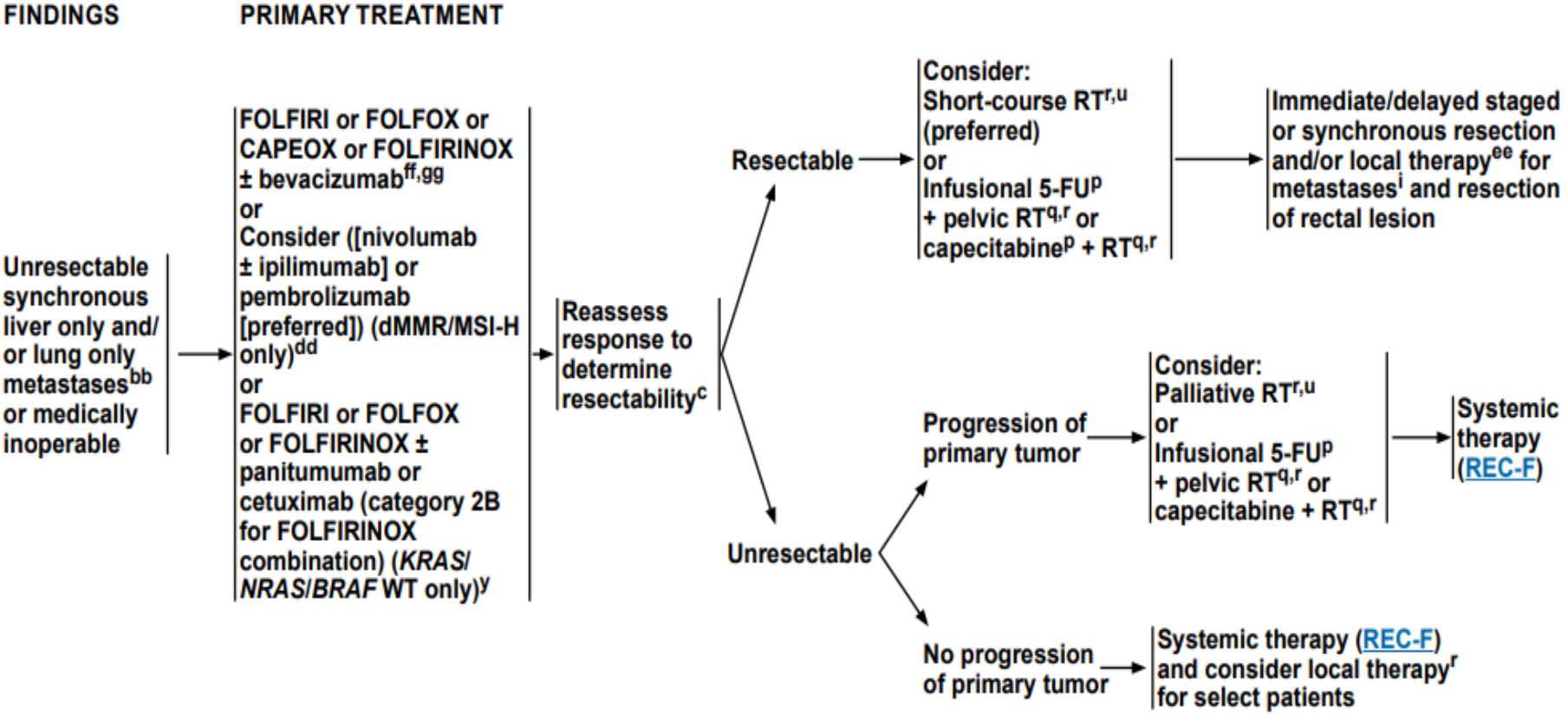
Discussion



Anal cancer radiotherapy

- EBRT or brachytherapy
- **Neoadjuvant to competitive EBRT and CHT**
- The original **"Nigro regimen"** of this therapy includes chemotherapy in the first and fifth weeks with continuous radiotherapy.
- D1-D5 for 5 weeks: 5-Fu 1000 mg/m2/day by continuous i.v. infusion D1-D4 and D29-D32 + Mitomycin 10 mg/m2 i.v. Dl and D29.

The lymphatic drainage of the anal canal ends in three levels of lymph nodes:

- **The lymph of the lower part of the anal canal**, including the skin of the perineum, is drained into the superficial inguinal lymph nodes. Anastomoses of lymphatic vessels enable the drainage of lymph from the lower part of the anal canal towards the femoral lymph and external iliac lymph nodes.
- **Lymphatic drainage of the anus** at the level of the dentate line ends with lymph nodes along the internal iliac artery, i.e. in internal pudendal, hypogastric and obturator lymph nodes.
- **The lymphatic network of the upper part of the anal canal** follows the drainage of the lymphatic vessels of the rectum, flowing into the perirectal and upper hemorrhoidal lymph nodes.

