SBRT for Cholangiocarcinoma

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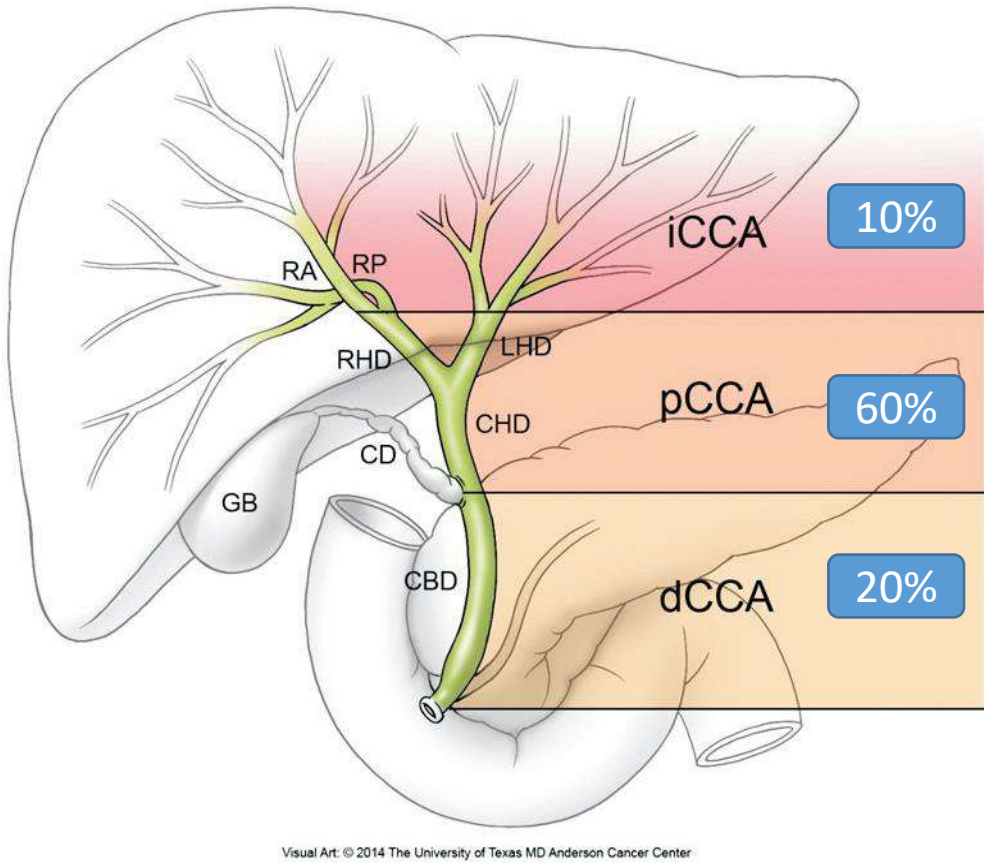
Classification - CCA

- Cancer of the epithelial cells of bile ducts, occurs anywhere along the biliary tree between the ducts in the liver and the papilla of Vater
- Each subtype showing different epidemiological, molecular and therapeutic characteristics
- The 5-year survival rate of ECCA is 17%, while the 5-year survival rate of ICCA is only 5%



Cholangiocarcinoma

- Cholangiocarcinoma (CCA) is the second most commonly occurring primary hepatobiliary cancer, accounting for 10%-20% of all primary hepatic carcinomas
- The 5-year OAS - 2% to 15% - ICC

  2%-30% ECC
- The majority 60% - 70% are diagnosed at a late stage and are treatedwith palliative therapy, particularly chemotherapy.
- Occurrence of CCA is rare but the global incidence rate particularly ICC, has steadily increased over the past 15 years

Diagnosis

- Diagnostic criteria include:

  (i) positive or strongly suspicious intraluminal brush or biopsy;

  (ii) a radiographic malignant appearing stricture plus either CA 19-9 of >100 U/ml in the absence of acute bacterial cholangitis or polysomy on FISH,

  (iii) a well-defined mass on cross-sectional imaging.

Of note, there is no requirement for pathologic confirmation of a tissue diagnosis.

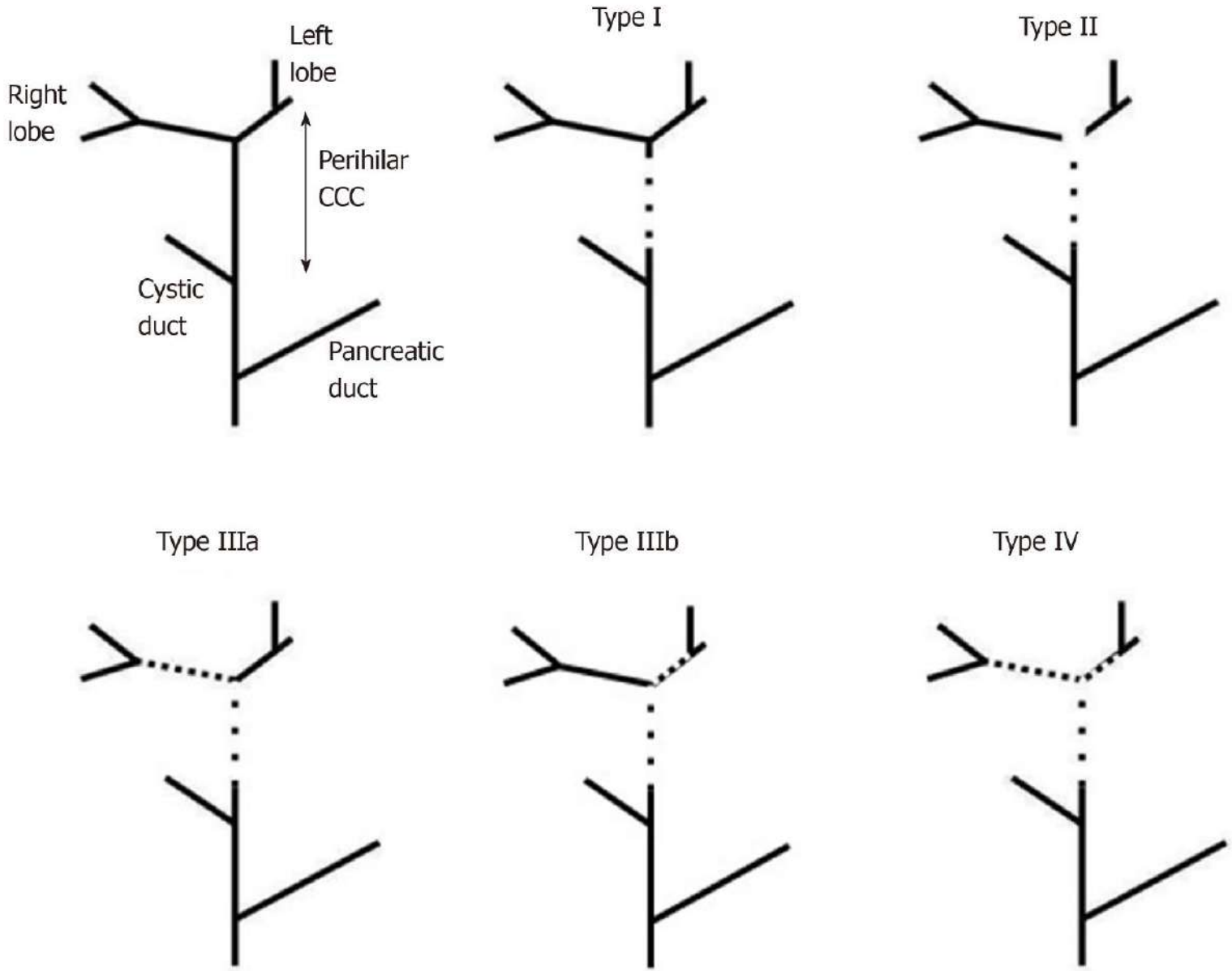


Figure 1 Schematic representation of extrahepatic and intrahepatic bile ducts (until second order) showing Bismuth-Corlette classification. CCC: Cholangiocarncioma.

Treatment

- Radical resection is the only cure for primary CCA
- Median overall survival times of 28 months (range 9–53 months)

Resection rates

PHCCC - 50%

IHCCC - 60%

- For patients with inoperable tumors survival rates 7–12 months – Pall CT of gem-Cis
- Other local tumor-directed therapies
- - EBRT
  -Transarterial chemoembolization (TACE),
  - radiofrequency ablation (RFA),
  - selective internal radiotherapy (SIRT)

RADIOTHER APY for CCA

- Adjuvant
- Neoadjuvant
- Palliative for unresectable tumors

Adjuvant RADIOTHERAPY FOR resectable CCA

- Horgan et al. (meta-analysis 20 studies) - adjuvant chemotherapy or adjuvant chemoradiotherapy had a better survival benefit than surgery alone for patients with positive lymph nodes and R1 resection (OR, 0.49; $P \leq 0.004$ and OR, 0.36; $P \leq 0.002$)

- Existing guidelines and consensus recommend – PORT for positive margins or regional lymph nodes

- SWOG S0809 is the only prospective study of adjuvant radiotherapy after CCA

Neoadjuvant Radiotherapy for CCA

- Recommended for patients with high recurrence risks.
- For tumor length ≤ 6 cm, conventional radiotherapy or (SBRT 40 Gy/5F)
- For tumors larger than >6 cm in length, TACE is suggested to shrink tumors first.
- Neoadjuvant chemoradiotherapy combined with liver transplantation or resection is a new treatment option for advanced ICCA.

Role of liver transplantation

- Although liver transplantation alone was found to be a dismal failure in patients with hilar CC
- Promising option in patients with unresectable lesions when it is used in combination with neoadjuvant chemoradiotherapy.
- Excellent results, with 5-year recurrence-free survival rates of 65–70% in patients with unresectable tumours

Original Article

J Gastrointest Oncol 2017;8(1):180-18

High dose chemoradiation for unresectable hilar cholangiocarcinomas using intensity modulated external beam radiotherapy: a single tertiary care centre experience

Reena Engineer[1], Shaesta Mehta[2], Nikhil Kalyani[1], Suresh Chaudhari[3], Tejas Dharia[4], Nitin Shetty[4]
Supriya Chopra[1], Mahesh Goel[5], Suyash Kulkarni[4], Shyam Kishore Shrivastava[1]

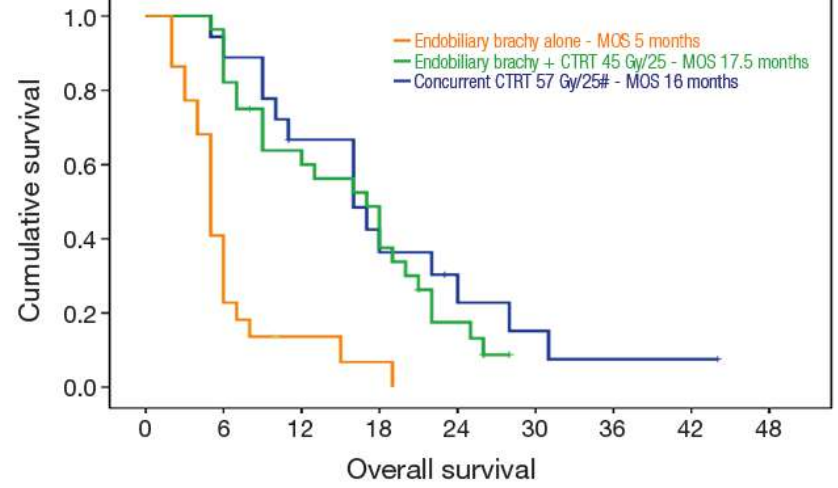


Figure 1 Kaplan Meier curves for type of radiation and ov survival. MOS, median overall survival.

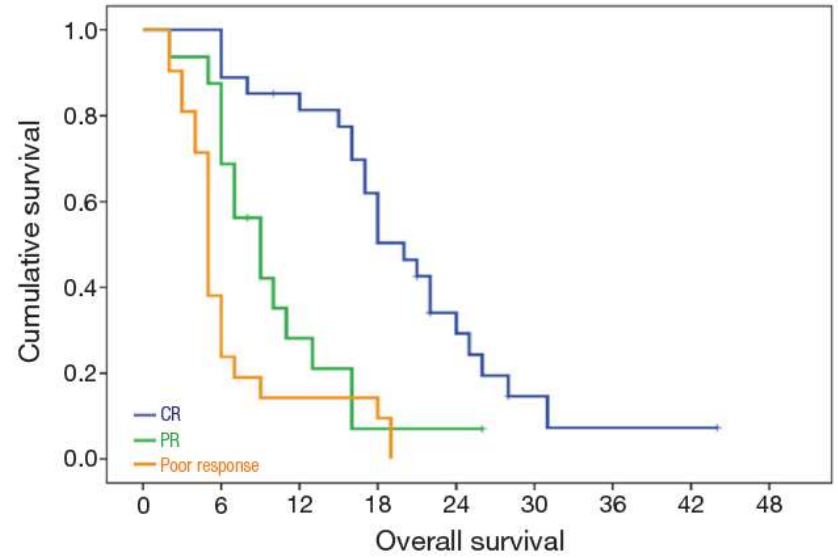


Figure 2 Response to radiation and survival (P=0.001).

