Radiotherapy in management of pancreatic, hepatic & biliary tract tumors

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Problems

- RT is uncommonly done in these diseases, hence even more uncommonly discussed
- Lack of awareness of the role of RT in hepato-biliary tumors
- Lack of technology to safely deliver RT in hepato-biliary tumors
- Lack of randomised data

Carcinoma Pancreas: Where does RT fit?

- Adjuvant RT +/- CT
- Neo-adjuvant RT + CT
- Palliative RT
- Intra-operative RT

Adjuvant RT for completely resected Ca pancreas

- The data is confusing!
- 4 main RCTs
- Still no consensus on whether RT +/- CT is a standard component of adjuvant therapy for Ca pancreas.

- Options are : (1) Adjuvant chemotherapy alone (GEM-based)

  (2) Adjuvant CT-RT (FU/GEM-based)

  (3) Adjuvant CT-RT + adjuvant chemotherapy

GITSG trial

- N=46 (completely resected with microscopically negative margins)
- Observation vs FU-based CT-RT
- RT was split course (20 Gy/10#→2 week gap→20Gy/10#)
- Interim analysis itself showed striking survival advantage for adjuvant CT-RT.
- Median survival for obs vs adj were 10.9 months vs 21 months (p=0.03)

Arch Surg 1985;120(8):899-903.

EORTC 40891

- N=218 (curatively resected head/periampullary tumors)
- Observation vs FU-based CT-RT
- RT was again split course, total dose 40Gy/20#
- Non-significant trend towards improved median survival with adjuvant therapy seen in carcinoma head of pancreas patients (17.1 months vs 12.6 months)

Ann Surg 1999;230(6):776-782; discussion 82-84.

ESPAC-1

- N=289 (completely resected)
- 4 arms: (1) Observation (2) Chemotherapy alone (FU) (3) CT-RT (4) CT-RT followed by chemotherapy alone
- No statistically significant difference in survival between the 4 arms.
- Chemotherapy vs no chemotherapy→ statistically significant median survival advantage (20.6 months vs 15.5 months, p=0.009)
- Chemoradiation vs no chemoradiation→ statiscally significant median survival DISADVANTAGE (15.9 months vs 17.9 months, p=0.05)

Lancet 2001;358(9293):1576-1585.

RTOG 9704

- N=538 (carcinoma pancreas)
- FU-based CT-RT vs GEM-based CT-RT
- No statistically significant survival difference between the 2 arms, possibly due to protocol non-compliance.
- In subset analysis of carcinoma head of pancreas patients, GEM-based CT-RT showed significant median survival advantage (20.6 months vs 15.9 months, p=0.033)

Ann Surg Oncol. 2011 May;18(5):1319-26. Epub 2011 Mar 10.

Why adjuvant Gem?
CONKO-001

- N=386 (curatively resected)
- Observation vs 6 cycles of GEM (4-weekly regime)
- No statistically significant difference in median overall survival
- Statistically significant difference in median disease-free survival for GEM vs Obs (13.9 months vs 6.9 months, $p<0.01$)

JAMA 2007;297:267.

Optimum adjuvant protocol: NCCN guideline 2011

- Postoperative imaging studies + serum CA 19-9 level (to ensure no biochemical or radiographic evidence of persistent disease)→

6 months of 5-FU or gemcitabine as systemic therapy OR
5-FU-based chemoradiation

- Gemcitabine +RT as a component of adjuvant therapy is still non-standard & cannot be endorsed.
- Capecitabine has similar efficacy to intravenously administered 5-FU, and is an appropriate substitute.

Adjuvant RT dose & techniques

- Dose= 50 to 60 Gy @ 1.8-2 Gy/#
- Hypofractionated protocols are also well-tolerated (57Gy/25#)
- Conformal techniques are essential
- Highly conformal techniques like IMRT and stereotactic radiotherapy are also possible & allow dose-escalation.
- Image guidance is a must for more conformal therapies

RTOG contouring guidelines for adjuvant RT for pancreas

CTV must include:

1. Post-operative bed
   - Based on location of initial tumor from pre-operative imaging and pathology reports
2. Anastomoses
   - Pancreaticojejunostomy(PJ)
   - Choledochal or hepaticojunostomy
3. Abdominal nodal regions
   - Peripancreatic
   - Celiac
   - Superior mesenteric
   - Porta hepatis
   - Para-aortic

Neo-adjuvant CT-RT

- Rational approach in borderline resectable and locally advanced/ unresectable settings.
- Locally advanced→>180-degree arterial invasion OR occlusion of the SMV/PV system WITHOUT gross disease outside the pancreatic primary.
- However, there is a lack of strong survival advantage data.