- Anal canal tumor metastases almost never develop in the liver
- The lower the tumor is localized from the rectum to the anal canal, the less frequent are the metastases in the liver and more often in the inguinal fossa, lungs and bodies of the spinal vertebrae.

Treatment of cancer of the anus

T1, well differentiated
Local surgical excision only: **T<2 cm, well differentiated, with superficial spread and negative excision margins. It is only recommended for patients who will have frequent follow-up. In a well-selected group, this therapy achieves local control >90%.** **It is not indicated if the sphincter or >40% of its circumference is affected (it would cause incontinence, so chemo + radiotherapy is recommended).** **Radiotherapy alone: total dose of 65 Gy with 45 Gy prophylactically to lymph nodes.**
T1-2, N0, postoperative resection margins close to the tumor or microscopically involved by the tumor
- **Consider implementing a shortened course of concurrent chemo RT: RT- 30 Gy + 1 cycle of chemotherapy: mitomycin + 5-FU.** - **If the resection margins are microscopically positive: RT - 45Gy (36 Gy+ 9 Gy boost to the primary tumor) + 2 cycles of chemotherapy: mytomycin + 5FU.** - **surgical treatment post-operative chemotherapy (5-FU/leucovorin - 1 cycle) - competitive chemotherapy (5-FU/LV - 2 cycles) + radiotherapy (45 Gy) -> chemotherapy (5-FU/LV - 2 cycles)**
Stage I-III with an intact sphincter
- **Competitive radiotherapy + chemotherapy (5-FU/mytomycin)**
Stage IV disease
- **Therapy for palliative purposes: surgery, radiotherapy or chemotherapy - individualized treatments.**
Tumors of the anal margin
- **Wide local surgical excision with resection margins >1 cm.** - **Chemoradiotherapy with irradiation of inguinal lymph nodes, and if the primary tumor was localized above the dentate line, irradiation of pelvic lymph nodes is also recommended (chemotherapy 5FU/mytomycin, RT 45-60Gy).** - **- If postoperatively T1N0 and well differentiated - monitoring - frequent observations.**

Treatment of cancer of the anus

- RT-CHT is the method of choice in the primary treatment of cancer of the anal canal larger than 2 cm and involves EBRT of the primary tumor and inguinal lymph nodes, with the simultaneous (concomitant) administration of chemotherapy, which contains 5-Fu and mitomycin C and/or cisplatin. Chemotherapy in combination with radiotherapy is prescribed during the first and fifth weeks of radiotherapy.
- Sometimes brachytherapy (intraluminal or interstitial) is applied along with EBRT.
- EBRT is combined with HT, where in the first phase, the locoregional radiation technique, a dose of 40 to 45 Gy is applied to the target volume in 20 to 25 fractions

Target volumes

- **GTV** includes the primary tumor and macroscopically enlarged lymph nodes, and based on the findings of endoscopy and imaging procedures (MR of the pelvis)
- **CTV 3060** includes GTV and all lymphatics in the basin of iliac (internal and external) lymph nodes, presacral and bilateral inguinal lymph nodes with the cranial border at the level of L5 - S1
- Further prescription of the dose depends on the stage of the disease and affected groups of lymph nodes, and radiation therapy is carried out using the shrinking field technique.
- PTV 3060
- Margin of 0.5 cm to 1 cm around CTV 3060 in all directions

PTV 4500

- It includes enlarged lymph nodes and elective lymph nodes in high-risk regions. Margin of 0.5 cm to 1 cm around CTV 4500 in all directions. Depending on the stage of the disease and the affected groups of lymph nodes, the therapeutic volumes are planned using the shrinking field technique and the prescription of a total dose of up to TD 50.4 Gy, i.e. up to TD 59.4 Gy

CTV 5040 (ie PTV 5940) Macroscopic residual disease after TD 45 Gy, i.e. tumors stage T3-T4, i.e. N1 nodal stage

- Using a local technique, a boost dose of 15 to 20 Gy is applied to the tumor.
- EBRT can also be performed in the pronation position, using a three-field technique - (direct posterior and two lateral beam fields) that include the tumor/tumor bed and regional lymph nodes.
- In this case, the inguinal lymph nodes are irradiated separately from the AP/PA beam fields, via direct fields, with electrons.
- RT with a local technique can also be performed in some patients using interstitial or endoluminal brachytherapy, while a boost dose to the inguinal lymph nodes can also be applied with electrons.