SBRT IN CHOLANGIOCARCINOMA

SBRT in intrahepatic cholangioca

AUTHOR	INSTITUTE	N	TREATMENT TYPE	TUMOR VOLUME	RT DOSE MEDIAN (RANGE)	1 YR OS	1 YR LC	TOXICITIES>/= GRADE3
Barney et al 2012	Mayo Clinic, USA , retrospective	10	SBRT	16–412.4 mL	6 3 Gy /3 fr	73%	100%	20% (1 grade 5 liver failure,1 grade 3 biliary stenosis)
Dewas et al.2012	Lille, France , retrospective	6	SBRT	0.5–11.2 cm	39–45 Gy /3-4 fr	100%	100%	NS
Goyal et al.2010	Case WesternReserve University, USA, retrospective	3	SBRT	80–818 mL	24–45 Gy / 1–3 fr	0 %	67%	0%

SBRT in intrahepatic cholangioca

AUTHOR	INSTITUTE	N	TREATMENT TYPE	TUMOR VOLUME	RT DOSE MEDIAN (RANGE)	1 YR OS	1 YR LC	TOXICITIES>/= GRADE3
Tse et al.2008	PrincessMargaret Hospital,Canada, phase I	10	SBRT	10–465 mL	32.5 (28.2–48)Gy /6fractions	58%	65%	20%
Goodman et al.2010	Stanford University,USA phaseI	5	SBRT	<5 cm	18-30Gy single fraction	71%	23% 1-year local failurec	none
Ibarra et al.2012	Multi-institutional pooled analysis	11	SBRT	30.6–818.5 mL	30 (22–50) Gy /1-10 fractions	45%	50%	7% RILD only

Radiotherapy and Oncology 132 (2019) 42–47

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journal homepage: www.thegreenjournal.com

Original Article

Stereotactic body radiotherapy dose and its impact on local control and overall survival of patients for locally advanced intrahepatic and extrahepatic cholangiocarcinoma

Thomas B. Brunner [a,l,*], Oliver Blanck [b], Victor Lewitzki [c], Nasrin Abbasi-Senger [d], Felix Momm [e], Oliver Riesterer [f], Marciana Nona Duma [g,h], Stefan Wachter [i], Wolfgang Baus [j], Sabine Gerum [k], Matthias Guckenberger [f], Eleni Gkika [a]

82 lesions in 64 patients with cholangiocarcinoma were treated with SBRT at nine German and
Swiss centers between July 1999 and September 2016.

The median BED ratio of the maximal dose in the PTV divided by the prescribed dose was 1.4 (95% CI 1.03–2.29; range 1.0–2.40). Median overall survival time of all 64 patients was 15 months (95% CI – months) from start of SBRT. The actuarial survival rate was 61% (57–65%) and 34% (32–37%) at one, and two years, respectively from the first day of radiotherapy (Fig. 1A). Median overall survival from diagnosis was 27 months (95% CI 24.9–28.5 months). The actuarial survival rate was 81% (77–85%) and 55% (51–59%) and 40% (37–43%) at one, two, and three years, respectively from diagnosis. In a total of 82 cholangiocarcinoma lesions treated with SBRT, 14 local relapses were observed and up to 37 months after SBRT corresponding to a total rate of 18%. The local control rates of 82 lesions after one, two, and three years were 89% (% CI 86–92%), 73% (68–77%), and 73% (67–79%), respectively

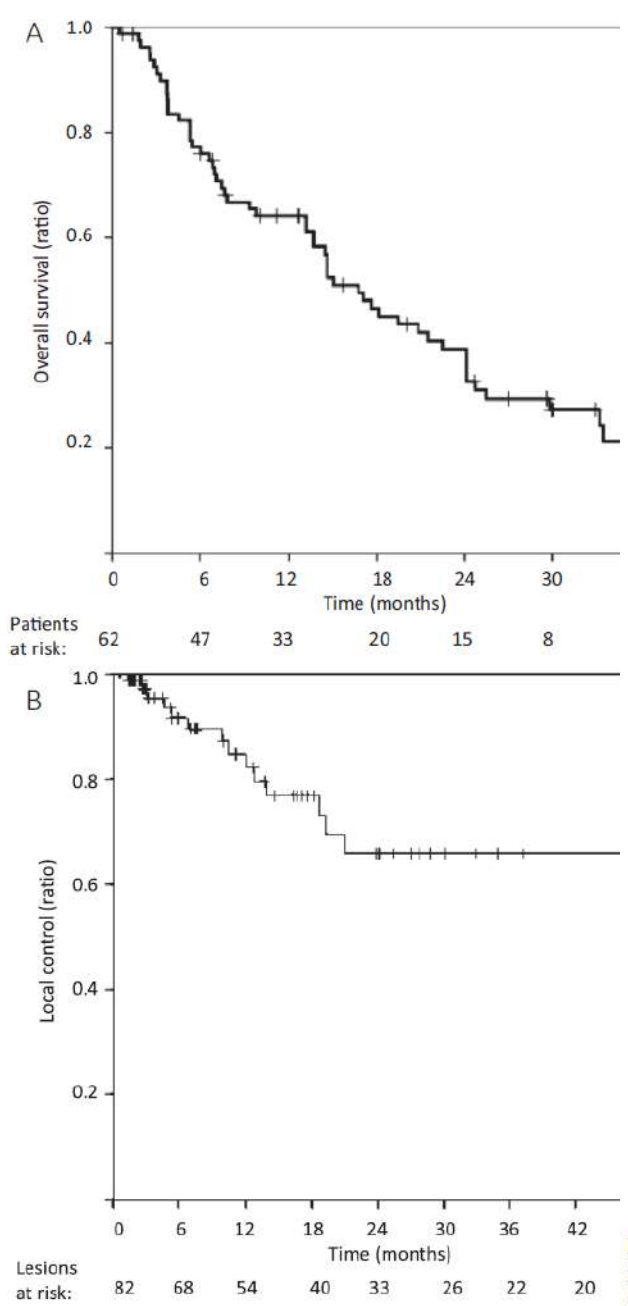

Fig. 1. Kaplan–Meier estimate of (A) OS in 64 patients with 82 lesions from t day of radiotherapy with a median OS of 16.8 months. (B) Effect of radiation local control (LC) and overall survival (OS) from the time of stereotacti radiotherapy. Kaplan–Meier estimate of LC in 82 lesions.

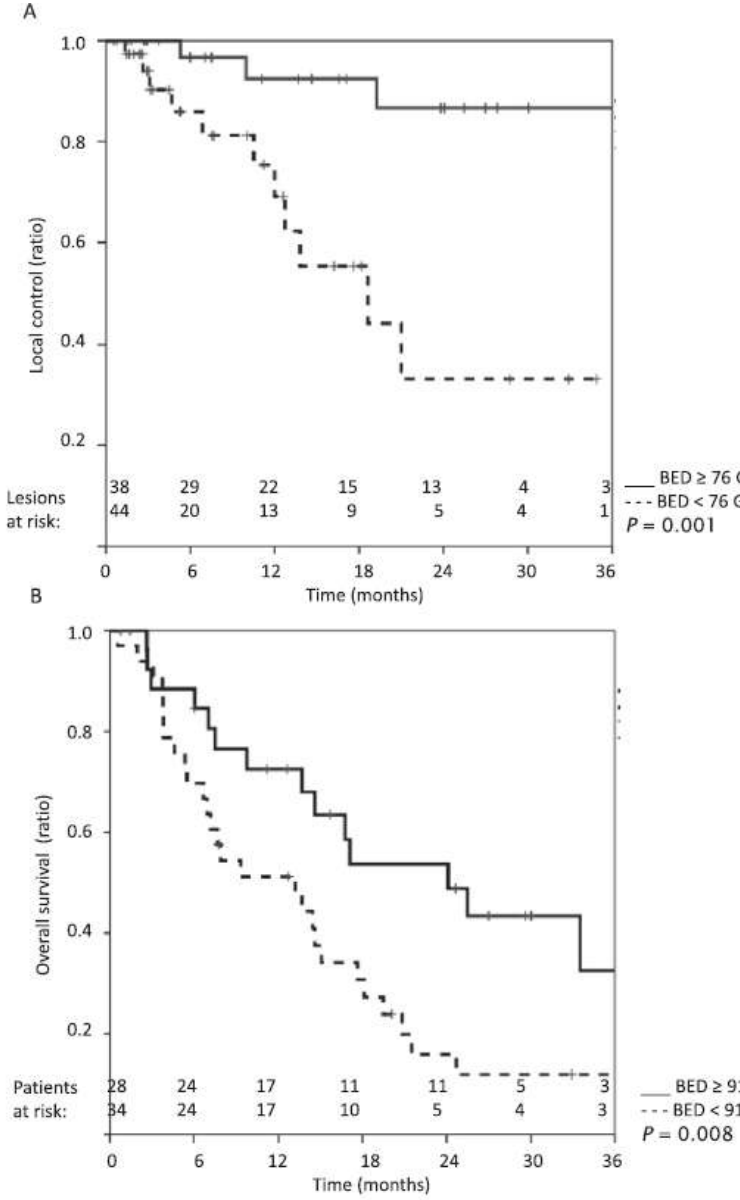

Fig. 2. (A) Effect of radiation dose on local control (LC) and (B) overall surviv from the time of stereotactic body radiotherapy. Kaplan–Meier estimate of (82 lesions according to biologic equivalent dose (BED) of the D_{mean} less than or 76 Gy or more illustrate the superiority of the higher dose. (B) Kaplan estimate of OS in 64 patients with 82 lesions according to biologic equivale (BED) of the D_{max} less than 91 Gy or 91 Gy or more illustrate the superiority higher dose.

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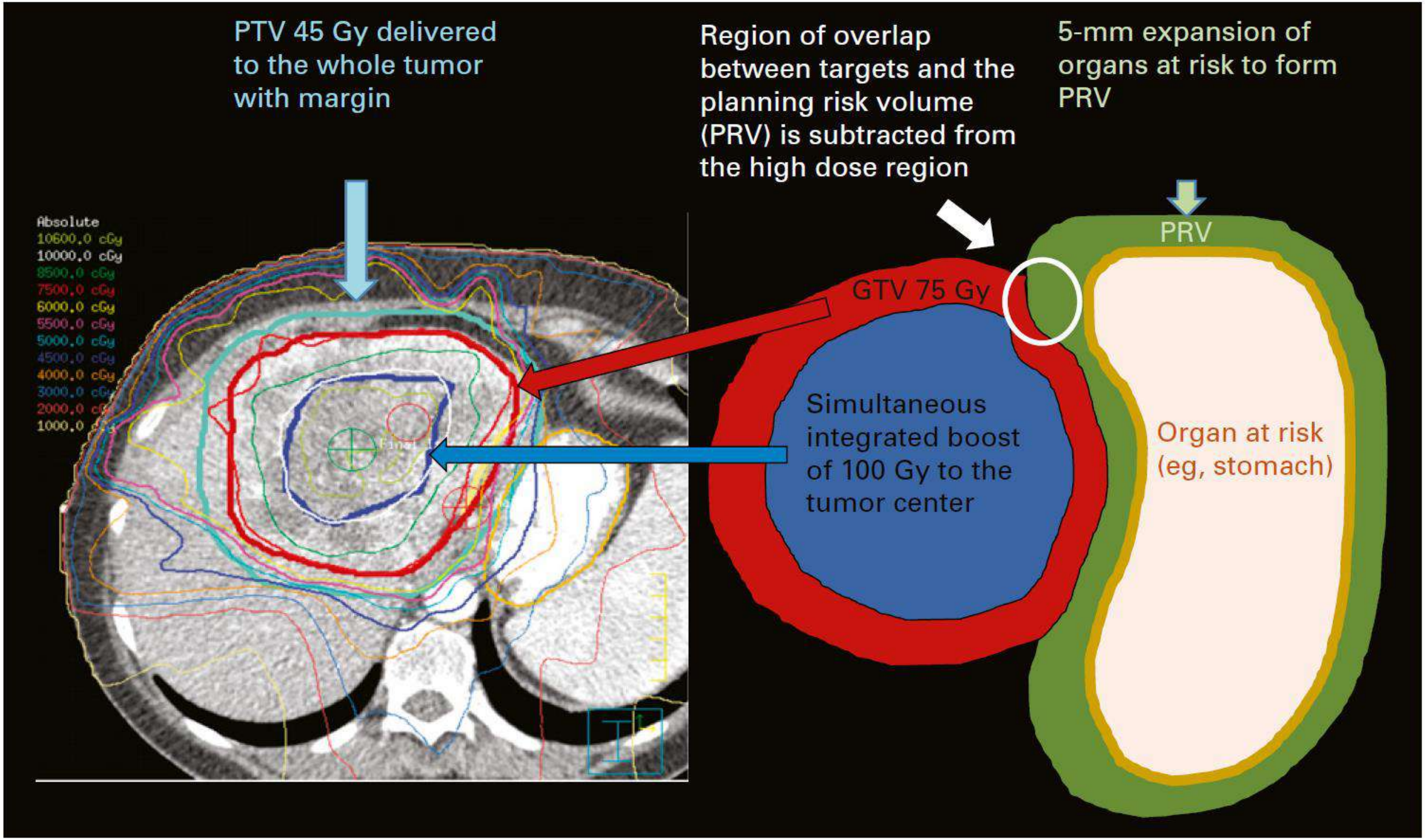
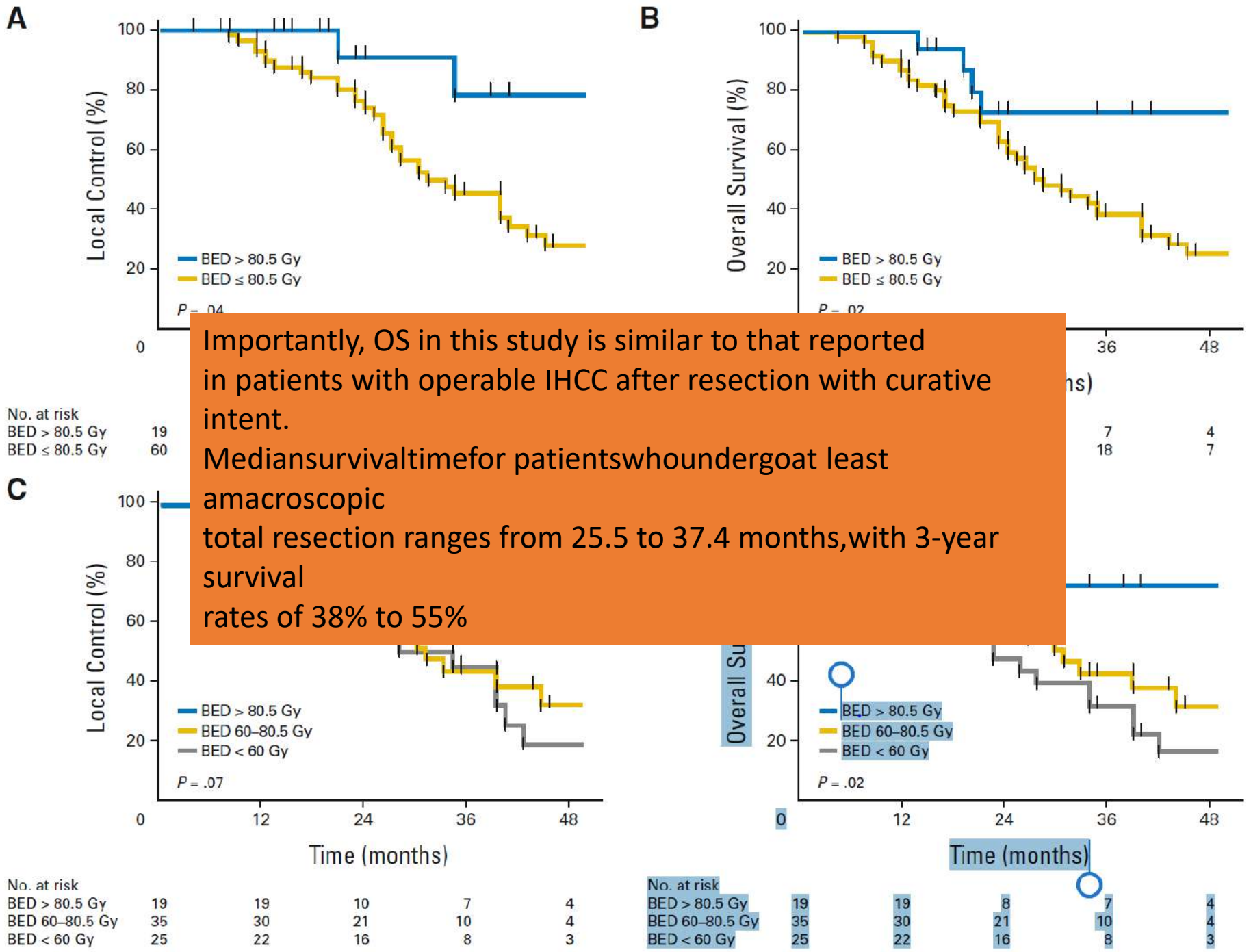
JOURNAL OF CLINICAL ONCOLOGY

Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis

Randa Tao, Sunil Krishnan, Priya R. Bhosale, Milind M. Javle, Thomas A. Aloia, Rachna T. Shroff, Ahmed O. Kaseb, Andrew J. Bishop, Cameron W. Swanick, Eugene J. Koay, Howard D. Thames, Theodore S. Hong, Prajnan Das, and Christopher H. Crane

Common fractionation regimens	
50.4 Gy in 28 fx	19 (24)
58.05 Gy in 15 fx	14 (18)
60 Gy in 30 fx	4 (5)
67.5 Gy in 15 fx	7 (9)
75 Gy in 25 fx	5 (6)


PTV 45 Gy delivered to the whole tumor with margin
Region of overlap between targets and the planning risk volume (PRV) is subtracted from the high dose region
5-mm expansion of organs at risk to form PRV
Absolute
10600.0 cGy
10000.0 cGy
9500.0 cGy
7500.0 cGy
6000.0 cGy
5500.0 cGy
5000.0 cGy
4500.0 cGy
4000.0 cGy
3000.0 cGy
2000.0 cGy
1000.0
GTV 75 Gy
Simultaneous integrated boost of 100 Gy to the tumor center
PRV
Organ at risk (eg, stomach)



Importantly, OS in this study is similar to that reported in patients with operable IHCC after resection with curative intent.

Mediansurvivaltimefor patientswhoundergoat least amacroscopic

total resection ranges from 25.5 to 37.4 months,with 3-year survival

rates of 38% to 55%

Strahlenther Onkol
https://doi.org/10.1007/s00066-018-1367-2

ORIGINAL ARTICLE

Efficacy of stereotactic body radiotherapy for unresectable or recurrent cholangiocarcinoma: a meta-analysis and systematic review

Jeongshim Lee[1,2] · Won Sup Yoon[3] · Woong Sub Koom[1] · Chai Hong Rim[3]

Received: 5 April 2018 / Accepted: 28 August 2018

Eleven studies (226 patients) were included.
Median SBRT dose was 45 (range 30–55) Gy in 3–5 fractions.

The pooled 1-year LC rate - 81.8% - (EQD2) ≥71.3Gy_2
- 74.7% EQD2 <71.3Gy_2.
The median OS was 13.6 (range 10–35.5) months.

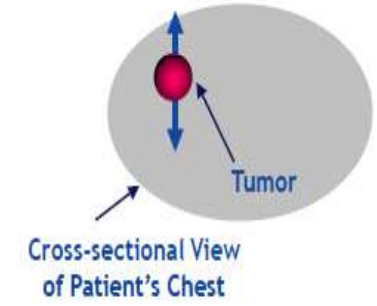
Pooled 1-year OS rate was 53.8%
Pooled 1-year LC rate was 78.6%
Most common toxicity was duodenal ulcer and gastric ulcer
Grade ≥3 of less than 10% and the late incidence of 10–20%.

Challenges of RT for liver tumor

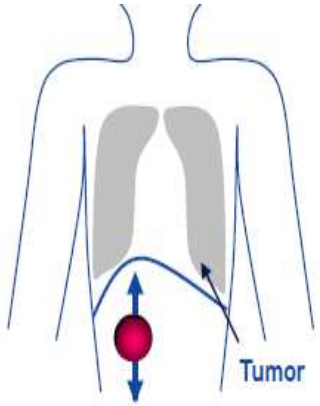
Liver is moving organ

↓

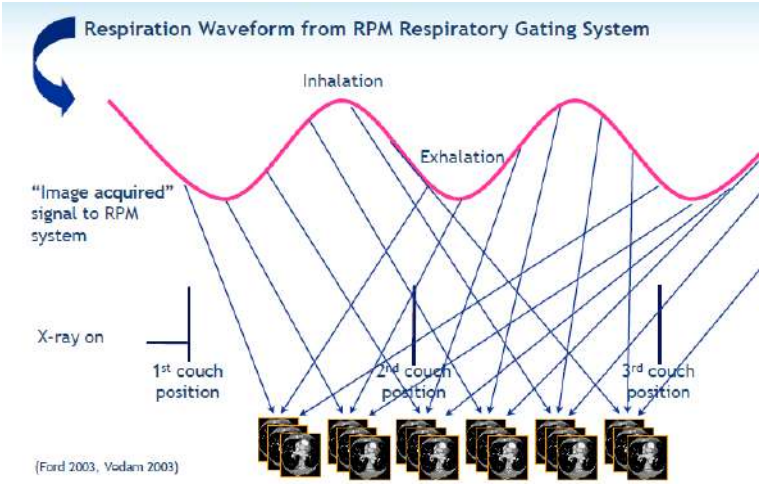
Liver tumor is moving target



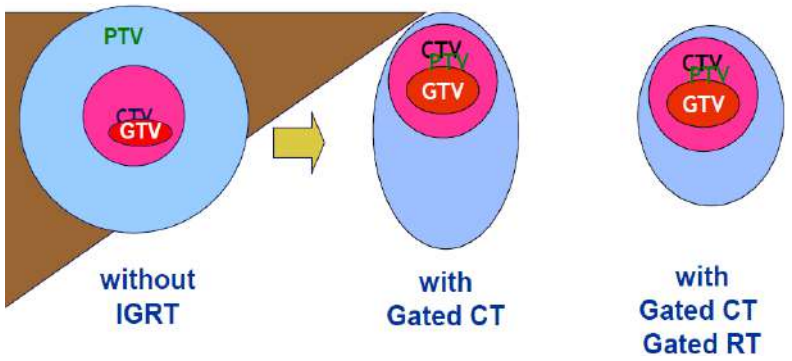
motion Anterior / Posterior



motion Superior / Inferior

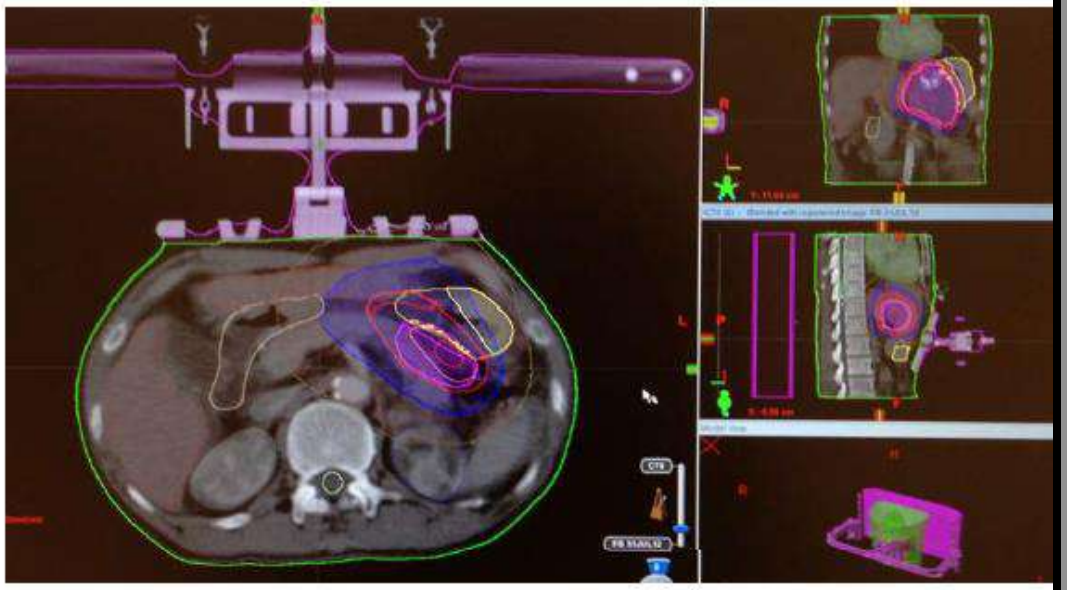


4D-RT = IGRT (Image-guide radiotherapy)



Stereotactic Ablative Radiation: Process

Stereotactic Coordinates
Very High Precision



Stringent Target Delineation, Precision in Treatment execution using Multiple Imaging Modalities

SBRT replaces Surgery for Medically Inoperable NSCLC

RT doses

- Conventional-dose (45–50.4 Gy upto 60Gy) + concurrent chemotherapy, especially when extensive lymph node metastasis is present and the radiotherapy target area is large.
- Patients with localized CCA should be treated with SBRT.
- SBRT -irradiate only the primary tumor and metastatic lymph nodes,
- Not to include high-risk lymph node drainage areas.
- SBRT dose 30–50 Gy/3–5F. Depends on the distance between the target area and organs at risk and the number of organs at risk

TARGET AREA DETERMINATION

- The clinical target volume (CTV) - CT or MRI visible tumors.
- Comparing CT, MR, and PET/MR for CCA target delineation

Compared with CT or MR, targeting CCA based on 18F-FDG PET/MR enables more accurate detection of positive lymph nodes, reducing the risk of missing lymph nodes, and thus accurately defining the GTV (Delaby G et al)

Target expansion

- In 2017, Socha et al. further defined the lymph node region of CTV in radiotherapy planning by comparing the postoperative recurrence of the existing research data.
- It is necessary to determine the radiotherapy range of high-risk lymph nodes according to the location of the primary tumor.
- 2017,Marinelli et al. - correlation between the location of primary biliary tract tumor and lymph node involvement rate.
- ICCA – the drainage area of high-risk lymph nodes should vary according to the location of primary focus,
- ECCA - the target area should include primary tumor bed and regional lymph nodes,

ONKOLOGIE

Original Article · Originalarbeit

Onkologie 2013;36:484–490
DOI: 10.1159/000354630

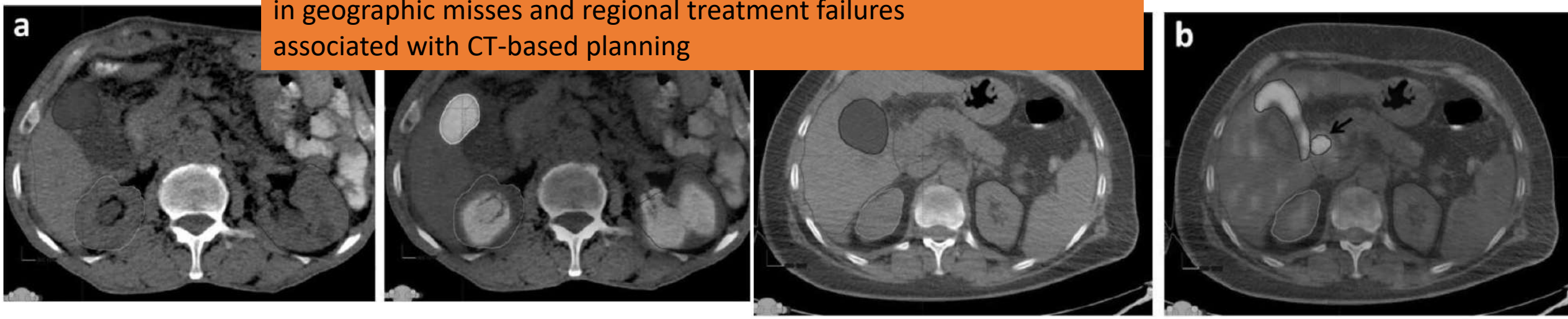
Published online: August 19, 2013

Comparison of Computed Tomography- and Positron Emission Tomography-Based Radiotherapy Planning in Cholangiocarcinoma