CT-RT vs RT for advanced pancreatic cancer: 2 RCTs

Mayo Clinic:

- N=64
- FU-RT vs placebo-RT
- Median survival significantly better in CT-RT arm (10.4 vs 6.3 months)

Lancet 1969;2(7626):865-867.

GITSG:

- N=194
- 3 arms: RT alone (60Gy) vs CT-RT (40Gy) vs CT-RT (60 Gy)
- Significantly improved TTP & OS with CT-RT
- No significant difference between high- & low-dose CT-RT arms

Cancer 1981;48(8):1705-1710.

CT-RT vs CT for advanced pancreatic cancer: 4 RCTs

ECOG:

- FU vs FU-RT (40Gy)
- No median survival difference between the 2 arms

J Clin Oncol 1985;3(3):373-78.

GITSG:

- SMF vs SMF-RT (54Gy)
- Significant improvement in median survival for CT-RT arm (9.4 vs 7.4 months)

J Natl Cancer Inst 1988;80(10):751-755.

FFCD-SSRO :

- GEM alone vs
- CDDP+FU+RT (60Gy)→GEM
- Unusually low median survival in the CT-RT arm (8.4 months)
- Unusually high median survival in the GEM-alone arm (14.3 months)
- Poor compliance due to inclusion of CDDP, high dose of RT, inclusion of nodal volumes→ protocol violations in the CT-RT arm.

ECOG 4201:

- GEM-RT (50.4 Gy) followed by weekly GEM vs GEM alone
- Closed early due to poor accrual

J Clin Oncol 2006;24(18S):4008.

Role of biologic therapy: NCICTG trial

- N= (advanced pancreatic cancer)
- 2 arms: (1) Gemcitabine alone at 1,000 mg/m^2 weekly for 7 weeks, then 1 week off, followed by gemcitabine days 1, 8, 15, every 28 days

  (2) Gemcitabine + erlotinib at a dose of 100 to 150 mg orally daily.
- Overall survival was improved for the gemcitabine + erlotinib arm compared with patients receiving gemcitabine alone (191 vs. 177 days, respectively; hazard ratio for death 0.82; P <.02).

- First trial to demonstrate a very small, but statistically significant survival advantage for a gemcitabine-doublet over gemcitabine alone.
- First trial to show improved survival by integrating a targeted agent into standard therapy for advanced pancreatic cancer.

J Clin Oncol 2007;25:1960.

Optimum protocol for locally advanced disease

- Gemcitabine-based chemotherapy for 2 to 4 months →consolidation with chemoradiation (FU/Capecitabine + 50-50.4 Gy) in patients who do not have rapidly progressive distant disease.
- If patients are responding to chemotherapy (objective radiographic response/ CA 19-9 level decline) after 2 months and tolerating therapy well→ continue for 2 more months.
- If radiographic local progression/CA 19-9 level plateau or increase/local symptomatic progression/ chemotherapy is poorly tolerated,→ Chemoradiation .
- If distant progression during chemotherapy→ 2-week course 30 Gy of 5-FU or capecitabine-based chemoradiation ONLY in patients with symptomatic primary tumors.

Long-term results of full-dose gemcitabine with radiation therapy compared to 5-fluorouracil with radiation therapy for locally advanced pancreas cancer ☆

Jiayi Huang [a], John M. Robertson [a,*], Jeffrey Margolis [b], Savitha Balaraman [b], Gary Gustafson [c], Prem Khilanani [d], Laura Nadeau [b], Robert Jury [e], Bruce McIntosh [f]

Methods: From January 1998 to December 2008, 93 patients with LAPC were treated either with 5FURT ($n = 38$) or GemRT ($n = 55$). 5FURT consisted of standard-field radiotherapy given concurrently with infusional 5-FU or capecitabine. GemRT consisted of involved-field radiotherapy given concurrently with full-dose gemcitabine (1000 mg/m^2 weekly) with or without erlotinib. The follow-up time was calculated from the time of diagnosis to the date of death or last contact.

