08 Hepato-pancreato-biliary cancer (HPB)

Liver

Liver malignancies are either primary or secondary liver cancers. Primary liver cancer comprises hepatocellular carcinoma (HCC) and biliary tract cancers, which include intrahepatic cholangiocarcinoma (IHC).

Primary liver cancer

The incidence of primary liver cancer in the UK is estimated at 6,200 new cases per year and is projected to rise by 38% by 2035. It is currently the eighth most common cause of cancer death in the UK (2017–2019).[1]

Optimal treatment of primary liver cancers relies on a multidisciplinary approach, taking into account disease stage, liver function, medical co-morbidities (particularly presence of liver cirrhosis) and patient fitness. It is recommended that the treatment selection and subsequent radiation therapy delivered to patients with HCC or biliary tract cancers should only proceed following formal specialist hepatobiliary multidisciplinary team review and involve the care of a hepatologist.

The American Society for Radiation Oncology (ASTRO) has recently published a guideline on the use of external beam radiotherapy (EBRT) in the treatment of primary liver malignancies, which has been endorsed by the European Society for Therapeutic Radiation Oncology (ESTRO).[3]

Liver cancers are often treated with highly conformal EBRT delivered in hypofractionated schedules or stereotactic ablative body radiotherapy (SABR).* The ASTRO guidelines cover the definition of hypofractionation (including moderate hypofractionation and ultra-hypofractionation) and SABR.[3]

* We are applying the term SABR to include the term SBRT (stereotactic body radiotherapy). The definition of SABR and ultra-hypofractionation is as per the *ASTRO external beam radiation therapy for primary liver cancers: an ASTRO clinical practice guideline*.

Hepatocellular carcinoma

The Barcelona Clinic Liver Cancer (BCLC) group staging, prognosis and treatment guidelines were updated in 2022 and are commonly cited when making clinical decisions regarding the treatment of HCC.[4] Retrospective and prospective studies have demonstrated the safety and efficacy of EBRT (SABR and proton beam therapy [PBT]) in all BCLC stages.[5]

The European Society for Medical Oncology (ESMO) and the American Association for the Study of Liver Diseases (AASLD) have published guidance recommending EBRT as a treatment option for selected patients with HCC.[6] Furthermore, the National Comprehensive Cancer Network (NCCN) 2022 guidelines recommend the use of EBRT for liver-confined HCC.[7]

EBRT can also be considered for palliation of HCC.[3]

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Radical treatment

Hypofractionation/ultra-hypofractionation

Radiotherapy for HCC should aim for a biological equivalent dose (BED) 10 as close to 100 Gy as possible, in as few fractions as possible, while still meeting the mandatory organ-at-risk (OAR) constraints defined by SABR-C.[8,9] The fractionation schedule prescribed should be adapted depending on location in relation to the proximity to the high-risk zone and tumour size.[8] Larger tumours may be treated in 10 or 15 fractions.[8]

A phase II randomised controlled trial (RCT) provides evidence for PBT delivered in a 15-fraction regimen, with a prescription dose ranging from 67.5 Gy for peripheral tumours to 58.05 Gy for central tumours located ≤2 cm from the porta hepatis.[10] The trial included tumours with HCC (53%) and IHC histology (47%) with median tumour size of 5.7 cm. It demonstrated a 95% 2-year local control with 3.6% rate of Child-Pugh score deterioration.[10]

The NRG Oncology GI-003 RCT is comparing proton versus photon treatments utilising the same stratified fractionation schedules described above of 5 and 15 fractions (NCT03186898) to determine if the treatment of HCC with protons compared with photons has an effect on overall survival.[10]

Stereotactic ablative body radiotherapy (SABR)

SABR is recommended for the treatment of HCC (histological or radiological diagnosis) in those unsuitable for surgery, transplant or transarterial chemoembolisation (TACE) or in those who have become refractory to TACE. Such patients should have a Child-Pugh score of A, have fewer than 5 discrete lesions and have no single lesion greater than 6 cm.[9,11,12]

The SABR Consortium Guidelines have utilised these inclusion and exclusion criteria with a recommended dose based on a risk-adapted approach dependent on the mean liver dose (MLD) delivered to liver-GTV structure.[13]

Preoperative and adjuvant radiotherapy

In HCC with macrovascular invasion (MVI) randomised phase III trials have demonstrated that EBRT improved survival when given pre-operatively compared with surgery alone and in conjunction with TACE compared with sorafenib alone.[14,15]

SABR has been shown to be a safe and effective option as a bridge to liver transplantation[16] (Grade C).

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Recommendations

Definitive radiation for HCC

SABR:

For selected patients with Child-Pugh A, solitary tumour only with maximum tumour diameter <5 cm and which meets OAR constraint for 3 fractions. This schedule is not recommended for treating more than one tumour region.