Cem Onal[a] Savas Topuk[a] Ali F. Yapar[b] Melek Yavuz[c] Erkan Topkan[a] Aydin Yavuz[c]

[a]Department of Radiation Oncology, [b]Department of Nuclear Medicine, Baskent University Medical Faculty, Adana Medical and Research Center, Kisla Campus, Adana, [c]Department of Radiation Oncology, Akdeniz University Medical Faculty, Antalya, Turkey

The potential benefit of PET/CT is the reduction in geographic misses and regional treatment failures associated with CT-based planning



Primary – Target region

- ICCA usually presents on CT as an unencapsulated homogeneous mass with irregular margins, low density, and irregular peripheral enhancement
- In 2002, Ebata et al. found that 80 of 253 cases had a microscopically positive margin with a median diffusion distance of 10 mm
- 2009 study of Bi et al,- pathological evaluation was approximately 0.4–8.0 mm larger than that in imaging
- Radiotherapy target area of biliary malignancy should include any tumor area seen in imaging; CTV should be expanded 10 mm based on GTV, the
- postoperative tumor bed should be included, and anastomosis should be included when the postoperative resection margin is positive.
- While considering the respiratory mobility and positioning error, PTV should be expanded 5 mm and up and down 7 mm based on CTV
- SBRT, it is recommended to irradiate only the primary tumor and metastatic lymph nodes , and not to include the high-risk lymph node drainage areas

Nodal target regions

- ICCA, highris \k lymph node drainage area should include the hilar lymph
- node, hepatoduodenal lymph node, celiac trunk lymph node, posterior pancreatic head lymph node, mesenteric lymph node, and para-aortic lymph node drainage area.
- If the primary focal point of ICCA is in the left hepatic lobe, the high-risk lymph node drainage area should include the lesser curvature of the stomachand left gastric lymph node drainage area.
- For pCCA, it should include the hepatoduodenal lymph nodes, hilar lymph nodes, celiac trunk, epigastric para-aortic lymph nodes and lymph nodes behind the head of the pancreas. While for dCCA, it should include hilar lymph nodes, hepatoduodenal lymph nodes, retro pancreatic lymph nodes, mesenteric lymph nodes, and the abdominal aortic drainage area. For the celiac trunk lymph nodes, their inclusion should be considered based on theimaging evaluation results, considering their low recurrence rate

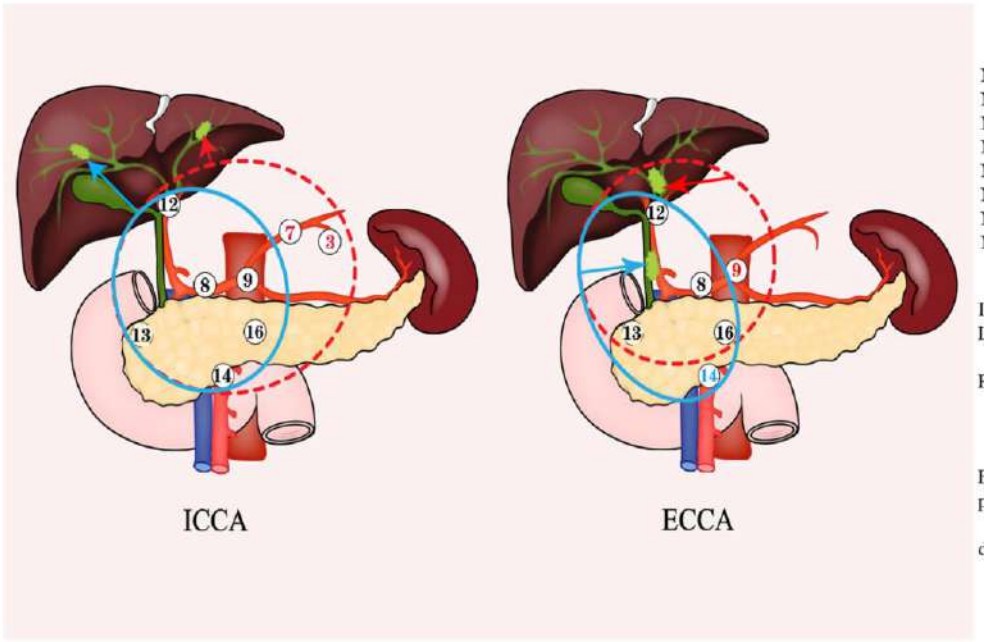


FIGURE 2 | Lymph node delineation in cholangiocarcinoma. The left figure shows the range of LNS with high risk in ICCA, t
range of LNS for left ICCA, and the blue line represents corresponding LNS for right ICCA; The right figure represents the co
for ECCA, the red dotted line represents the corresponding LNS area for pCCA, and the blue line represents the correspond
ECCA, extrahepatic cholangiocarcinoma; ICCA, intrahepatic cholangiocarcinoma; pCCA, perihilar cholangiocarcinoma; dCCA
node stations.

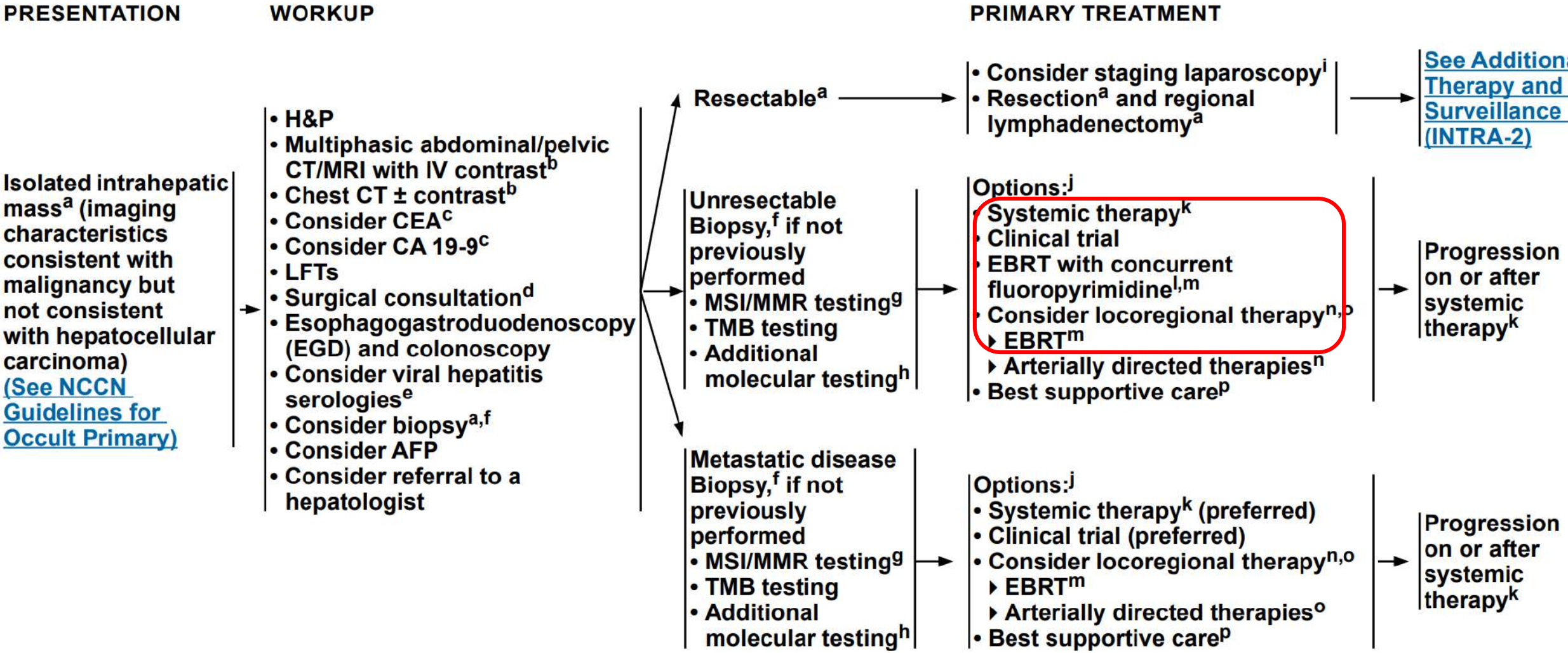
Targeted Therapy and Immunotherapy Combined With Radiotherapy

- New drug options are available for advanced CCA, such as the combination of dabrafenib and trametinib has produced promising results for BRAFV600E-mutated CCA, and
- isocitrate dehydrogenase (IDH1) inhibitor has also revealed successful results for biliary tumors.
- In addition to this, current immunotherapy represented by immune checkpoint inhibitors has shown significant advantages in a variety of malignancies. Radiation therapy has a direct cytotoxic effect on tumor cells and can produce certain antitumor immune responses by influencing the microenvironment and affecting distant tumor cells by releasing proinflammatory

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Biliary Tract Cancers: Intrahepatic Cholangiocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion



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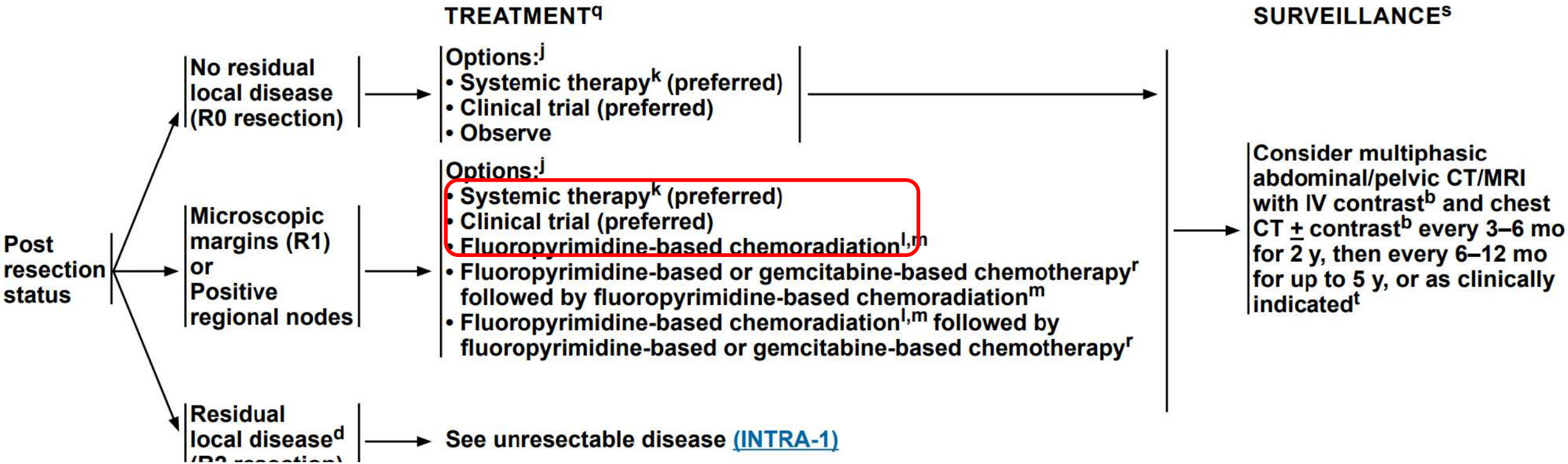
NCCN Guidelines Index
Table of Contents
Discussion



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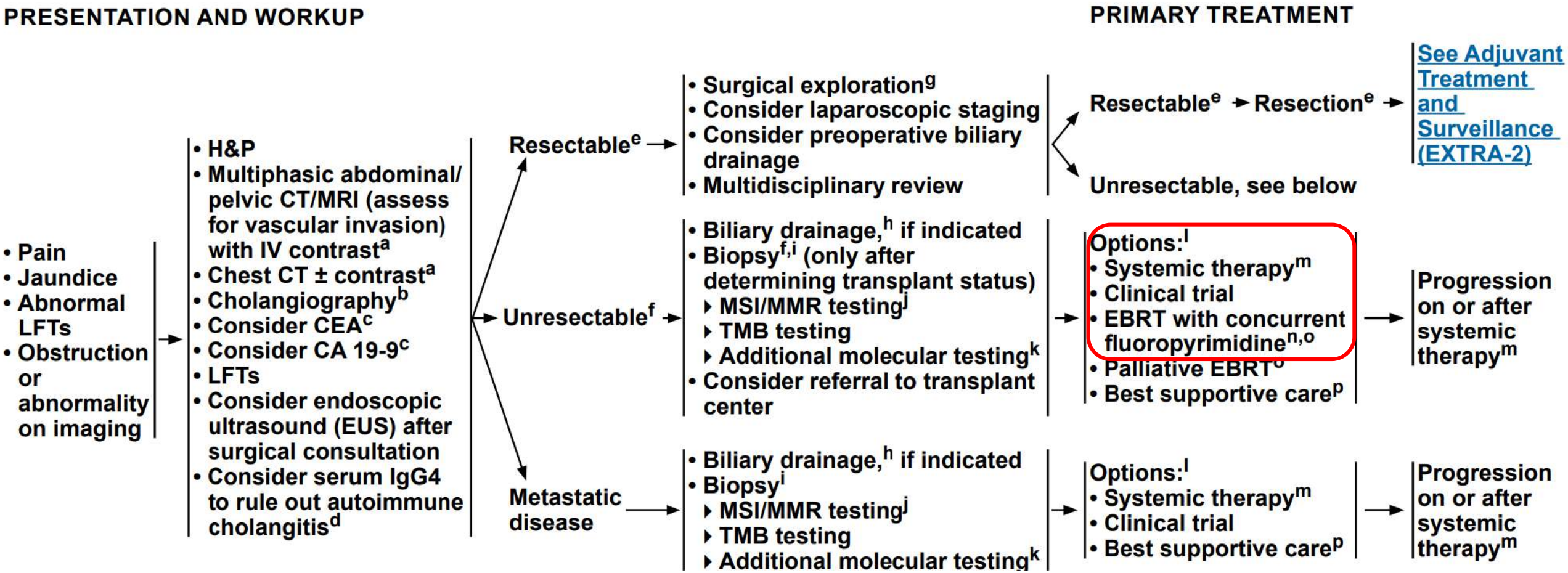
NCCN Guidelines Index
Table of Contents
Discussion