Results: Patient characteristics were not significantly different between treatment groups. The overall survival (OS) was significantly better for GemRT compared to 5FURT (median 12.5 months versus 10.2 months; 51% versus 34% at 1 year; 12% versus 0% at 3 years; 7% versus 0% at 5 years, respectively; all $P = 0.04$). The OS benefit of GemRT was maintained on subset analysis without concurrent erlotinib or with sequential gemcitabine (all $P < 0.05$). The rates of distant metastasis, subsequent hospitalization, acute and late grade 3–5 gastrointestinal toxicities were not significantly different between the GemRT and 5FURT groups.

Conclusions: GemRT was associated with an improved OS compared to standard 5FURT. This approach yielded long-term survivors and was not associated with increased hospitalization or severe gastrointestinal toxicity.

Radiotherapy and Oncology 99 (2011) 114–119

CONCURRENT CHEMORADIOTHERAPY TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER: GEMCITABINE VERSUS 5-FLUOROURACIL, A RANDOMIZED CONTROLLED STUDY

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Conclusion: GEM CCRT appears more effective than 5-FU CCRT for locally advanced pancreatic cancer and has comparable tolerability.

Int. J. Radiation Oncology Biol. Phys., Vol. 57, No. 1, pp. 98–104, 2003

NACT-RT in operable Ca pancreas: SFRO-FFCD 9704:

- N=41. Phase II trial
- Operable pancreatic cancer
- Treated by neo-adjuvant RT 50 Gy with conc CDDP-5FU→ curative surgery
- 27/40 patients received the full protocol
- 26/41 patients could be operated, of whom 80% had R0 resection.
- HP revealed major pathologic response in 50% of resected specimens.
- Local recurrence rate= 4%
- 2-yr survival rate=32%

Int. J. Radiation Oncology Biol. Phys., Vol. 65, No. 5, pp. 1471–1478, 2006

Annals of Oncology 20: 1387–1396, 2009

Adjuvant OR Neo-adjuvant for operable Ca pancreas

Results: Using Kaplan-Meier analysis we found that the median overall survival of patients receiving neoadjuvant RT was 23 months vs. 12 months with no RT and 17 months with adjuvant RT. Using Cox regression and controlling for independent covariates (age, sex, stage, grade, and year of diagnosis), we found that neoadjuvant RT results in significantly higher rates of survival than other treatments (hazard ratio [HR], 0.55; 95% confidence interval, 0.38–0.79; $p = 0.001$). Specifically comparing adjuvant with neoadjuvant RT, we found a significantly lower HR for death in patients receiving neoadjuvant RT rather than adjuvant RT (HR, 0.63; 95% confidence interval, 0.45–0.90; $p = 0.03$).

NEOADJUVANT RADIATION IS ASSOCIATED WITH IMPROVED SURVIVAL IN PATIENTS WITH RESECTABLE PANCREATIC CANCER: AN ANALYSIS OF DATA FROM THE SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) REGISTRY

Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 4, pp. 1128–1133, 2008

Intra-operative Radiotherapy

- Rational strategy in unresectable/ borderline resectable cases.
- Best results with pre-op EBRT + IORT> post-op EBRT alone OR IORT alone.

Intra-operative radiotherapy (IORT) in pancreatic cancer: Joint analysis of the ISIORT-Europe experience

Results: From 1985 to 2006, a total of 270 patients were enrolled in the study from five European Institutions. Surgery was performed in 91.5% of cases and complicated by adverse events in 59 cases. External radiotherapy (ERT) preceded surgery in 23.9% of cases. One-hundred and six patients received further ERT. After surgery + IORT, median follow-up was 96 months (range 3–180). Median local control was 15 months, 5-year local control was 23.3%. Median overall survival was 19 months, while 5-year survival was 17.7%. A significantly greater local control and survival were observed in patients undergoing preoperative radiotherapy (LC: median not reached; OS: median 30 months) compared to patients treated with postoperative ERT alone (LC: median 28 months; OS: median 22 months), and to patients submitted to IORT exclusively (LC: median 8 months; OS: median 13 months) ($p < 0.0001$).

Radiotherapy and Oncology 91 (2009) 54–59

Carcinoma Biliary Tree

- Few trials, compared to pancreatic cancer
- Most trials include both cholangiocarcinoma & carcinoma gall bladder
- Adjuvant and neo-adjuvant protocols are similar to that of Ca pancreas (except that Gemcitabine alone has less of a role in standard therapy)
- Encouraging results with IG-IMRT and SBRT in recent years.

