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 treated with 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: Cholangiocarcinoma.
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 ≤ 0.004 and OR, 0.36; P ≤ 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
High dose chemoradiation for unresectable hilar cholangiocarcinomas using intensity modulated external beam radiotherapy: a single tertiary care centre experience

Reena Engineer¹, Shaesta Mehta², Nikhil Kalyani¹, Suresh Chaudhari⁴, Tejas Dharia⁴, Nitin Shetty⁴ Supriya Chopra¹, Mahesh Goel⁵, Suyash Kulkarni¹, Shyam Kishore Shrivastava¹
SBRT IN CHOLANGIOCARCINOMA
# SBRT in intrahepatic cholangioca

<table>
<thead>
<tr>
<th>AUTHOR</th>
<th>INSTITUTE</th>
<th>N</th>
<th>TREATMENT TYPE</th>
<th>TUMOR VOLUME</th>
<th>RT DOSE MEDIAN (RANGE)</th>
<th>1 YR OS</th>
<th>1 YR LC</th>
<th>TOXICITIES&gt;=/=GRADE3</th>
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<tbody>
<tr>
<td>Barney et al 2012</td>
<td>Mayo Clinic, USA, retrospective</td>
<td>10</td>
<td>SBRT</td>
<td>16–412.4 mL</td>
<td>63 Gy /3 fr</td>
<td>73%</td>
<td>100%</td>
<td>20% (1 grade 5 liver failure, 1 grade 3 biliary stenosis)</td>
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<td>Dewas et al.2012</td>
<td>Lille, France, retrospective</td>
<td>6</td>
<td>SBRT</td>
<td>0.5–11.2 cm</td>
<td>39–45 Gy /3-4 fr</td>
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<td>100%</td>
<td>NS</td>
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<td>Goyal et al.2010</td>
<td>Case Western Reserve University, USA, retrospective</td>
<td>3</td>
<td>SBRT</td>
<td>80–818 mL</td>
<td>24–45 Gy / 1–3 fr</td>
<td>0%</td>
<td>67%</td>
<td>0%</td>
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## SBRT in intrahepatic cholangioca

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<tr>
<td>Tse et al.2008</td>
<td>Princess Margaret Hospital, Canada, phase I</td>
<td>10</td>
<td>SBRT</td>
<td>10–465 mL</td>
<td>32.5 (28.2–48) Gy /6fractions</td>
<td>58%</td>
<td>65%</td>
<td>20%</td>
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<td>Goodman et al.2010</td>
<td>Stanford University, USA phasel</td>
<td>5</td>
<td>SBRT</td>
<td>&lt;5 cm</td>
<td>18-30Gy single fraction</td>
<td>71%</td>
<td>23%</td>
<td>none</td>
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<td>Ibarra et al.2012</td>
<td>Multi-institutional pooled analysis</td>
<td>11</td>
<td>SBRT</td>
<td>30.6–818.5 mL</td>
<td>30 (22–50) Gy /1-10 fractions</td>
<td>45%</td>
<td>50%</td>
<td>7% RILD only</td>
</tr>
</tbody>
</table>
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\textsuperscript{a,1,*}, Oliver Blanck\textsuperscript{b}, Victor Lewitzki\textsuperscript{c}, Nasrin Abbasi-Senger\textsuperscript{d}, Felix Momm\textsuperscript{e}, Oliver Riesterer\textsuperscript{f}, Marciana Nona Duma\textsuperscript{g,h}, Stefan Wachter\textsuperscript{i}, Wolfgang Baus\textsuperscript{j}, Sabine Gerum\textsuperscript{k}, Matthias Guckenberger\textsuperscript{f}, Eleni Gkika\textsuperscript{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.
Ablative Radiotherapy Doses Lead to a Substantial Prolongation of Survival in Patients With Inoperable Intrahepatic Cholangiocarcinoma: A Retrospective Dose Response Analysis