PRINCIPLES OF RADIATION THERAPY[1]

Treatment Information (continued)

Table 1: Dose Specification of Primary and Nodal Planning Target Volumes: RTOG-0529[4]

TNM Stage	Primary Tumor PTV Dose	Involved Nodal PTV Dose	Nodal PTV Dose
T1, N0	50.4 Gy (28 fxs at 1.8 Gy/fx)	N/A	42 Gy (28 fxs at 1.5 Gy/fx)
T2, N0	50.4 Gy (28 fxs at 1.8 Gy/fx)	N/A	42 Gy (28 fxs at 1.5 Gy/fx)
T3–4, N0	54 Gy (30 fxs at 1.8 Gy/fx)	N/A	45 Gy (30 fxs at 1.5 Gy/fx)
T any, N+ (≤3 cm)	54 Gy (30 fxs at 1.8 Gy/fx)	50.4 Gy (30 fxs at 1.68 Gy/fx)	50.4 Gy (30 fxs at 1.68 Gy/fx)
T any, N+ (>3 cm)	54 Gy (30 fxs at 1.8 Gy/fx)	54 Gy (30 fxs at 1.8 Gy/fx)	54 Gy (30 fxs at 1.8 Gy/fx)

PRINCIPLES OF RADIATION THERAPY[1]

Treatment Information (continued)

Table 2: DP-IMRT Dose Constraints for Normal Tissues[6]

Organ	Dose (Gy) at <5% Volume	Dose (Gy) at <35% Volume	Dose (Gy) at <50% Volume
Small bowel†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)
Femoral heads	44	40	30
Iliac crest	50	40	30
External genitalia	40	30	20
Bladder	50	40	35
Large bowel†	45 (<20 cc)	35 (<150 cc)	30 (<200 cc)

Organs are listed in order of decreasing priority.
† Dose constraints are based on absolute volume instead of % volume.

Benign conditions – indications for radiotherapy

- RT for non-malignant indications certainly has a place in modern medicine, and there is considerable evidence for the utility of low- to intermediate-dose RT for treating a range of specific indications.

- RT at these doses is relatively easy to administer, has few symptomatic side effects and often provides good long-term control and improved quality of life

- Consequently, although the doses required to treat benign disease are generally lower than those used to treat cancer, caution is advised when considering RT for these conditions in children and young adults.

Table 1. Benign diseases for which intermediate dose radiotherapy has utility

Benign disease	Pathology	Predominant age groups (years)	Approximate total dose (Gy)[a]	At-risk normal tissues[b]	Comments	Study
Ocular disease						
Pterygium	Fibrovascular proliferating tissue	Early 20s to old age	20–50	Lens, sclera, anterior brain structures	Surgery is preferred option; adjuvant RT can improve outcome	Ali et al[1]
Choroidal haemangioma	Proliferation of normal vasculature	30–50	20	Lens, anterior brain structures	Rarely used; would require discussion in specialist centre	Frau et al[2]
Age-related macular degeneration	Neovascularization	>65	20	Lens, anterior brain structures	No longer routinely used, but subject to ongoing research	Evans et al[3]
Reactive lymphoid hyperplasia/orbital pseudotumour	Idiopathic orbital inflammation	Median 40–50	20	Orbit, anterior brain structures	Steroids are first line treatment. RT effective if inadequate response to steroids	Mendenhall and Lessner[4]
Thyroid eye disease	Autoimmune	20–40	20	Orbit, anterior brain structures	Steroids are first line treatment. RT considered if impaired mobility/ diplopia	Bartalena et al[5]
Orthopaedic/musculoskeletal disease						
Heterotopic ossification of the hip	Extraskeletal new bone formation	50–80	7	Pelvic bones and muscles	Adjuvant post-surgery	Lo et al[6]
Plantar fasciitis	Inflammation and degeneration	40–60	3–6	Tissues of foot (skin, muscle)	RT indicated if failed conservative management for 6–12 months	Heyd et al[7] and Niewald et al[8]
Aneurysmal bone cyst	Benign osteolytic bone lesion	Children and young adults	30	Bone, other tissues depending on site	Rarely used; useful for cysts in anatomically difficult locations and for recurrence following surgery	Heyd and Seegenschmiedt[9]
Vertebral haemangiomas	Benign vascular proliferation	All ages	36–40	Bone, soft tissue, spinal cord	Rarely used; evidence suggests useful for control of pain relief	Taylor et al[10] and Heyd et al[11]
Keloid	Abnormal fibroblasts, reduced apoptosis, increased collagen and cytokines	10–30	5–12	Depends on site of keloid	Adjuvant post-surgery	Ragoowansi et al[12]
Dupuytren's disease	Benign fibroblastic proliferation of the palmar fascia	50–70	30	Tissues of hand (skin, muscle)	In early progressive disease, prevents progression and need for surgery	Seegenschmiedt et al[13]
Ledderhose disease (plantar fibromatosis)	Benign fibroblastic proliferation of the plantar fascia	20–40	30	Tissues of foot	RT reduces pain and improves function	Seegenschmiedt et al[14]
Pigmented nodular synovitis	Proliferation of synovial membranes	20–40	35–40	Depends on site	May also be suitable for instillation of radionuclide	O'Sullivan et al[15]

(Continued)

McKeown SR, et al. Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. Br J Radiol. 2015;88(1056):20150405.