SEER Database
Adjuvant RT for Extrahepatic Cholangiocarcinoma

- 1988-2003 (4758 patients): Significant difference in overall survival between Surgery +RT vs Surgery alone ($p<0.001$) & between RT/Surgery/both vs none ($p<0.001$)

Int. J. Radiation Oncology Biol. Phys., Vol. 74, No. 4, pp. 1191–1198, 2009

- 1973-2003 (2323 patients): Adjuvant RT is not associated with any improvement in OS/DFS.

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 1, pp. 189–198, 2011

Todoroki et al

- N=63 (cholangiocarcinoma)
- 49 patients had curative resection, of which 29 patients received adjuvant RT.
- IORT + p/o EBRT (n=17) vs p/o EBRT alone (n=6) vs IORT alone (n=6)
- 5-yr survival rates were 39.2% vs 0% vs 16.7%.
- Statistically significant improvement in 5-yr survival rates for IORT+EBRT vs resection alone (39.2% vs 13.5%)

Int J Radiat Oncol Biol Phys 2000;46:581.

Ben-David et al

- N=28 (biliary malignancies)
- Adjuvant RT (54Gy median dose) +/-CT (54% cases).
- Significant survival differences between patients with R0 and R1 resections (24.1 vs 15 months) but NOT between those with R1 and R2 resections.

Int J Radiat Oncol Biol Phys 2006;66:772.

ADJUVANT EXTERNAL-BEAM RADIOTHERAPY WITH CONCURRENT CHEMOTHERAPY AFTER RESECTION OF PRIMARY GALLBLADDER CARCINOMA: A 23-YEAR EXPERIENCE

Methods and Materials: Twenty-two patients with primary and nonmetastatic gallbladder cancer were treated with radiation therapy after surgical resection. Median radiation dose was 45 Gy. Eighteen patients received concurrent 5-fluorouracil (5-FU) chemotherapy. Median follow-up was 1.7 years in all patients and 3.9 years in survivors.

Results: The 5-year actuarial overall survival, disease-free survival, metastases-free survival, and local-regional control of all 22 patients were 37%, 33%, 36%, and 59%, respectively. Median survival for all patients was 1.9 years.

Conclusion: Our series suggests that an approach of radical resection followed by external-beam radiation therapy with radiosensitizing 5-FU in patients with locally advanced, nonmetastatic carcinoma of the gallbladder may improve survival. This regimen should be considered in patients with resectable gallbladder carcinoma.

Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 4, pp. 1030–1034, 2005

Chemotherapy alone as adjuvant therapy: 1 RCT

Takada et al:

- N=508 (resected biliary tract & pancreas tumors)
- MMC-5FU vs Obs
- No significant difference in survival across all sites
- Better survival with chemo for Ca GB, on subset analysis

Cancer 2002;95:1685

Chemotherapy alone for advanced biliary tract cancers: 1 RCT

ABC-02 trial:

- N=410
- Locally advanced non-metastatic cholangioca, ampullary ca, gall bladder ca
- CDDP + GEM (3-weekly) x 8 cycles vs GEM (4-weekly) x 6 cycles
- Significant median overall survival benefit in doublet arm (11.7 vs 8.1 months, p<0.001)
- Doublet is also well-tolerated, with only neutropenia-associated infections being significantly more compared to the single-drug arm.
- The CDDP-GEM doublet has now become a standard of care for adjuvant therapy in biliary tree cancers.

N Engl J Med 2010;362:1273-81.

Other agents for unresectable disease

Multicentre phase I–II trial of capecitabine and oxaliplatin in combination with radiotherapy for unresectable pancreatic and biliary tract cancer: The CORGI-U study

Radiotherapy and Oncology 95 (2010) 292–297

Background and Purpose: In this multicentre phase I–II trial we evaluated the feasibility and efficacy of capecitabine and oxaliplatin followed by the combination of these two drugs with radiotherapy in patients with locally advanced pancreatic or biliary tract cancer.