<table>
<thead>
<tr>
<th>Common fractionation regimens</th>
<th>50.4 Gy in 28 fx</th>
<th>58.05 Gy in 15 fx</th>
<th>60 Gy in 30 fx</th>
<th>67.5 Gy in 15 fx</th>
<th>75 Gy in 25 fx</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>19 (24)</td>
<td>14 (18)</td>
<td>4 (5)</td>
<td>7 (9)</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>
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

Simultaneous integrated boost of 100 Gy to the tumor center

Organ at risk (e.g., stomach)
Importantly, OS in this study is similar to that reported in patients with operable IHCC after resection with curative intent. Mediansurvival time for patients who undergo at least amacropscopic total resection ranges from 25.5 to 37.4 months, with 3-year survival rates of 38% to 55%.
Efficacy of stereotactic body radiotherapy for unresectable or recurrent cholangiocarcinoma: a meta-analysis and systematic review

Jeongshim Lee¹,² · Won Sup Yoon³ · Woong Sub Koom¹ · Chai Hong Rim³

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) ≥71.3Gy²
74.7% EQD2 <71.3Gy².
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

4D-RT = IGRT (Image-guide radiotherapy)
Stereotactic Ablative Radiation: Process

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

Cem Onal\textsuperscript{a}  Savas Topuk\textsuperscript{a}  Ali F. Yapar\textsuperscript{b}  Melek Yavuz\textsuperscript{c}  Erkan Topkan\textsuperscript{a}  Aydin Yavuz\textsuperscript{c}

Department of Radiation Oncology, \textsuperscript{b}Department of Nuclear Medicine, Baskent University Medical Faculty, Adana Medical and Research Center, Kisla Campus, Adana, \textsuperscript{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, high risk 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 stomach and 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 the imaging evaluation results, considering their low recurrence rate.

![Image](image.png)
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
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Biliary Tract Cancers: Intrahepatic Cholangiocarcinoma

**Presentation**
- Isolated intrahepatic mass (imaging characteristics consistent with malignancy but not consistent with hepatocellular carcinoma) (See NCCN Guidelines for Occult Primary)

**Workup**
- H&P
- Multiphasic abdominal/pelvic CT/MRI with IV contrast
- Chest CT ± contrast
- Consider CEA
- Consider CA 19-9
- LFTs
- Surgical consultation
- Esophagogastroduodenoscopy (EGD) and colonoscopy
- Consider viral hepatitis serologies
- Consider biopsy
- Consider AFP
- Consider referral to a hepatologist

**Primary Treatment**
- **Resectable**
  - Consider staging laparoscopy
  - Resection and regional lymphadenectomy

- **Unresectable**
  - Biopsy, if not previously performed
  - MSI/MMR testing
  - TMB testing
  - Additional molecular testing
  - Options:
    - Systemic therapy
    - Clinical trial
    - EBRT with concurrent fluoropyrimidine
    - Consider locoregional therapy
    - Arterially directed therapies
    - Best supportive care

- **Metastatic disease**
  - Biopsy, if not previously performed
  - MSI/MMR testing
  - TMB testing
  - Additional molecular testing
  - Options:
    - Systemic therapy (preferred)
    - Clinical trial (preferred)
    - Consider locoregional therapy
    - Arterially directed therapies
    - Best supportive care

**Discussion**
See Additional Therapy and Surveillance (INTRA-2)
Progression on or after systemic therapy

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**TREATMENT**

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<th>No residual local disease (R0 resection)</th>
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<tbody>
<tr>
<td>Options:</td>
</tr>
<tr>
<td>- Systemic therapy(^k) (preferred)</td>
</tr>
<tr>
<td>- Clinical trial (preferred)</td>
</tr>
<tr>
<td>- Observe</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Residual local disease (R0 resection)</th>
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<tr>
<td>See unresectable disease (INTRA-1)</td>
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</table>

<table>
<thead>
<tr>
<th>Microscopic margins (R1) or Positive regional nodes</th>
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<tr>
<td>Options:</td>
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<tr>
<td>- Systemic therapy(^k) (preferred)</td>
</tr>
<tr>
<td>- Clinical trial (preferred)</td>
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</tbody>
</table>