Benign disease	Pathology	Predominant age groups (years)	Approximate total dose (Gy)[a]	At-risk normal tissues[b]	Comments	Study
Peyronie's disease	Wound healing disorder of tunica albuginea of the penis	30–70	9–30	Lower pelvis	Currently rarely used; can be useful for pain relief in intractable case	Taylor et al[10] and Niewald et al[16]
Chronic eczema	Pruritic chronic inflammatory skin disease	All	4–5	Various; depends on site of lesions	Only very rarely recommended for intractable condition in adults	Taylor et al[10] and Sumila et al[17]
Lentigo maligna	Atypical melanocyte proliferation	>60	45–50	Various; depends on site of lesion	Surgery preferred option; when contraindicated RT can provide good outcome	Tsang et al[18]
Psoriasis	Autoimmune T-cell-mediated disorder	All ages from young adult	6–8	Various; depends on site of lesions	Rarely used; some evidence for utility in recalcitrant disease particularly involving nail beds	De Vries et al[19]
Trigeminal neuralgia (SRS)	Uncertain	Peak 60–70 (>90% over age 40 years)	Max. point dose 80–90	Brainstem	Very small treatment field, usually carried out with Gamma Knife	Taylor et al[10]
Meningioma	Benign tumour	Wide age range; incidence increases with age	50–55 (or 14 Gy for SRS)	Various; depends on site of lesion	SRS tends to be for smaller lesions, particularly in base of skull	Taylor et al[10]
Arteriovenous malformation in brain (SRS)	Vascular anomaly	10–40	Ideally >20 for SRS	Various; depends on site of lesion	Can occur throughout brain and vary in size. Treatment more effective and safer with smaller lesions	Taylor et al[10]
Acoustic schwannoma	Benign tumour	Majority over 40	12 (SRS) 45–56	Brainstem, facial nerve, cochlea	Other options include surgery or surveillance depending on size, hearing and rate of growth	Combs et al[20]
Head and neck						
Sialorrhoea	Excessive drooling often because of severe neurological disorder	Elderly	10–20	Oral cavity/oropharynx, parotid	RT is effective at reducing saliva flow. RT can be used if anti-cholinergics and/or botulinum toxin ineffective	Assouline et al[21]
Salivary pleomorphic adenoma	Benign tumour of the salivary gland	30–60	50	Adjacent head and neck structures, *e.g.* oropharynx	Surgery with clear margins offers high local control. Adjuvant RT improves local control in high-risk patients (with positive margins/recurrent disease)	Mendenhall et al[22]
Glomus tumour	Paraganglioma, benign vascular tumour	Median 50	45	Adjacent head and neck structures, *e.g.* nasopharynx, oropharynx	Surgery or RT offer high rates of local control	Mendenhall et al[23]

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Benign disease	Pathology	Predominant age groups (years)	Approximate total dose (Gy)[a]	At-risk normal tissues[b]	Comments	Study
Juvenile nasopharyngeal angiofibroma	Rare benign vascular tumour	Median 14	35–45	Adjacent head and neck structures, *e.g.* nasopharynx, oropharynx	Surgery is treatment of choice. RT effective if unresectable. Surgery or RT considered for recurrence	Chakraborty et al[24]
Miscellaneous						
Hidradenitis suppurativa	Chronic inflammatory/ infective	Young adult	10	Depends on site	Only to be considered in refractory cases	Fronlich et al[25]
Gynaecomastia	Breast tissue hyperplasia	>60	10	Breast tissue, skin, lungs	Occurs in males on hormonal therapy for prostate cancer	Viani et al[26]

RT, radiotherapy; SRS, stereotactic radiosurgery.
This provides a summary of benign diseases for which intermediate dose RT has utility. Benign diseases that are no longer treated with RT are not included but are discussed elsewhere in the text.
[a]The total dose is only indicative and can vary considerably between centres and in different countries.
[b]It is assumed that skin is normally at risk; any other "at-risk" normal tissues are indicated, although these can vary in some situations. For detailed discussion of RT regimens, risks of RT and comparisons with other treatment options, see Taylor et al.[10]

McKeown SR, et al. Radiotherapy for benign disease; assessing the risk of radiation-induced cancer following exposure to intermediate dose radiation. Br J Radiol. 2015;88(1056):20150405.

THANK YOU FOR YOUR ATTENTION!