Current Status and Advances in Radiotherapy for Biliary Tract Cancers

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Abstract: Biliary tract cancers (BTCs) are insidious and carry extremely poor prognosis, with most patients unresectable at diagnosis. Radiotherapy is an important local treatment, but conventional methods cannot balance target dose and normal tissue protection due to complex anatomy adjacent to radiosensitive organs. In recent years, precise radiotherapy including IMRT, VMAT, IGRT, MRgRT and particle therapy has greatly improved accuracy. BED-based dose escalation, SIB and functional imaging-guided optimization further balance efficacy and safety. This review summarizes precise radiotherapy techniques, dosimetric optimization, clinical applications, current challenges and future directions.

***Keywords*:** biliary tract cancers; precise radiotherapy; dosimetric optimization; clinical application

1. Introduction

Biliary tract cancers (BTCs) are aggressive heterogeneous malignancies originating from biliary epithelium, including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma (eCCA) and gallbladder cancer (GBC)(1). The incidence is rising globally, with a heavy burden in China.

Surgery remains the only potentially curative treatment, but most patients present with advanced disease. Even after curative resection, the local recurrence rate reaches 40%–50%, and the 5-year overall survival (OS) is below 30%(2). Radiotherapy is a core local treatment for improving local control and survival. However, BTC lesions lie near radiosensitive organs, and most patients have biliary obstruction or liver dysfunction, creating a key dilemma between dose escalation and organ protection.

Modern precise radiotherapy techniques including IMRT, VMAT, IGRT, SBRT and MRgRT have broken this bottleneck. These techniques deliver highly conformal dose distributions with rapid dose fall-off in normal tissues.

2. Modern Precise Radiotherapy Techniques

The biliary system has complex anatomy, and BTC lesions are often irregular and mobile with respiration, requiring high precision. Conventional techniques are gradually replaced by precise radiotherapy.

2.1 Photon Precise Radiotherapy

IMRT is the foundation of modern BTC radiotherapy. It modulates beam intensity non-uniformly to generate concave dose distributions matching irregular tumors, achieving high-dose coverage while reducing exposure to the liver, duodenum and stomach.

VMAT, an evolution of IMRT, delivers continuous dynamic beams via gantry rotation with synchronous modulation of MLC, dose rate and rotation speed.

2.2 Image-Guided Radiotherapy (IGRT)

IGRT acquires images before or during treatment, corrects setup errors and inter-fraction anatomical changes, preventing radiosensitive organs from entering high-dose regions.

2.3 Respiratory Motion Management

Respiratory diaphragmatic displacement causes tumor movement of 5–15 mm. Modern strategies include respiratory control (ABC, DIBH), abdominal compression, 4D-CT simulation and real-time tracking. .

2.4 Adaptive Radiotherapy and MR-Guided Radiotherapy

Adaptive radiotherapy (ART) dynamically adjusts plans via real-time imaging to ensure dose accuracy. MRgRT (1.5T MR-Linac) is the most advanced ART, enabling real-time respiratory tracking. The MOMENTUM study showed 99.7% online adaptive plan delivery, 5% grade 3–4 acute toxicity, 12% late toxicity and 67% 1-year OS for abdominal tumors. MRgRT reduces duodenal high-dose exposure and toxicity, representing a future direction, though accessibility is limited.

2.5 Particle Radiotherapy

Proton beam therapy (PBT) features the Bragg peak, with low entrance dose and zero exit dose. It reduces exposure to the normal liver, stomach, duodenum, kidneys and spinal cord, ideal for patients with poor liver function. A prospective study of 236 unresectable CCA patients treated with PBT showed that BED > 89 Gy_{10} achieved 65.2% 2-year LC, 20.0 months median OS (mOS), 36.9% 2-year OS, 4.0% grade 3 acute toxicity and 12.1% grade 3 late toxicity, with no severe RILD. However, high cost and limited availability restrict widespread use no severe RILD.

3. Radiotherapy Dosimetric Optimization

Dosimetric optimization resolves the conflict between dose escalation and normal tissue tolerance. Dose escalation to BED > 100 Gy significantly improves 1-year LC (83% vs. 22%). Patients with jaundice or liver insufficiency need 10%–20% BED reduction to avoid severe RILD.