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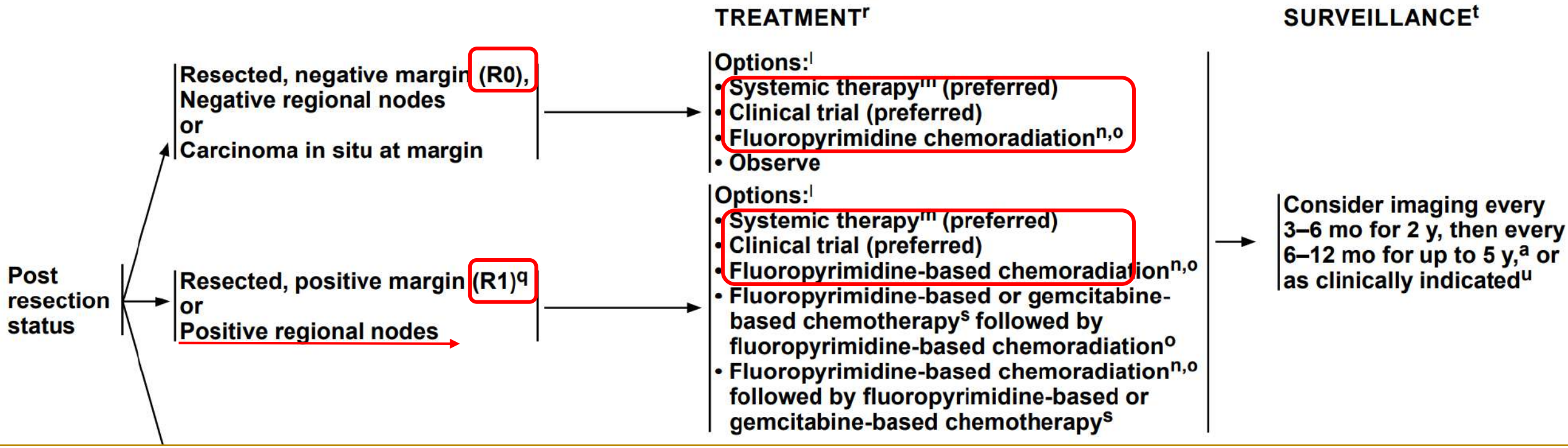
NCCN Guidelines Index
Table of Contents
Discussion



Case Capsule

Perihilar choloangiocarcinoma with type II block

Dr. Reena Engineer

Case Capsule

- 74yrs old gentleman Reformed smoker

k/c/o Diabetes and hypertension on medications

h/o MI underwent PTCA on ecospirin

h/o COPD and Obstructive sleep apnea

Past history of laparoscopic cholecystectomy for cholelithiasis in 2019

Family h/o pancreatic cancer in mother, prostate cancer in father, prostate and colon carcinoma in elder brother

Presenting complains

- h/o epigastric pain persistent over 2months
- h/o dyspepsia persisting over 2months
- No other complains

Evaluation

- CECT abdomen 13.5.22: Contrast enhancing soft tissue mass involving proximal CBD from the confluence of both hepatic ducts extending inferiorly 2cm in CBD, mild bilobar and IHBRD. Liver enlarged with caudate lobe hypertrophy. No suspicious focal liver lesion
- MRCP 16.5.22: Perihilar cholangiocarconoma with Type II communicating block
- Tumor markers:
  - CEA 5.99
  - CA 19.9 60.14
- LFT: Bilirubin 1.69, SGOT 135, SGPT 180
- Underwent ERCP and dual SEMS placement 25.5.22

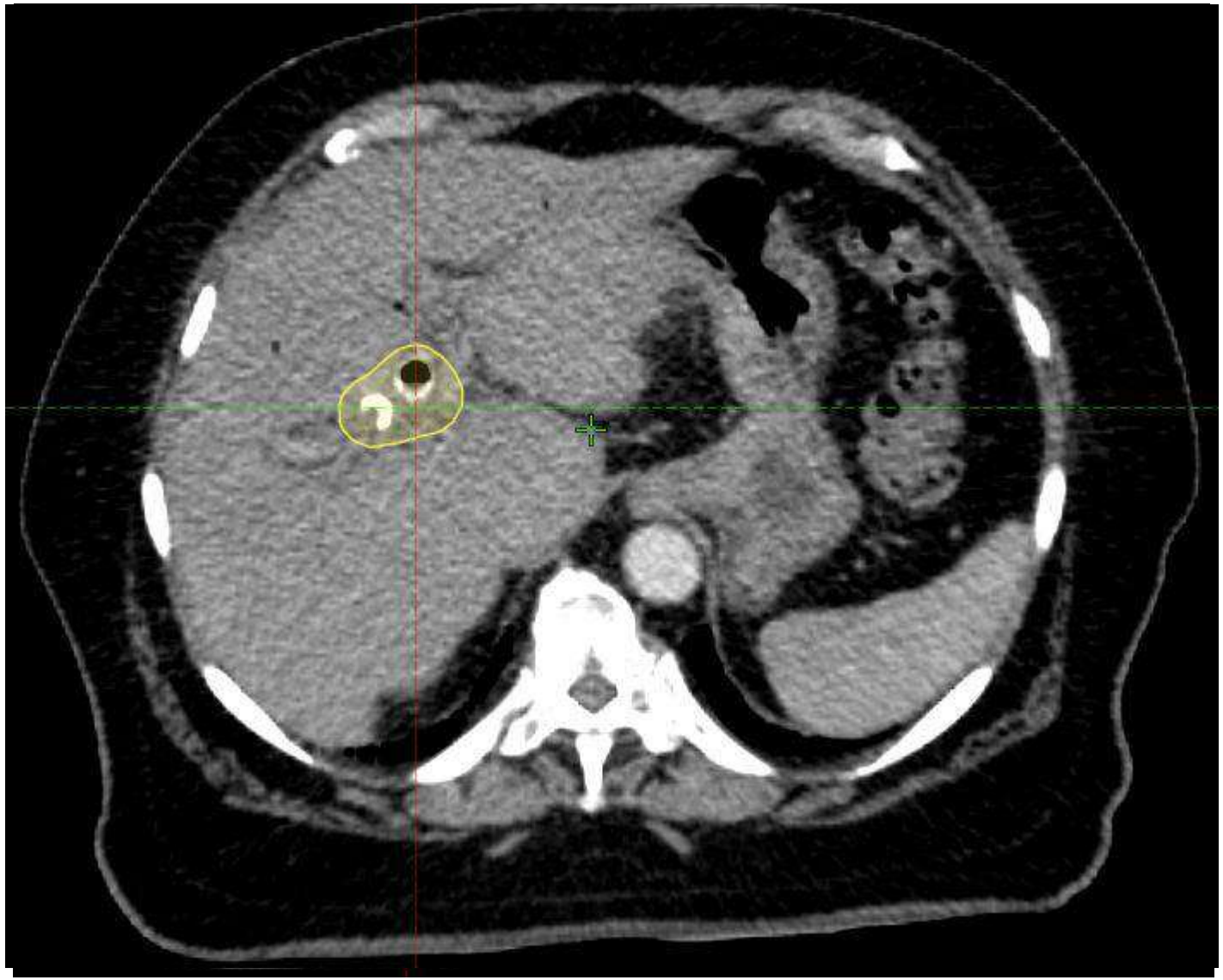
- As patient was willing for surgery, was planned for CTRT

Treatment Plan

- 4cycles GemOx (Gemcitabine+ Oxaliplatin) followed by CTRT (SBRT) followed by 4cycles GemOx

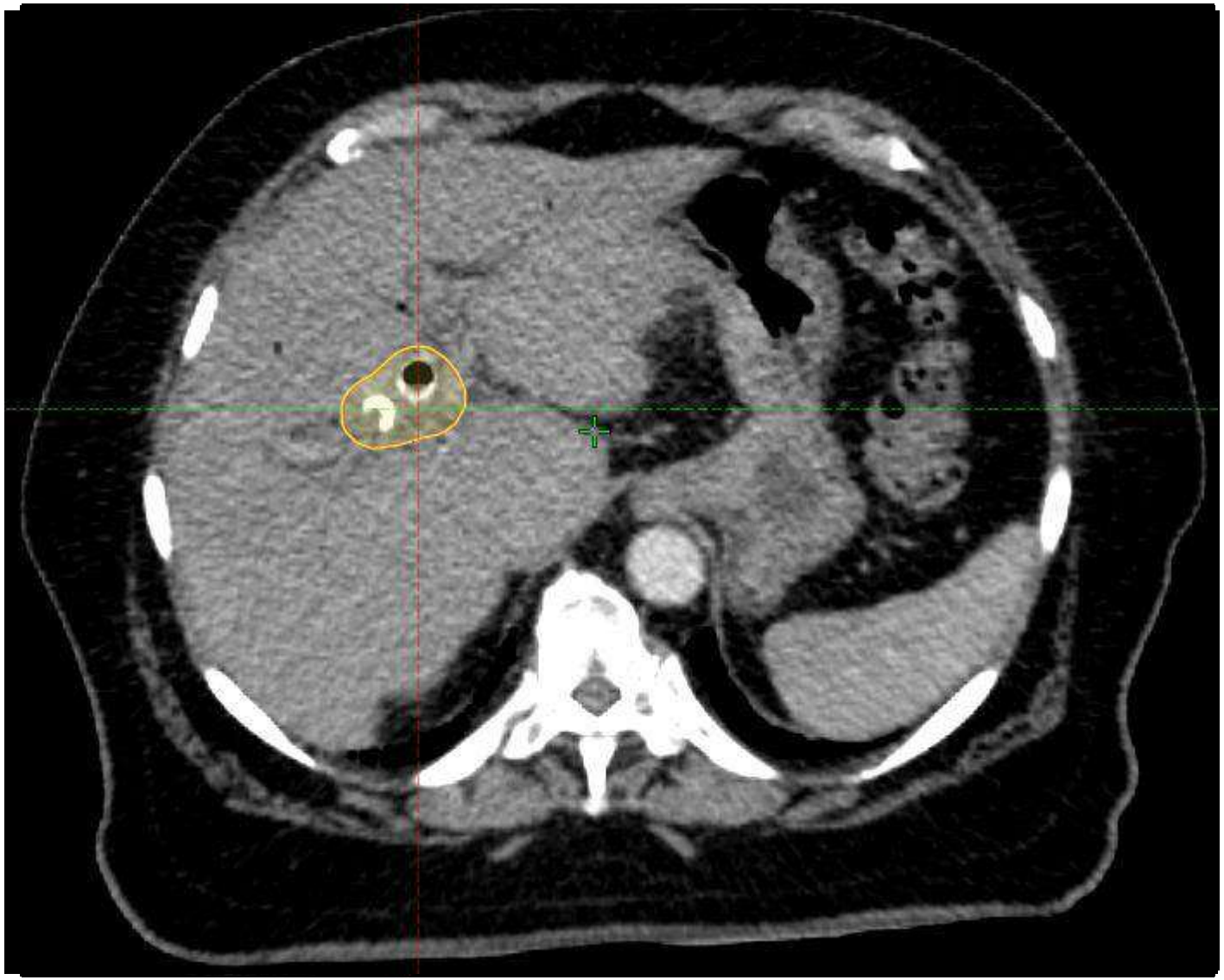
- Patient was skeptical about the side effects of chemotherapy and hence was reluctant to take any chemotherapy. Planned for SBRT alone.
- Patient simulated:
  supine position with arms overhead
  VACLOC with knee rest used for immobilization
  DEBH scan taken with 2.5mm slice thickness