Material and methods: Thirty-nine patients with inextirpable adenocarcinoma of the pancreas, gallbladder or extrahepatic bile ducts were included. Two cycles of XELOX (capecitabine 1000 mg/m^2 bid d1–14 + oxaliplatin 130 mg/m^2 d1, q3w) were followed by XELOX-RT (radiotherapy (50.4 Gy), combined with capecitabine 750–675 mg/m^2 bid every radiotherapy day and oxaliplatin 40–30 mg/m^2 once weekly). Primary end-points were tolerance (phase I) and objective response (phase II).

Results: The maximum tolerated doses of oxaliplatin and capecitabine to combine with irradiation were 30 mg/m^2 and 675 mg/m^2, respectively. Twenty-one percent (95% CI: 9–38%) of evaluable patients achieved partial response. Five patients went through surgery (three R0 resections). Two-year survival was 28%, and estimated local tumour control rate at 2 years was 72%. The most common grade 3–4 toxicity was nausea and vomiting.

Conclusions: XELOX-RT (30 mg/m^2 oxaliplatin/675 mg/m^2 capecitabine in combination with 50.4 Gy/28 fractions) was well tolerated and effective for locally advanced pancreatic and biliary tract cancer.

IMRT for pancreatico-biliary cancers

INTENSITY-MODULATED RADIOTHERAPY IN TREATMENT OF PANCREATIC AND BILE DUCT MALIGNANCIES: TOXICITY AND CLINICAL OUTCOME

Methods and Materials: Twenty-five patients with pancreatic and bile duct cancer were treated with IMRT. Twenty-three received concurrent 5-fluoruracil. One patient with a pancreatic primitive neuroectodermal tumor received concurrent etoposide and ifosfamide. Eight patients had resected tumors, and 17 had unresectable primary (n = 14) or recurrent (n = 3) tumors. Six patients underwent treatment planning with conventional three-dimensional four-field techniques for dosimetric comparison with IMRT.

Results: Compared with conventional RT, IMRT reduced the mean dose to the liver, kidneys, stomach, and small bowel. IMRT was well tolerated, with 80% experiencing Grade 2 or less acute upper GI toxicity. At a median follow-up of 10.2 months, no resected patients had local failure, and only 1 of 10 assessable patients with unresectable cancer had local progression. The median survival and distant metastasis-free survival of the 24 patients with adenocarcinoma was 13.4 and 7.3 months, respectively. Grade 4 late liver toxicity occurred in 1 patient surviving >5 years. The remainder of the assessable patients experienced no (n = 9) or Grade 1 (n = 4) late toxicity.

Int. J. Radiation Oncology Biol. Phys., Vol. 59, No. 2, pp. 445–453, 2004

Hepatocellular carcinoma

- Radiotherapy is an option in a number of different situations, but not the 1st choice.

- Radiotherapy for HCC is a complex issue due to:

(1) Respiratory motion

(2) Tolerance of surrounding normal GI tract

(3) Tolerance of liver itself, especially in the background of cirrhosis

- Any intervention in HCC has to consider not just the tumor size and stage, but also the Liver Function status.
- Earlier indices, like the Child-Pugh score, are still useful guides for deciding on/ against surgical intervetions.
- More global scores, such as the BCLC, are more useful, as they integrate the stage and the liver function, and can be directly used to determine prognosis & management

Child-Pugh Score

Measure	1 point	2 points	3 points
Total bilirubin, µmol/l (mg/dl)	<34 (<2)	34-50 (2-3)	>50 (>3)
Serum albumin, g/l	>3.5	2.8-3.5	<2.8
PT INR	<1.7	1.71-2.20	> 2.20
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Indications of RT in HCC

(1) As bridge to transplant (localised ds, CPS A/B)

(2) In patients refractory to TACE/RFA (localised/advanced ds, CPS A/B)

(3) In patients unsuitable for resection/transplant/RFA (localised/advanced ds, CPS A/B)

(4) In patients with portal invasion (advanced ds, CPS A/B)

(5) Palliative for symptom relief (metastatic ds OR CPS C)

Where is Radical RT possible?