OAR tolerance must be strictly followed: NCCN guidelines recommend stomach V45 Gy < 35%, liver V30 Gy ≤ 50%, or functional liver volume > 700 cc to prevent gastrointestinal ulceration/hemorrhage and RILD(3).

Simultaneous Integrated Boost (SIB) delivers gradient doses to target subvolumes in one session, boosting the tumor core while sparing normal tissues. A study of 74 unresectable BTC patients found that BED > 80.5 Gy correlated with lower progression risk (P = 0.046), higher 1-year PFS (29% vs. 24%, P = 0.050) and a trend toward OS benefit (66% vs. 62%, P = 0.069)(4).

4. Clinical Applications of Radiotherapy in BTCs

About 70%–80% of BTC patients are unresectable at diagnosis, with 5-year OS of only 5%–19%. Even after R0 resection, recurrence exceeds 50%, with 5-year OS 27%–37%. Radiotherapy plays an increasingly central role.

4.1 Postoperative Adjuvant Radiotherapy

Local recurrence after resection is 41%–52%. Positive margins (R1) and lymph node metastasis are independent prognostic factors. Adjuvant radiotherapy eradicates subclinical lesions and reduces recurrence.

The SWOG S0809 trial confirmed that adjuvant gemcitabine/capecitabine followed by chemoradiotherapy achieved mOS of 34–35 months for both R0 and R1 patients(5). For iCCA with vascular adhesion, postoperative IMRT (50–60 Gy) prolonged mOS (21.8 vs. 15.0 months) without increased toxicity(6). CSCO, NCCN and ESMO guidelines recommend adjuvant chemoradiotherapy for high-risk patients(7). Standard dose: 1.8–2.0 Gy/fraction, 45.0–50.4 Gy to lymph nodes, 54–60 Gy to tumor bed. Child-Pugh C patients are contraindicated; Child-Pugh B needs 10%–20% dose reduction.

4.2 Preoperative Neoadjuvant/Conversion Radiotherapy

Neoadjuvant radiotherapy aims to downstage tumors and improve R0 resection rate. Conversion radiotherapy aims to render unresectable tumors resectable. Both use concurrent chemoradiotherapy.

Studies showed neoadjuvant chemoradiotherapy achieved 47%–51.6% R0 resection rates for initially unresectable pCCA and GBC, with prolonged mOS(8). Indications: intrahepatic lesions ≤6 cm, Child-Pugh A, ECOG ≤1. Regimens: conventional fractionation (45–50.4 Gy/25–28f) or SBRT (40 Gy/5f) with concurrent fluoropyrimidines or gemcitabine.

4.3 Definitive Radiotherapy

For unresectable locally advanced BTC without distant metastasis, definitive radiotherapy combined with systemic therapy maximizes local control. Large tumors (>5 cm) use conventional IMRT/VMAT with 45.0–50.4 Gy and boost to ≥60 Gy if OARs allow. Small localized lesions use SBRT (1–5 fractions, BED >80.5 Gy) with strong tumor-killing efficacy.

4.4 Palliative Radiotherapy

Palliative radiotherapy effectively relieves pain, obstructive jaundice, bleeding and bone metastasis pain. For obstructive jaundice/gastrointestinal bleeding: short-course hypofractionation (20 Gy/5f, 30 Gy/10f). For bone metastasis: single dose (8–10 Gy/1f) or 20 Gy/5f. For poor performance or liver dysfunction: reduced dose (20–30 Gy/10–15f)(9).Palliative radiotherapy can also provide survival benefits in metastatic BTC(10).

5. Conclusion

Modern precise radiotherapy has enabled accurate dose escalation for biliary tract cancers. Techniques such as IMRT, VMAT, SBRT, IGRT, and ART allow precise dose delivery. BED-based optimization and SIB enhance tumor control. Radiotherapy plays a key role in adjuvant, neoadjuvant, conversion, definitive, and palliative settings.

Future advances rely on multidisciplinary integration of functional imaging, artificial intelligence, and combined therapy

including immunotherapy and targeted therapy. Precise radiotherapy has become an indispensable part of comprehensive multidisciplinary care for hepatobiliary tumors.

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