Contouring



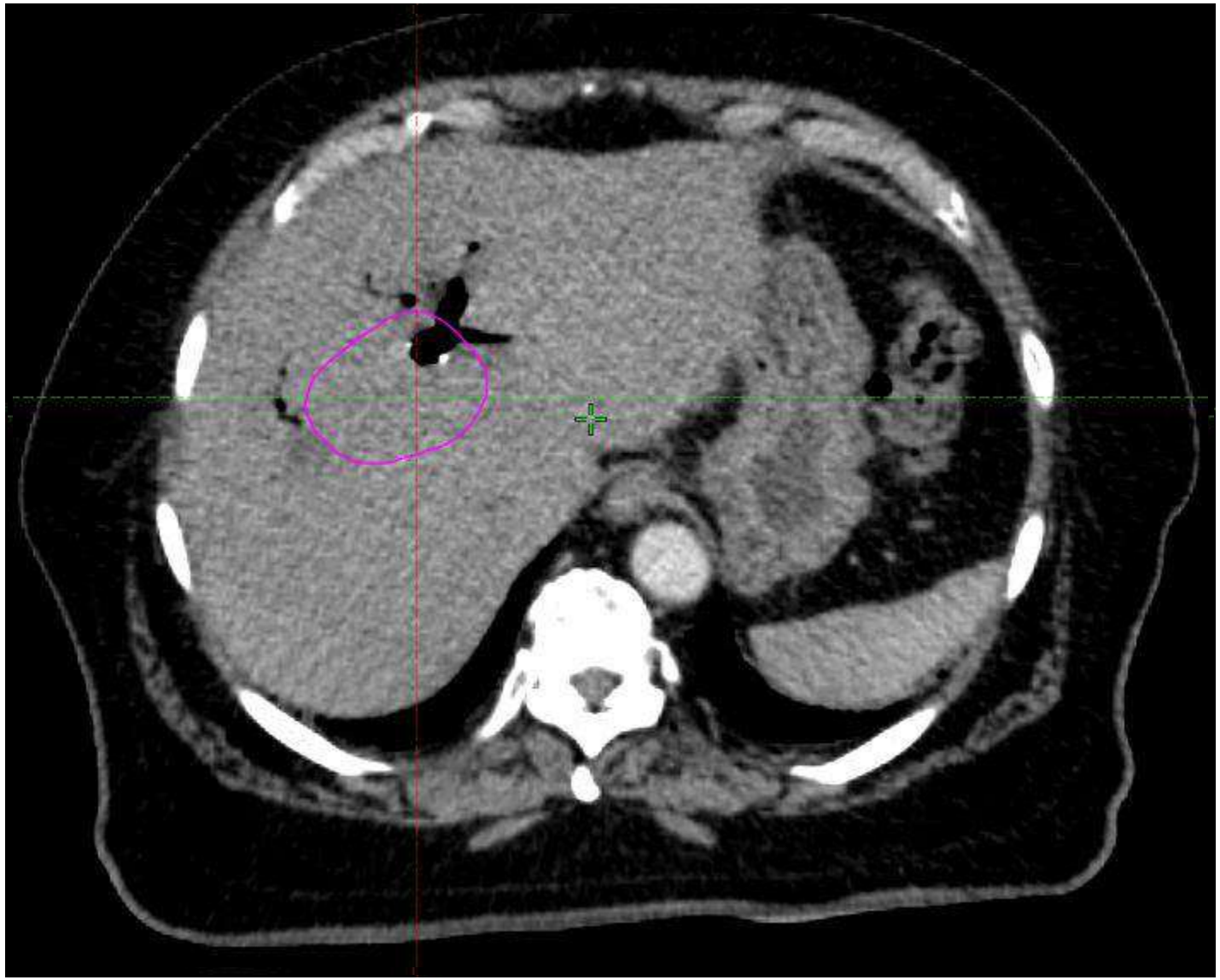
PTV_62.5Gy/15#

Contouring



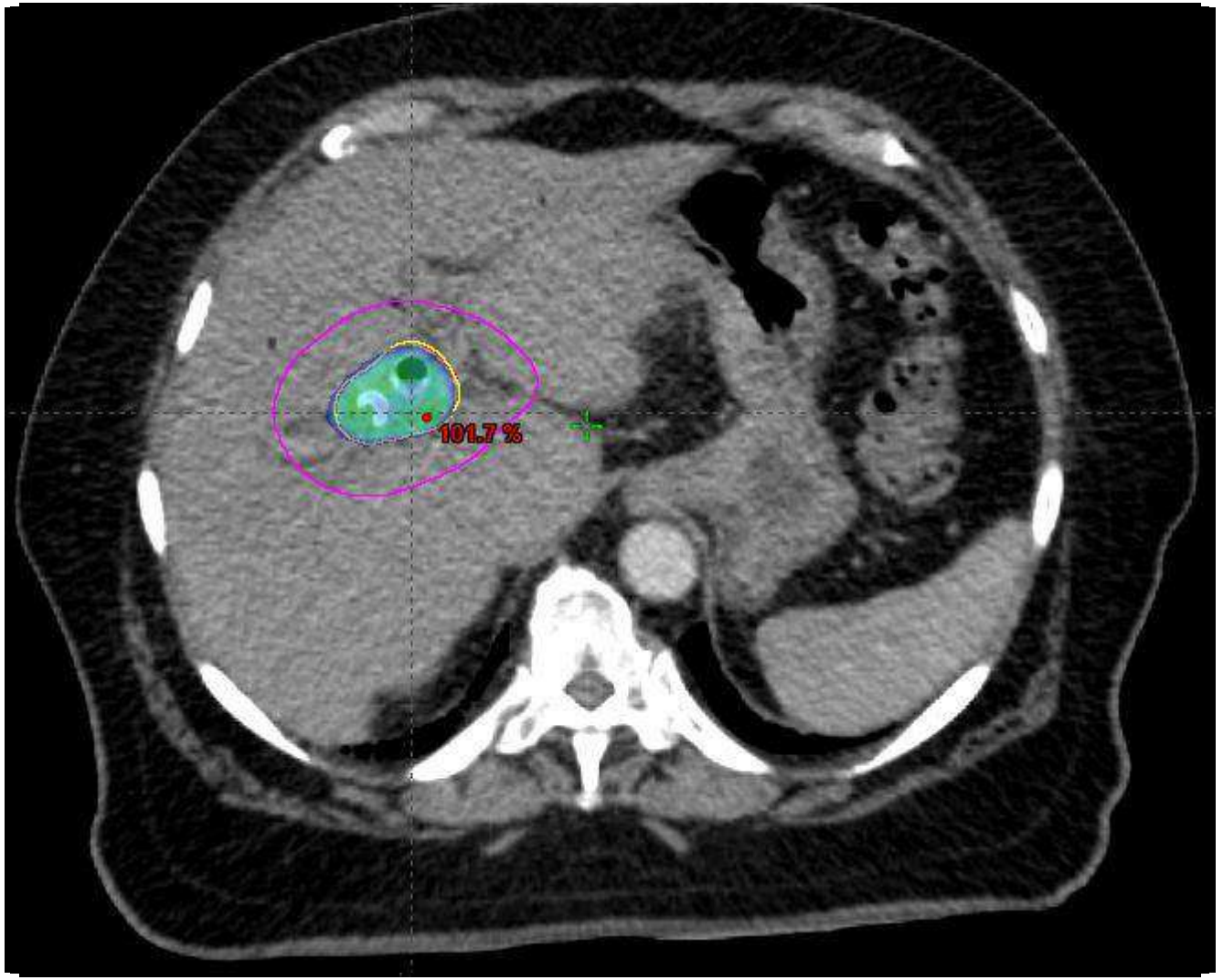
PTV_55Gy/15#

Contouring



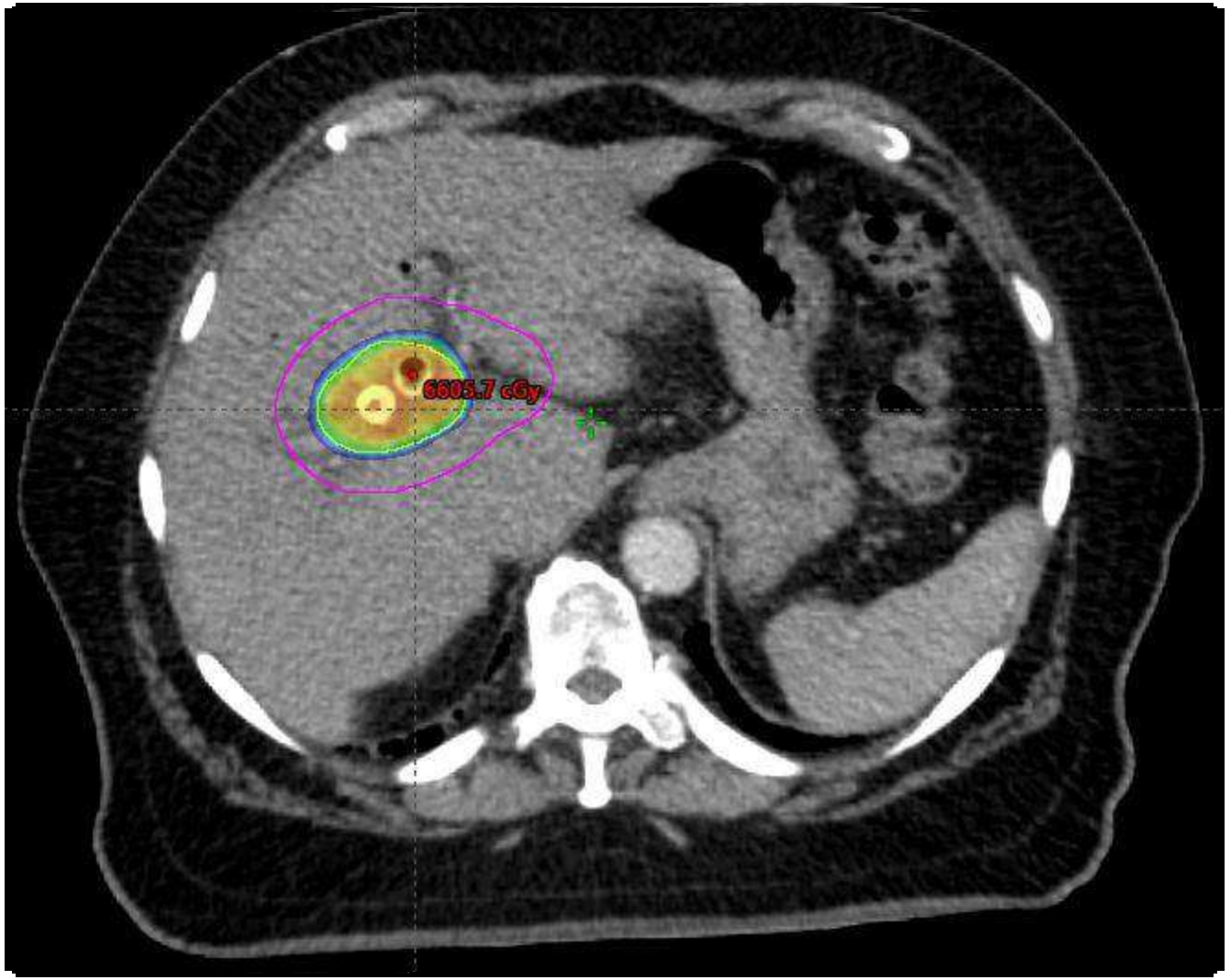
PTV_45Gy/15#

Planned using VMAT partial arc 181 to 90degrees
10MV photons
FFF beam
DEBH technique