• 45 Gy in 3 fractions (Grade B)

For all other patients having SABR:

• 30–50 Gy in 5 fractions (Grade B)

Hypofractionation:

• 45–67.5 Gy in 15 fractions (Grade B)
• 40–60 Gy in 10 fractions (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[2]

Biliary tract cancer (BTC)

The survival rates of IHC remain poor with observed 1-, 3- and 5-year survival of 36.3%, 12.8% and 8.1% respectively.[17] Surgery remains the only potential curative treatment option. In those suitable, surgery combined with chemoradiotherapy, radiotherapy or chemotherapy is associated with a reduced risk of mortality compared with those having non-surgical interventions alone.[17]

Radical radiotherapy

Conventional fractionation

Unresectable biliary tract cancers (excluding gallbladder cancer) may be treated with conventional fractionation of 50.4 Gy in 28 fractions with concurrent fluoropyrimidine.

Hypofractionation

In unresectable biliary tract cancers (excluding gallbladder cancer) hypofractionation with photon radiotherapy is an acceptable option for intrahepatic tumours, but such cases should only be treated at centres with experience.

The 15-fraction schedule has been used in the completed ABC 07 study with interim evidence of safety for this dose fractionation regime.

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Stereotactic ablative body radiotherapy (SABR)

Unresectable BTC can be treated with SABR to a dose of 50 Gy in 5 fractions (as per the ABC 07 study) in experienced centres.

Recommendations

Unresectable disease (BTC excluding gallbladder cancer)

Conventional fractionation:

• 50.4 Gy in 28 fractions with concurrent fluropyrimidine (Grade B)

Hypofractionation:

• 45–67.5 Gy in 15 fractions (Grade C)

SABR:

• 40–50 Gy in 5 fractions (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[2]

Preoperative radiotherapy

Hypofractionation

Preoperative chemoradiation, including with PBT, prior to liver transplantation improves survival.[18–20] The use of PBT enables optimal dose delivery while sparing the dose to the diseased background liver.[10]

Preoperative PBT for neoadjuvant treatment prior to orthotopic liver transplantation (OLT) is indicated in selected patients with IHC on a background of primary sclerosing cholangitis. The criteria have been defined as histological proof of hilar cholangiocarcinoma, less than 3 cm in size and with no evidence of metastases to the retroperitoneal lymph nodes or other sites. PBT is delivered at a dose of 67.5 Gy (RBE=1.1) to the primary tumour region and 45 Gy (RBE=1.1) to the elective nodal region in 15 fractions.

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Recommendations

Preoperative radiotherapy prior to OLT

Conventional fractionation:

- 45 Gy in 25 fractions concurrent with fluoropyrimidine followed by intraluminal brachytherapy boost 10–16 Gy to tumour (Grade C)

Hypofractionation:

- PBT: 45–67.5 Gy in 15 fractions (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[2]

Postoperative radiotherapy

Conventional fractionation

Postoperative EBRT using conventional intensity-modulated radiation therapy (IMRT) with concurrent fluoropyrimidine is an option for resected extrahepatic cholangiocarcinoma and gallbladder cancer.[21] Target volumes should cover the draining regional lymph nodes: porta hepatis, coeliac, superior mesenteric, gastrohepatic and para-aortic with 45 Gy in 1.8 Gy/fraction and the tumour bed, depending on margin positivity, with 50–60 Gy in 1.8–2 Gy/fraction as per SWOG S0809. SWOG S0809 reported a 2-year survival of 65% (95% CI, 53% to 74%) for patients undergoing postoperative radiotherapy with concurrent chemotherapy.[21]

Recommendation

Adjuvant radiotherapy following surgical resection

Conventional fractionation:

- 45 Gy in 1.8 Gy/fraction to the nodes and 50–60 Gy in 1.8–2 Gy/fraction to the tumour bed (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[2]

For details on treatment of liver oligometastases please refer to the 'Extracranial oligometastases' chapter.

Palliative treatment

Palliative radiotherapy may help alleviate the symptoms caused by the presence of primary and secondary liver cancers. It has been found to improve symptoms such as pain, abdominal discomfort and nausea and thereby improve quality of life.[22,23] Patients with a performance

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status of 0–2 and an estimated prognosis of 3 months or more should be considered for palliative radiotherapy.

Patients may be treated with 25 Gy in 5 fractions if the V10 Gy to the normal liver is <70% and the MLD is <15 Gy. If these constraints are not met, 8 Gy in 1 fraction can be used as an appropriate palliative dose.