- <3 lesions
- <6cm maximum size
- Normal LFTs (CPS A/B)
- No extrahepatic disease
- >2cm from GI tract
- >700cc of normal liver possible to be spared

Treatment of HBV/HCV

- Treatment of the underlying viral infection is often ignored, but is intimately related to both liver function and survival
- Most (70-80%) of HCC in Asia is due to HBV infection, while in the West, the commonest cause of HCC is HCV infection (5-20%)
- Referral to a gastroenterologist/hepatologist should be compulsory in all cases of HCC

Trans Arterial Radio Embolisation (TARE)

- Y^{90} microsphere commonly used
- Other radioisotopes used are I^{131},Re^{188},Ho^{166}
- TARE>TACE (longer TTP, lesser toxicity) but equivalent in survival

  Gastroenterology 140:497-507 e2, 2011
- 2 phase 3 RCTs of TARE in liver mets from CRC have shown TARE+Chemotherapy>Chemo alone (better RR and TTP, equivalent OS)

  J Clin Oncol 28:3687-3694, 2010

Interstitial Brachytherapy (Ir^{192})

- Particularly indicated in patients unsuitable for RFA: T>10cm OR <5cm from hilum
- Contraindication: Bilirubin>2mg%
- Flexible catheters are inserted at 1-2 cm intervals percutaneously under CT guidance
- No impact of size
- Impact of dose→ CTV D100> 20.4 Gy correlates with better prognosis

Int J Radiat Oncol Biol Phys 78:479-485, 2010

- Liver mets from CRC:1-yr Local control rate with ISBT>90%

Int J Radiat Oncol Biol Phys 78:172-179, 2010

- Survival advantage over Best Supportive Care

Int J Radiat Oncol Biol Phys 78:172-179, 2010

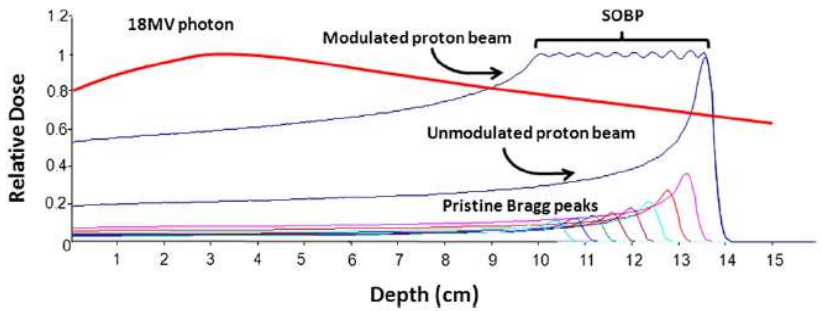
- Dosimetric advantage over SBRT: higher CTV dose with lower dose to peripheral rim of normal tissue

Charged Particle Therapy
Protons

- Protons have a dosimetric advantage due to Bragg Peak effect→ reduced dose to surrounding normal tissues (including liver) with reduced integral dose
- No radiobiologic advantage
- Range uncertainties are an issue, due to CT artefacts caused by presence of indwelling stents/ intraluminal contrast material

- Doses used 58-67CGE (hypofractionated regimen)
- Limited number of centres, expensive, data purely retrospective.
- Large series (Chiba et al; N=192):
- 5-yr local control rate= 86.9%,
- 5-yr OS rate =23.5%

Clin Cancer Res 11:3799-3805, 2005



Charged Particle Therapy
Carbon Ions

- Radiobiologic advantage over photons
- RBE=3
- OER=1.6 (photons 3-4)

- Doses used 50-80CGE (hypofractionated regimens)

- Retrospective series (Kato et al;N=24):
- 5-yr LC rate>80%
- 5-yr OS rate=25%

1. Int J Radiat Oncol Biol Phys 59:1468-1476, 2004

Dose Response relationship for HCC

The size of the portal venous thrombosis and dose (response rate 80% for BED ≥58 Gy and 22% for <58 Gy) predicted for response, whereas survival was associated with dose (1-year survival 59% and 29% for ≥58 Gy and <58 Gy, respectively) and Child-Pugh class (1-year survival 51% for A and 0% for B).

Toya R, Murakami R, Baba Y, et al: Conformal radiation therapy for portal vein tumor thrombosis of hepatocellular carcinoma. Radiother Oncol 84:266-271, 2007

Overall survival was higher for patients who received >50.4 Gy in 1.8-Gy fractions.

Liu MT, Li SH, Chu TC, et al: Three-dimensional conformal radiation therapy for unresectable hepatocellular carcinoma patients who had failed with or were unsuited for transcatheter arterial chemoembolization. Jpn J Clin Oncol 34:532-539, 2004

a biologic effective dose (BED) ≥53.1 Gy was associated with an improved 2-year overall survival (31% vs 22%).