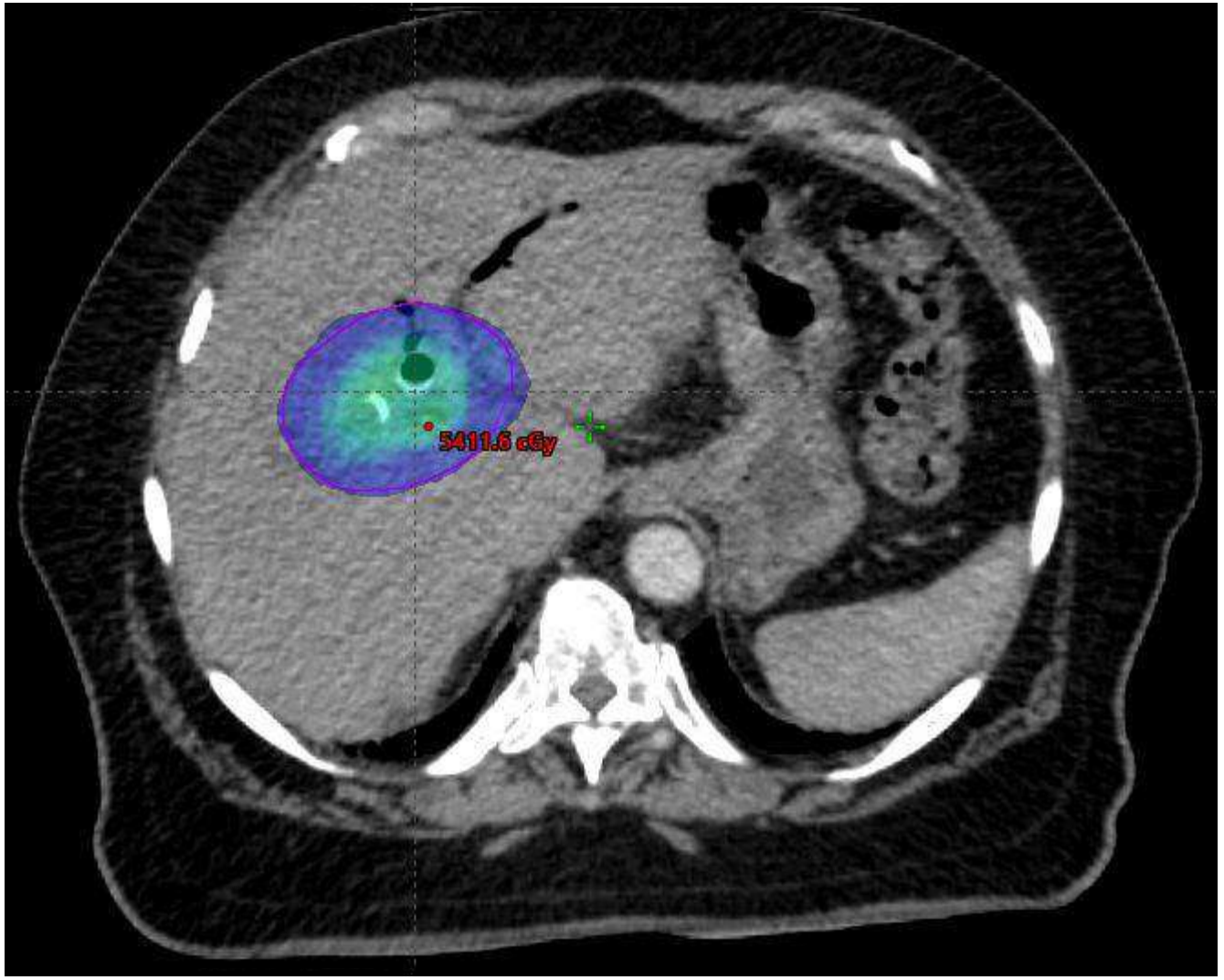
PTV_62.5Gy/15#

95% coverage



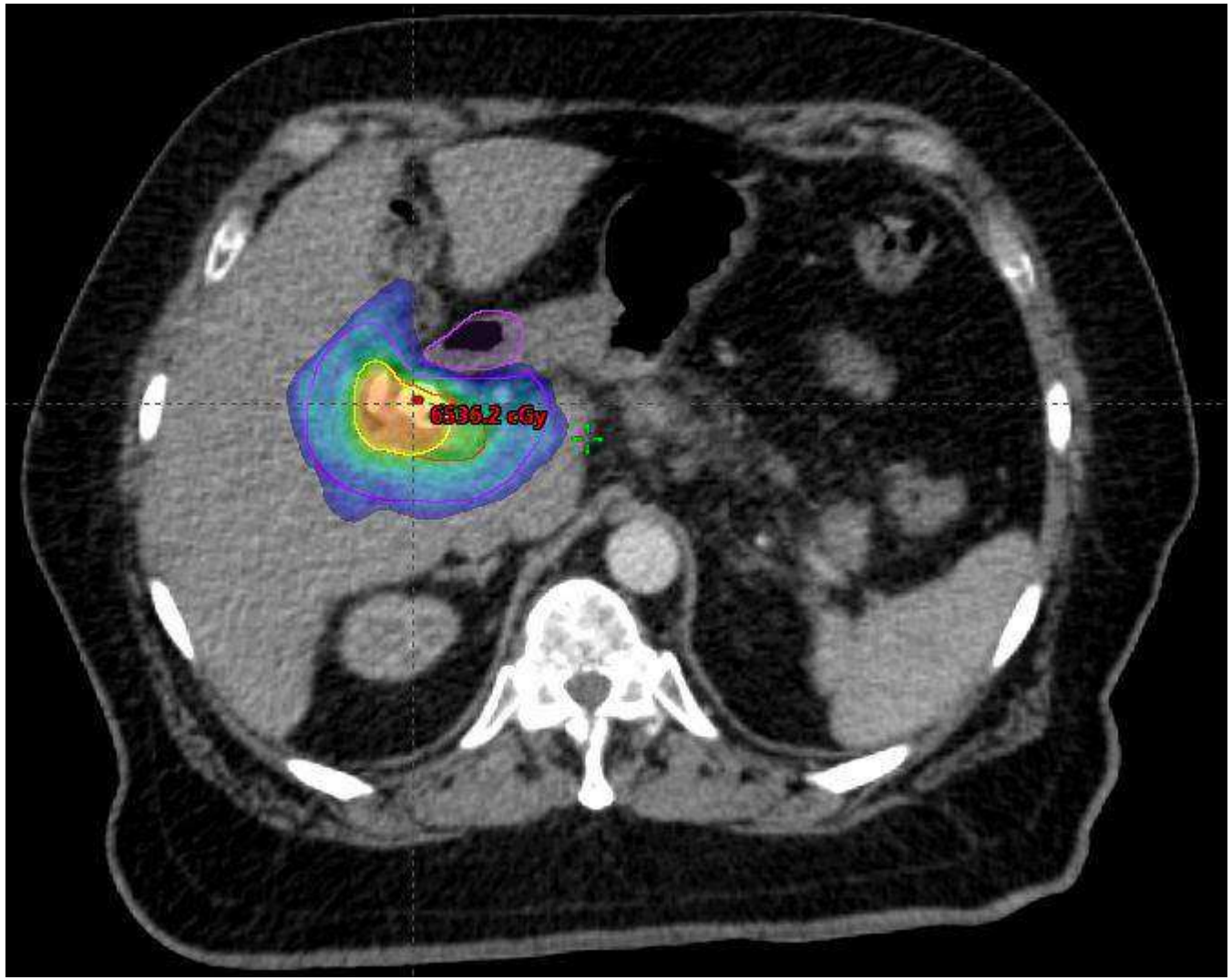
PTV_55Gy/15#

95% coverage



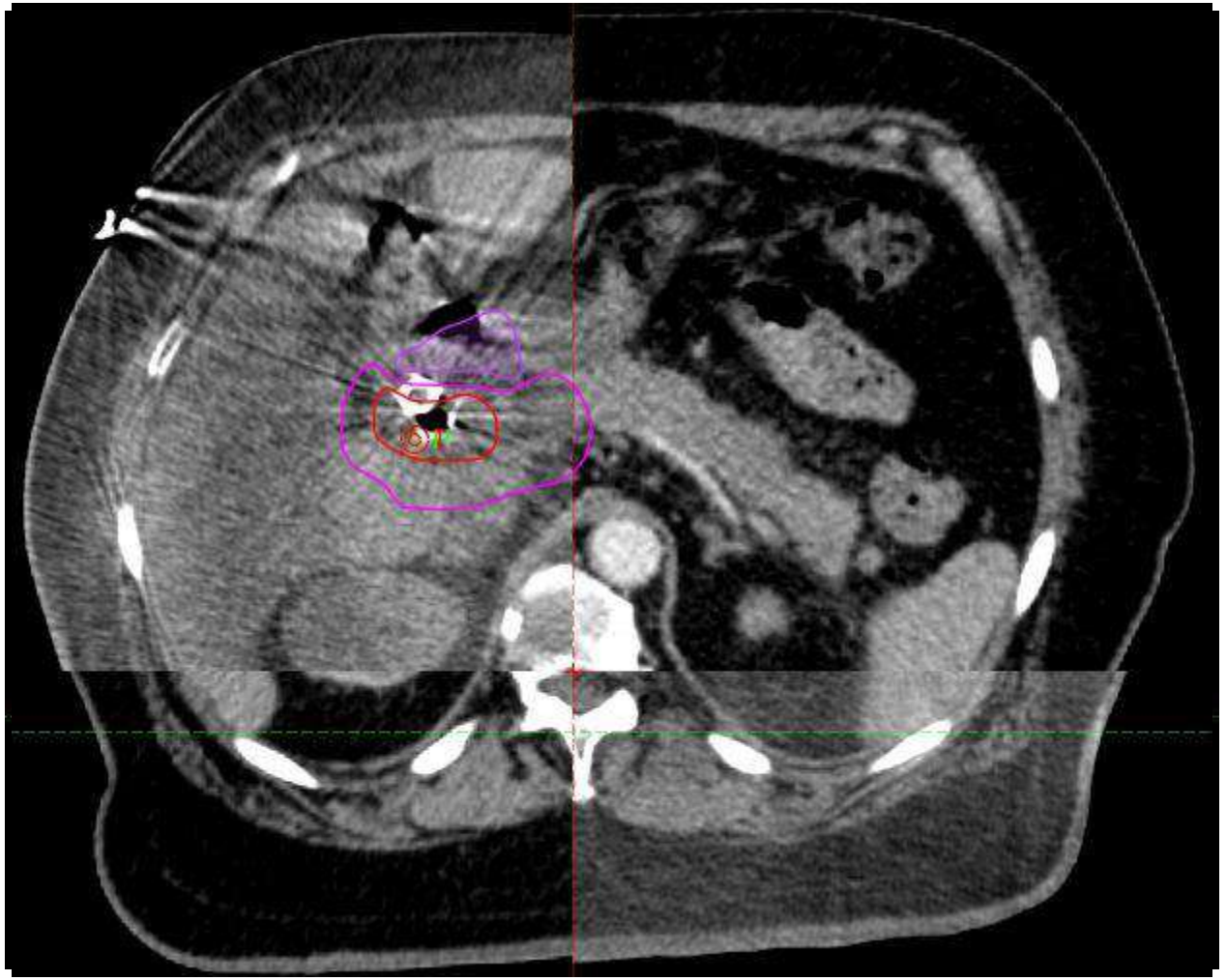
PTV_45Gy/15#

95% coverage
Ensuring
duodenal sparing



40Gy dose

Duodenum V45: 1cc
V40:3cc



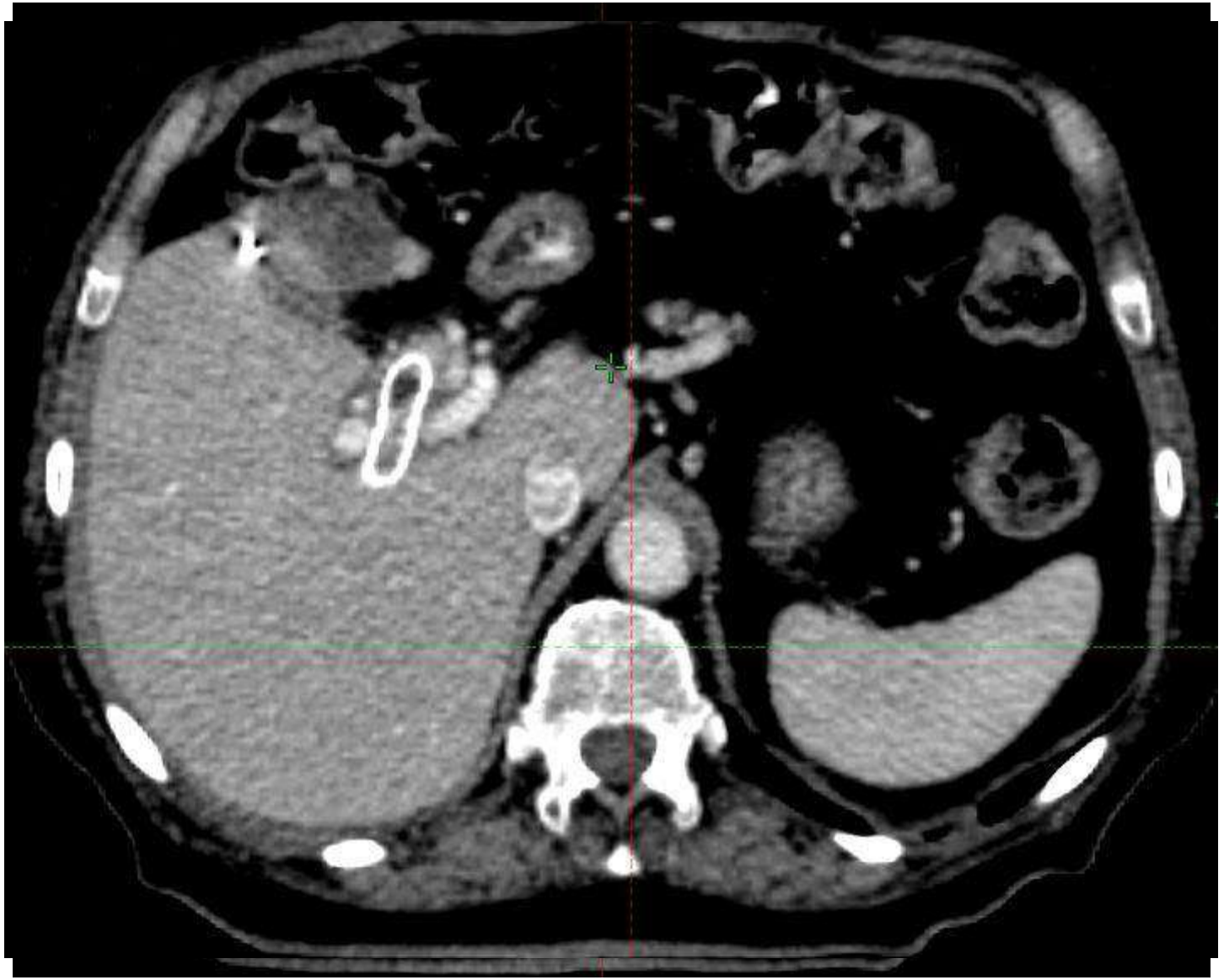
Plan implementation
CBCT matching

- Patient completed treatment with daily fractionation and no treatment gaps
- No significant skin, or GI toxicities

- Patient is called for follow up after 6weeks with PET CECT with triphasic scan for response assessment.