**SURVEILLANCE**

| Consider multiphasic abdominal/pelvic CT/MRI with IV contrast\(^b\) and chest CT ± contrast\(^b\) every 3–6 mo for 2 y, then every 6–12 mo for up to 5 y, or as clinically indicated\(^l\) |

\(^{a}\) Updated 2022
\(^{b}\) Updated 2019
\(^{c}\) Updated 2018
\(^{d}\) Updated 2017
\(^{e}\) Updated 2016
\(^{f}\) Updated 2015
\(^{g}\) Updated 2014
\(^{h}\) Updated 2013
\(^{i}\) Updated 2012
\(^{j}\) Updated 2011
\(^{k}\) Updated 2010
\(^{l}\) Updated 2009
\(^{m}\) Updated 2008
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Biliary Tract Cancers: Extrahepatic Cholangiocarcinoma

PRESENTATION AND WORKUP

- Pain
- Jaundice
- Abnormal LFTs
- Obstruction or abnormality on imaging
  - H&P
  - Multiphasic abdominal/pelvic CT/MRI (assess for vascular invasion) with IV contrast
  - Chest CT ± contrast
  - Cholangiography
  - Consider CEA
  - Consider CA 19-9
  - LFTs
  - Consider endoscopic ultrasound (EUS) after surgical consultation
  - Consider serum IgG4 to rule out autoimmune cholangitis

Resectable
  - Surgical exploration
  - Consider laparoscopic staging
  - Consider preoperative biliary drainage
  - Multidisciplinary review

Unresectable
  - Biliary drainage, if indicated
  - Biopsy (only after determining transplant status)
    - MSI/MMR testing
    - TMB testing
    - Additional molecular testing
  - Consider referral to transplant center

Metastatic disease
  - Biliary drainage, if indicated
  - Biopsy
    - MSI/MMR testing
    - TMB testing
    - Additional molecular testing

PRIMARY TREATMENT

Resectable
  - Resection
  - Surveillance (EXTRA-2)

Unresectable, see below

Options:
  - Systemic therapy
  - Clinical trial
  - EBRT with concurrent fluoropyrimidine
  - Palliative EBRT
  - Best supportive care

Options:
  - Systemic therapy
  - Clinical trial
  - Best supportive care

Progression on or after systemic therapy

Progression on or after systemic therapy

See Adjuvant Treatment and Surveillance (EXTRA-2)
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Biliary Tract Cancers: Extrahepatic Cholangiocarcinoma

**TREATMENT**

- **Resected, negative margin (R0),**
  - Negative regional nodes or Carcinoma in situ at margin
    - **Options:**
      - Systemic therapy (preferred)
      - Clinical trial (preferred)
      - Fluoropyrimidine chemoradiation
        - Observe
      - **Options:**
        - Systemic therapy (preferred)
        - Clinical trial (preferred)
        - Fluoropyrimidine-based chemoradiation
          - Fluoropyrimidine-based or gemcitabine-based chemotherapy followed by fluoropyrimidine-based chemoradiation
          - Fluoropyrimidine-based chemoradiation followed by fluoropyrimidine-based or gemcitabine-based chemotherapy

- **Resected, positive margin (R1),**
  - Positive regional nodes

**SURVEILLANCE**

- Consider imaging every 3–6 mo for 2 y, then every 6–12 mo for up to 5 y, or as clinically indicated
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 complaints

• h/o epigastric pain persistent over 2 months
• h/o dyspepsia persisting over 2 months
• 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 IHBBD. 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
Contouring

PTV_45Gy/15#
Planned using VMAT partial arc 181 to 90 degrees
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 6 weeks with PET CECT with triphasic scan for response assessment.
Patient 2
Gold marker placement to be done 5-7 days before RT planning

PET CT should be used for contouring GTV using FDG avidity
Gold marker placement
Use PET CT to contour the GTV using FDG avidity of lesion.

GTV and PTV 55Gy/10#
PTV_55Gy/10#

95% coverage
Ensuring duodenal sparing
V45
PTV_50Gy/10#
95% coverage