Recommendations

- 25 Gy in 5 fractions (Grade C)
- 30–40 Gy in 10 fractions (Grade C)
- 8 Gy in 1 fraction (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[2]

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Pancreas

Radical treatment

Standard treatment for patients with locally advanced inoperable pancreatic cancer* consists of chemotherapy, which may be followed by radiation or chemoradiation in responding or stable disease after induction chemotherapy.[1,2]

* Locally advanced inoperable pancreatic cancer includes patients who are medically unfit for surgery and/or surgically unresectable.

Conventionally fractionated radiotherapy with concurrent chemotherapy

The use of conventionally fractionated radiotherapy (50.4–54 Gy in 28–30 fractions) with concurrent chemotherapy following induction chemotherapy has been investigated and has not been shown to improve overall survival (OS) compared with chemotherapy alone[1,2] (Level 1b).

In the LAP07 trial, 54 Gy in 30 fractions was used with concurrent capecitabine following 4 months of gemcitabine chemotherapy with or without erlotinib. While median OS did not improve with the addition of chemoradiotherapy (CRT) (16.5 versus 15.2 months; p=0.08), chemoradiotherapy was associated with reduced rates of local progression (32% versus 46%; p=0.03) and a trend towards improved progression-free survival (PFS)[2] (hazard ratio [HR], 0.78; p=0.06) (Level 1b).

In the SCALOP-2 trial, dose escalation from 50.4 Gy in 28 fractions to 60 Gy in 30 fractions combined with capecitabine was evaluated. There was no improvement in median OS (15.6 versus 16.9 months). However, 1-year local progression (no metastasis) was reduced (26.7% to 15.2%) and 1-year local progression (with or without metastasis) was reduced (33.3% to 23.9%).[3] There was no significant added toxicity of the 60 Gy regimen compared with the 50.4 Gy regimen (Level 1b).

Hypofractionated radiotherapy with concurrent chemotherapy

Since the COVID-19 pandemic, a hypofractionated regimen of 45 Gy in 15 fractions has been used with concurrent capecitabine.[4] This dose and fractionation was based on published data (predominantly retrospective US experience) where this dose had been used within dose-escalated regimens of up to 67.5 Gy, delivered using a simultaneous integrated boost (SIB) approach. A dose of 45 Gy in 15 fractions was recommended in COVID-19 guidance[4] because the biological equivalent dose (BED) 10 of this dose was comparable to the standard 50.4 Gy in 28 fractions regimen used in the UK (Level 2b).

Dose escalation with a SIB up to 67.5 Gy in 15 fractions is not recommended outside of a clinical trial or study with robust quality-assured image guidance.[5,6]

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Recommendations

Conventionally fractionated or hypofractionated radiotherapy with concomitant chemotherapy following induction chemotherapy:

- 50.4 Gy in 28 fractions over 5.5 weeks (Grade B)
- 54–60 Gy in 30 fractions over 6 weeks (Grade B)
- 45 Gy in 15 fractions over 3 weeks (Grade C)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[7]

Stereotactic ablative body radiotherapy (SABR)

Patients with locally advanced non-metastatic pancreatic cancer (LANMPC) may be eligible for SABR if no progression after initial systemic treatment has been seen or they are part of clinical trials.[8–11]

Initial trials demonstrated the safety and efficacy of delivering doses of 33–35 Gy in 5 fractions,[12] and the safety of increasing dose to 40 Gy in 5 fractions has been demonstrated in prospective clinical trials[13] (Level 2b).

SABR was compared with conventional fractionation in the CRiSP (conventionally fractionated radiation therapy versus stereotactic body radiation therapy for locally advanced pancreatic cancer) meta-analysis.[14] The meta-analysis reported an estimate for 2-year OS of 26.9% for SABR versus 13.7% for conventionally fractionated radiotherapy (CFRT). The estimate for acute grade 3/4 toxicity was 5.6% for SABR versus 37.7% for CFRT. Petrelli *et al*[15] performed a systematic review and pooled analysis of 19 trials in SABR for locally advanced pancreatic cancer (LAPC), where the range of doses delivered was 18–50 Gy in 1–8 fractions. The median OS was 17 months (Level 2a).

Recommendation

SABR following induction chemotherapy:

- 33–40 Gy in 5 fractions delivered daily (with a minimum 16–18 hours gap) or on alternate days over 2 weeks
- Treatment gaps should be kept to ≤4 days (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[7]

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Preoperative chemoradiotherapy

Preoperative radiotherapy was investigated during the PREOPANC study,[16] where a dose of 36 Gy in 15 fractions was used in combination with full-dose gemcitabine. There was improvement in median OS (15.7 months versus 14.3 months), but the 5-year OS rate was 20.5% with neoadjuvant chemoradiation and 6.5% with upfront surgery, and this was consistent across the prespecified subgroups, including resectable and borderline resectable pancreatic cancer. In addition, R0 resection was achieved in 72% in the neoadjuvant chemoradiotherapy group compared with 43% in the upfront surgery group (p<0.001) (Level 1b). The predefined subgroup of patients with suspected resectable pancreatic ductal adenocarcinoma (PDAC) showed no significant difference in OS, disease-free survival (DFS), locoregional failure-free interval (LFFI) and distant metastases-free survival (DMFI). The predefined subgroup of patients with suspected borderline resectable PDAC showed a significantly improved OS, DFS and LFFI for preoperative chemoradiotherapy.