Seong J, Lee IJ, Shim SJ, et al: A multicenter retrospective cohort study of practice patterns and clinical outcome on radiotherapy for hepatocellular carcinoma in Korea. Liver Int 29:147-152, 2009

Is there a dose response relationship for Liver Metastasis?

Results: Forty-two patients with 62 metastases were treated with two dose levels of 40 Gy in four Dose per Fraction (23) and 45 Gy in three Dose per Fraction (13). Median follow-up was 14.3 months (range, 3–23 months). Actuarial local control for 1 and 2 years was 90% and 86%, respectively. At last follow-up, 41 (66%) complete responses and eight (13%) partial responses were observed. Five lesions were stable. Nine lesions (13%) were locally progressed. Overall survival was 94% at 1 year and 48% at 2 years. The most common toxicity was Grade 1 or 2 nausea. One patient experienced Grade 3 epidermitis. The dose level did not significantly contribute to the outcome, toxicity, or survival.

Int. J. Radiation Oncology Biol. Phys., Vol. 81, No. 3, pp. e39–e47, 2011

Prognosis for liver metastases, varies on the primary (CRC vs breast/lung) & presence of extra-hepatic metastases

SBRT (for 1-3 lesions, <5-6cm size)

- Stereotactic Body Radiotherapy means precise delivery of high doses of hypofractionated radiotherapy to disease sites outside the brain.
- May use a Stereotactic Body Frame +/- abdominal compression plate, to counter setup error & respiratory motion respectively.
- However, an SBF, is neither fool-proof, nor cheap.

- Thus, SBRT often replaces the physical body frame with image-guidance for equal or even better accuracy.
- Motion management can include:

Compensating for motion:

(1) generation of ITV with static beam delivery

(2) gating

(3) tracking

Controlling/reducing motion:

(1) voluntary breath holding techniques

(2) active breathing control (ABC)

Problems in assessing the impact of SBRT

- SBRT dose schedules are extremely heterogenous
- Even the dose prescription methods are heterogenous, with the dose prescribed variously to the isocentre/ tumor periphery and prescription isodose between 60-95%.
- The lower the prescription isodose to the tumor periphery, better dose fall-off to surrounding normal tissue, but more inhomogenous dose at the centre of the tumor
- Biological modelling for the high doses per fraction typically used in SBRT, are inadequate, hence the need for vigilance

Dose constraints

Conventional RT

- Liver: 1/3 vol <50 Gy
  2/3 vol<35 Gy
  3/3 vol<30 Gy
- Kidney: 1/3 vol<50 Gy
  2/3 vol<28 Gy
  3/3 vol<23 Gy
- Stomach: 1/3 vol<60 Gy
  2/3 vol<55 Gy
  3/3 vol<50 Gy
- Spine: Max <45 Gy

SBRT

- Liver: 1/3 vol <21 Gy
  ½ vol /700cc<15 Gy
- Spine: Max<15 Gy
- Stomach: 5cc<15 Gy
- Kidney: 1/3 vol <15 Gy

For conventionally fractionated 3DCRT/IMRT, the dose constraint used is Normal Liver V30Gy<33%

Radiation Induced Liver Disease (RILD)

Classic RILD

- Occurs 2-3 months post-RT
- Associated with hepatomegaly,ascites +/- jaundice
- Due to veno-occlusive disease
- Seen in healthy livers

Non-classic RILD

- Occurs 1wk-3 months post-RT
- Seen in cirrhotic livers
- Rise of SGOT/SGPT with worsening of liver function
- Without features of classic RILD

Treatment: Once established, RILD is difficult to manage and is invariably fatal in the absence of transplant therapy.
Medical management with diuretics, etc is only symptomatic

Take Home Messages

- Despite conflicing data, adjuvant chemoradiotherapy is viable and rational for pancreatico-biliary malignancies
- GEM-based protocols are superior to 5FU-based protocols
- Neo-adjuvant chemoradiotherapy is viable for locally advanced disease
- Dose-escalation is possible for conformal techniques

Take Home Messages

- Radiotherapy has multiple indications in the setting of HCC & liver metastasis
- Imaging has a key role in diagnosis and tumor delineation of HCC
- Image-guidance is of key importance for hepato-biliary tumors, for control of respiratory motion

Thank you