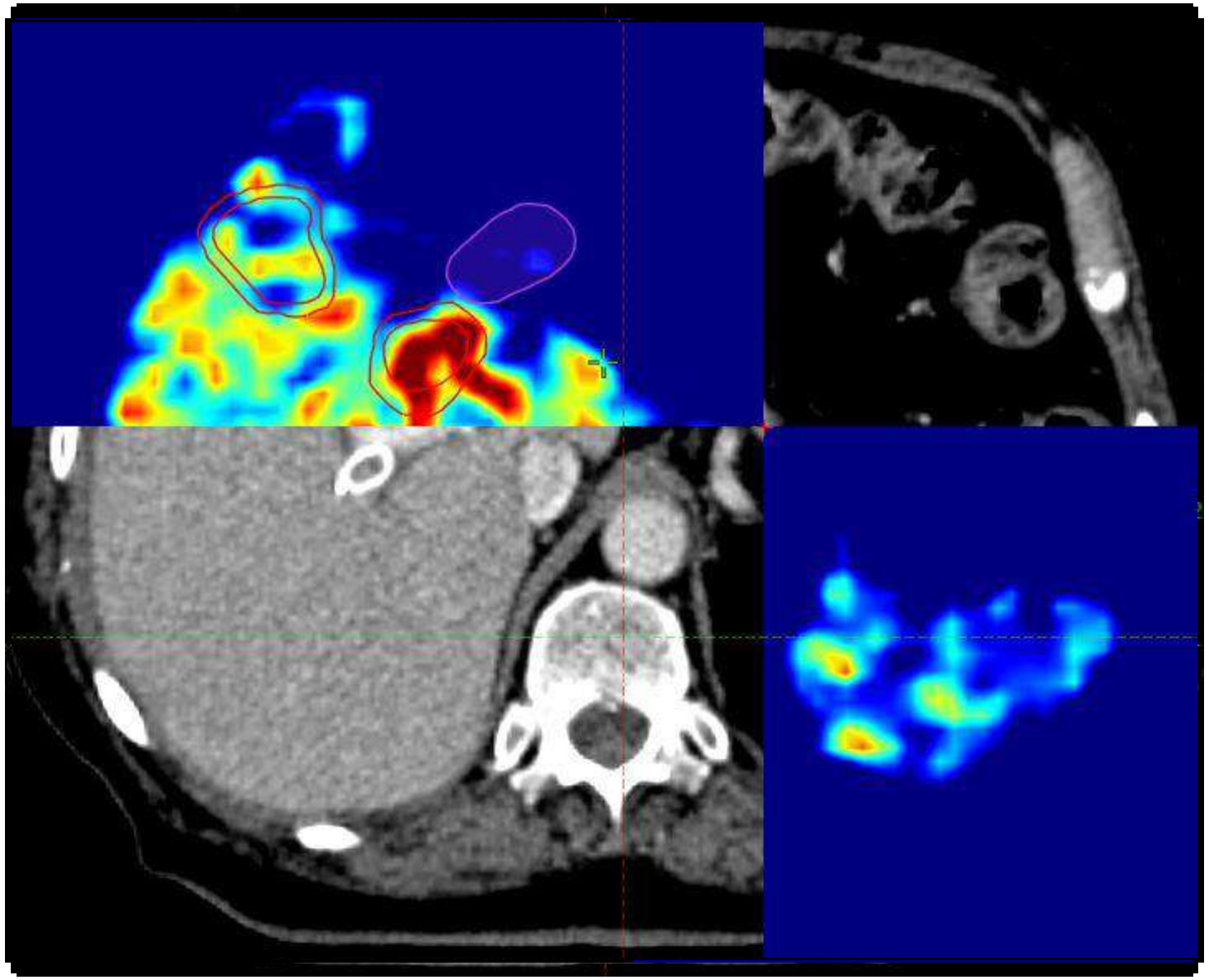
Patient 2
Gold marker placement to be done 5-7days before RT planning

PET CT should be used for contouring GTV using FDG avidity



Gold marker placement

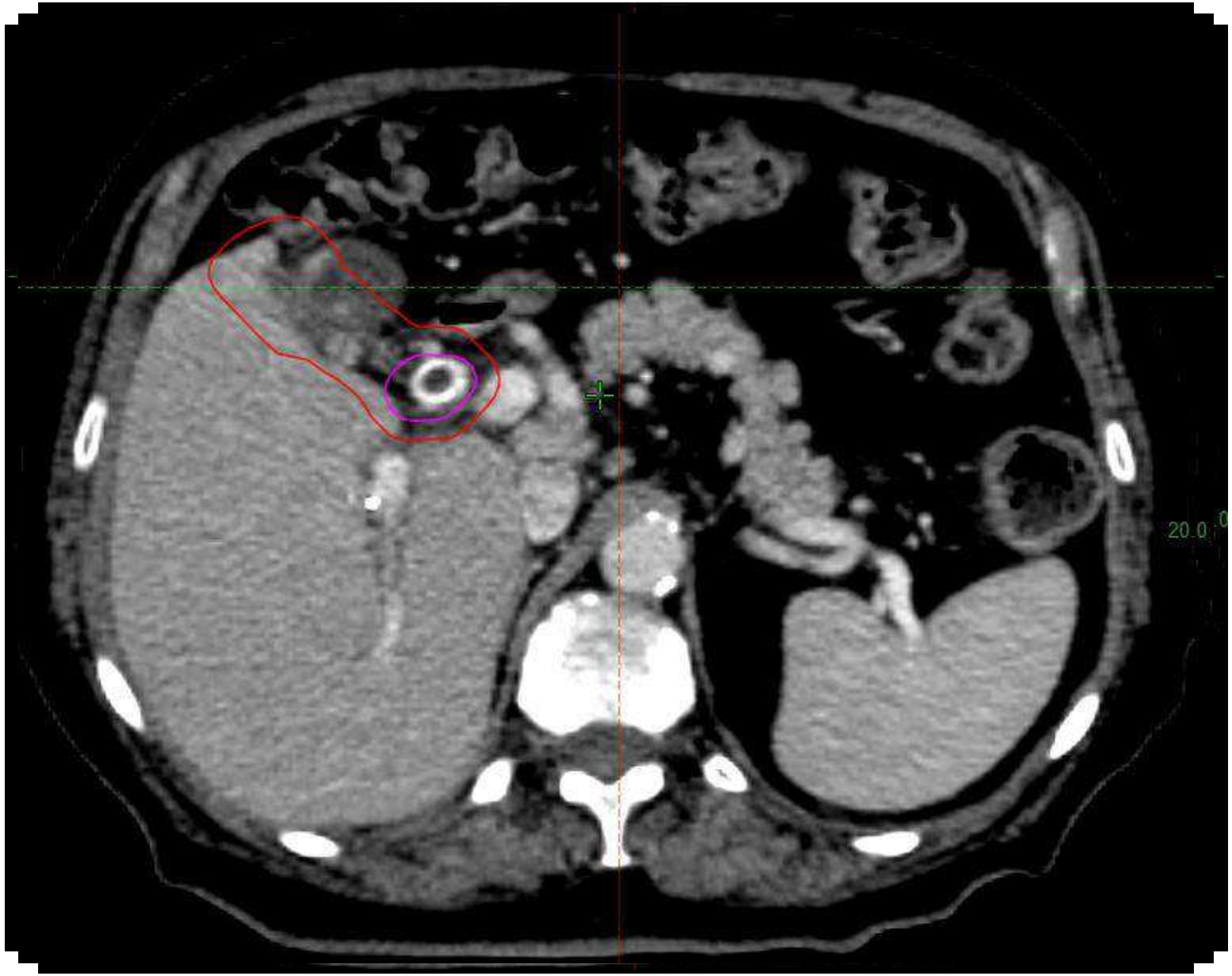
Contouring



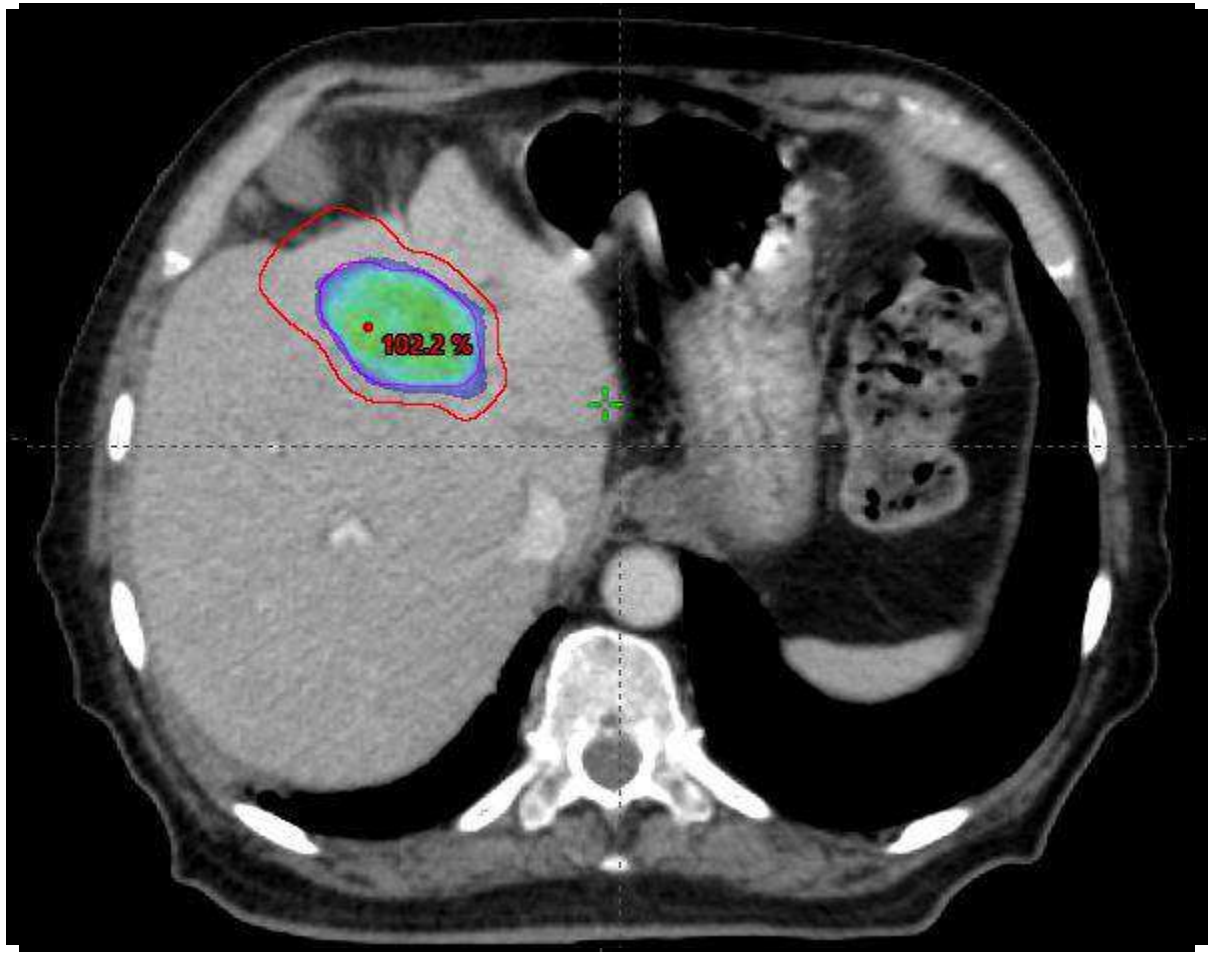
Use PET CT to contour the GTV using FDG avidity of lesion

GTV and PTV 55Gy/10#

Contouring

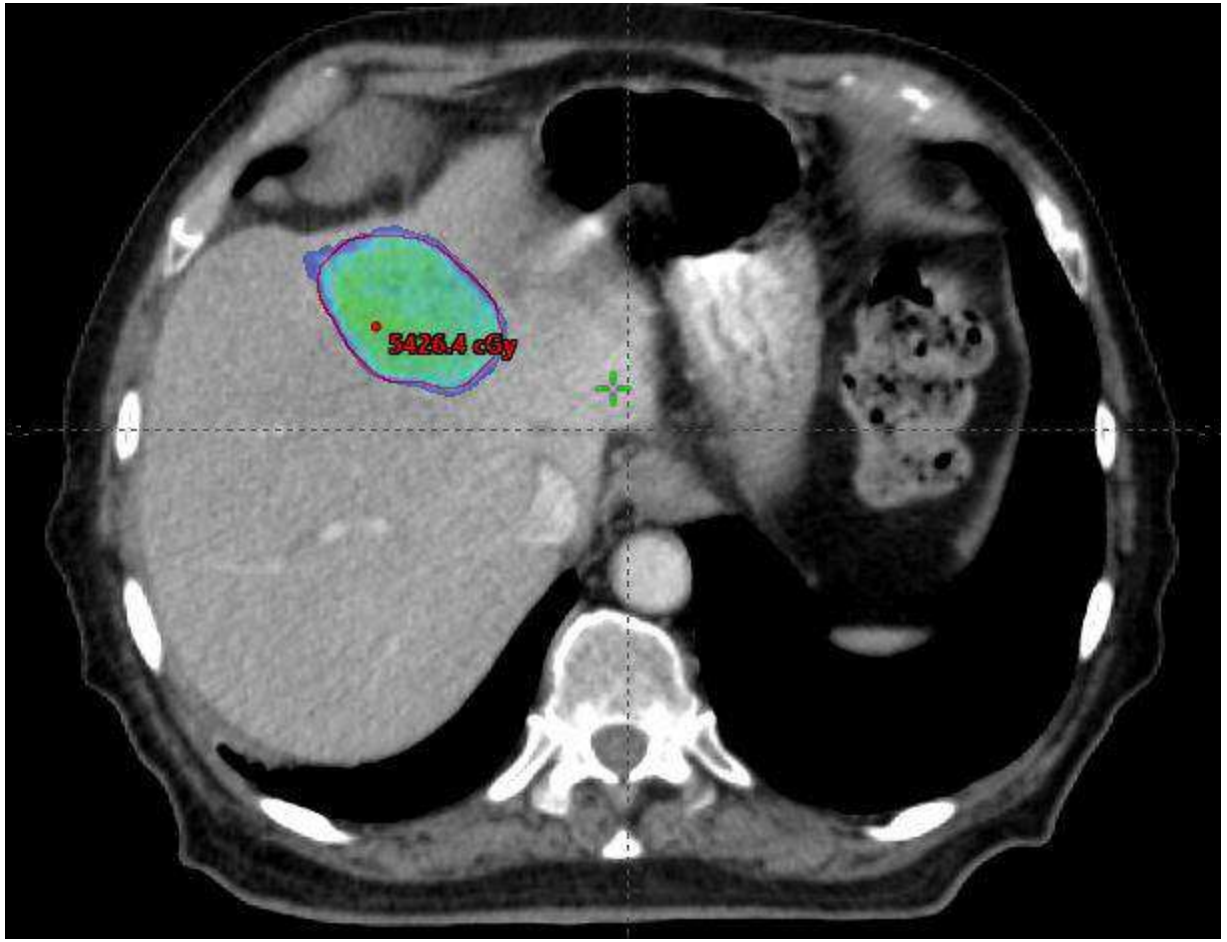


PTV_55Gy/10#



PTV_55Gy/10#

95% coverage
Ensuring
duodenal sparing
V45



PTV_50Gy/10#
95% coverage

Thank you!