The more recent PreopPanc 2 trial[17] comparing neoadjuvant Folfirinox versus gemcitabine and gemcitabine concurrent chemoradiation has demonstrated no difference in clinical outcomes. Median OS was 21.9% versus 21.3%, respectively (hazard ratio 0.87; 95% confidence interval [CI] 0.68–1.12; p=0.28). Resection rates (77% versus 75%, respectively; p=0.7). The serious adverse rates (49% versus 43%, respectively; p=0.26) were similar between treatment arms.

The CONKO-007 trial studied the role of sequential chemotherapy and chemoradiotherapy for patients with initially unresectable disease. Patients received induction chemotherapy for 3 months (gemcitabine or FOLFIRINOX), then were randomised to continuing chemotherapy or chemoradiation (50.4 Gy in 28 fractions with concurrent gemcitabine). Median PFS (HR 0.919, p=0.540) and OS (HR 0.964, p=0.766) did not differ significantly in both arms. However, PFS rate was higher in the CRT arm after 2 years. OS rates for circumferential resection margin (CRM) negative R0 surgery at 87.5% (1 year) and 67.2% (2 years) were significantly higher (p<0.01) than for CRM plus R0 surgery at 66.7% (1 year) and 41.2% (2 years), as well as for patients without or with incomplete surgery at 68.5% (1 year) and 26.4% (2 years).[18]

A retrospective multicentre study (AEGO group), which included patients with both borderline resectable pancreatic cancer and LAPC, suggested a signal for improved outcomes with the addition of consolidation of chemoradiation prior to surgery after induction FOLFIRINOX, particularly in those with borderline resectable disease. In those with borderline resectable pancreatic cancer, DFS was improved (23.9 versus 16.6 months, p=0.01) and there was a trend to improved OS (not reached versus 28.7 months, p=0.09) after preoperative CRT. The median dose given was 50 Gy (range 49–54 Gy) in 1.8–2 Gy per fraction and was given predominantly with concurrent capecitabine.[19]

The ESPAC-5F prospective study randomised patients with borderline resectable disease to either immediate surgery or neoadjuvant therapy (2 cycles of GEMCAP, 4 cycles of neoadjuvant FOLFIRINOX or chemoradiation with 50.4 Gy in 28 fractions with concurrent capecitabine). The resection rate was the same in each arm (62% for immediate surgery and 55% for neoadjuvant therapy, p=0.668) and the R0 resection rate was 15% and 23% respectively. However, the 1-year survival rate was higher in those who received neoadjuvant therapy: 40% for immediate surgery and 77% for neoadjuvant therapy (HR=0.27, 95% CI 0.13–0.55).[20]

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Recommendations

Preoperative chemoradiotherapy (should be considered as a treatment option, particularly in borderline resectable pancreatic cancer):

- 36 Gy in 15 fractions over 3 weeks (Grade A)
- 50.4 Gy in 28 fractions over 5.5 weeks (Grade B)
- 54 Gy in 30 fractions over 6 weeks (Grade B)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[7]

Adjuvant chemoradiotherapy

Adjuvant radiotherapy may be considered in selected cases following multidisciplinary team discussion for patients with high-risk features on postoperative histology, following a complete course of adjuvant chemotherapy. Radiotherapy is delivered with concurrent fluoropyrimidine or gemcitabine chemotherapy. Doses of 50.4 Gy in 28 fractions have been used in this situation.[21–25]

Recommendation

Adjuvant chemoradiotherapy, following adjuvant chemotherapy:

- 50.4 Gy in 28 fractions over 5.5 weeks (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[7]

Palliative treatment

Palliative radiotherapy can be considered for relief of pain or for haemostasis.

There is little evidence available to inform dose and fractionation, so regimen should be selected on an individual patient basis.

Recommendations

Palliative radiotherapy:

- 30–36 Gy in 10–12 fractions over 2 weeks (Grade D)
- 20–25 Gy in 5 fractions over 1 week (Grade D)
- 8–10 Gy in 1 fraction (Grade D)

The types of evidence and the grading of recommendations used within this review are based on those proposed by the Oxford Centre for Evidence-Based Medicine.[7]

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