PANCREATIC CANCER: NEOADJUVANT & ADJUVANT THERAPY

Timing of therapy – neoadjuvant (prior to surgery), intraoperative, or adjuvant (after surgery)
Types of therapy – chemotherapy, radiation (external beam or intraoperative), or combination of chemoradiation therapy (CRT)
Goal of these therapies – Improve resectability rate and overall outcome and a therapeutic option for definitive local therapy

- Pancreaticoduodenectomy curative in only 20% of patients that are resectable
- Only 10% of patients with either + resection margins or nodal disease are cured of their disease by surgery alone (Cameron et al. Am J Surg 1991)
- An option for unresectable tumors (extrapancreatic involvement, encasement of SMV, SMV-portal vein confluence, SMA, aorta, IVC, or celiac axis

QUESTION: *What are the benefits to the various therapies and how do they improve resectability or overall survival?*

Neoadjuvant therapy for potentially resectable pancreatic cancer
Theory – the benefit from partial shrinkage of the cancer to allow complete removal of the cancer
5FU-based Regimens
Hoffman et al. J Clin Oncol 1998
Study included 53 pts with potentially respectable pancreatic CA received external beam radiation (EBR), concurrent infusional 5FU, mitomycin, followed by resection
Results – complete resection possible in 24/41 with median survival of **10-16 months**

Staley et al. Am J Surg 1996
Study combined preop CRT with resection and IORT
Administered EBR to 39 pts
Results – local control achieved 79%, 19% of pts still alive after 4 years with median survival of 19 months. **GI toxicity seen**
Modification – in 35 pts, preop radiation given over 2 weeks with 5 FU followed by resection with IORT
Modified results – 27/35 able to undergo resection and 20 /27 resected completely with **median survival of 25 months** and **23% still alive after 3 years**

Wolff et al. Proc Am Soc Clin Oncol 2002
Study used Gemcitabine-based CRT, more toxic shown to enhance local effects
Results - 86 pts received weekly treatments with radiation, curative resection accomplished in 73%, 58% had >50% tumor necrosis in surgical specimens and **median survival was 37 months**

Summary of Neoadjuvant Therapy for Resectable Pancreatic Cancer

- Initial reports showed no worsening of perioperative morbidity and mortality
- Questionable use of a single chemotherapeutic agent
- Newer approaches still tolerable with increasing radiation doses, adding intraoperative radiation (IORT), or optimizing chemotherapy regimen
- No real improvement in resectability or overall survival

- Still the efficacy remains uncertain
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Adjuvant therapy following surgical resection

3 BIG Studies

GITSG study – Combo of EBRT with 5FU with locally advanced unresectable pancreatic cancer, followed by maintenance chemotherapy for 2 years or until disease progression

- Results showed improved survival
- Study terminated after 8 years due to poor patient accrual (43 pts available for analysis)
- Treated vs. untreated had a **median survival of 20 vs. 11 months** and a **two year survival rate (20 vs. 10%)**

EORTC study – Tried to reproduce the findings of the GITSG study

- 114 pts with respectable pancreatic cancer received either postop 5FU and radiotherapy or observation
- Postop chemotherapy did not show significant improvement in median survival or 2 year survival
- Study criticized for many reasons

ESPAC-1 trial – Randomized pts in 2x2 factorial design

- Compared adjuvant CT, CRT, CRT followed by CT, and observation
- Again poor accrual therefore published data in 2 articles and pooled the data
- CRT vs. no CRT (68 pts enrolled)
- Adjuvant chemotherapy vs. no chemotherapy (188 pts enrolled)
- 2x2 factorial design consisting of CRT(n=73) vs. chemotherapy(n=75) vs. CRT/chemotherapy(n=72) vs. observation (n=69)
- Pooled data showed no difference between pts receiving postop CRT and not receiving it **(median survival 16.1 vs. 15.5 months)**
- In contrast, 238 pts who received postop CT alone vs. 235 pts who did not receive it **median survival was 19.7 vs. 14 months**

Summary

- Multiple randomized studies still show an unclear benefit
- No studies confirm GITSG data
- Other GI cancers, survival benefit seen in gastric and rectal cancer for patients receiving adjuvant CRT and CT

Benefit of postoperative CRT in resectable pancreatic cancer

3 Uncontrolled Series showing retrospective data suggesting benefit for postoperative CRT in pancreatic cancer

Yeo et al. Ann Surg 1997

Hopkins series – Largest of the 3 series, showed 99 pts receiving EBRT with 5FU for 4 months, 21 pts received intensive therapy with EBR plus prophylactic hepatic irradiation followed by 5FU and leucovorin for 4 months, 53 pts declined post op therapy

Results – Any postoperative therapy was associated with a significantly better **median survival (20 vs. 14 months)**, however more intensive therapy was not associated with a survival advantage

Lim et al. Ann Surg 2003

Medicare series – Similar degree of benefit from adjuvant CRT derived from SEER database. 3 year survival and median survival was greater among pts getting adjuvant CRT **(29 vs. 12.5 months)**

Picozzi et al. Am J Surg 2003

Interferon + 5FU + Cisplatin study – Again showed a benefit to adjuvant therapy with concurrent radiation. At the mean follow-up of 32 months, 67% of patients were still alive and **2, 3, 5-year survival rates ranged from 64, 64 and 55% respectively. 70% had treatment related toxicity.** Confirmatory results underway.

Benefit of postoperative chemotherapy alone

Neoptolemos et al. N Eng J Med 2004

- ESPAC-1 trial suggests a benefit from 6 months of postoperative leucovorin-modulated 5FU with resectable tumors compared to those not receiving any therapy
- CT associated with a significantly longer median survival rate (23 vs. 11 months)
- Ongoing German trial comparing gemcitabine alone vs. no postop therapy

Postoperative radiation alone

Farrel et al. Ann Surg 1997

- Adjuvant EBRT after curative resection reduces local recurrence rates but does not improve overall survival
- Some studies showed benefit of IORT in conjunction with surgical resection
- IORT permits delivery of high-dose radiation directly to areas at highest risk of local recurrence, while minimizing toxicity to the tissues

Therapeutic options for definitive unresectable local therapy

J Natl Cancer Inst 1988; 80: 751

External Beam Radiation (EBRT) alone

- Resolution of cancer-related pain seen in 35-65% of patients in this study as well as improvement in cachexia and obstructive symptoms

CT + Radiation vs. Radiation alone

- Number of studies evaluated 5FU and EBRT were synergistic
- Median survival rate of 10 to 11 months
- Standard of care for locally advanced pancreatic cancer
- Unclear whether gemicitabine alone would demonstrate similar results

Gemcitabine based CRT regimens

- Extremely toxic combination for patients
- Phase II trial showed 43 pts having grade 3-4 hematologic toxicity and 34% of pts had GI toxicity (Grade 3-4)
- Favorable results over 5FU seen a small Chinese trial and showed a significant longer median survival (14.5 vs. 6.7 months)

CRT followed by IORT

- Allows high dose radiation to be delivered directly to the areas of the tumor without destruction of surrounding normal tissues
- 3 Different Studies:

- 27 pts with locally advanced disease got combined preop and postop ERBT with or without CT and IORT
- This study had a failure rate of 36% and a **2 year survival rate of 28% and median survival of 17 months**
- *RTOG study* – 51 pts got postop ERBT and 5FU and **the median survival was only 9 months**
- Last study – 49 pts gave periop CT, IORT and postop EBRT and had a **median survival of 16 months and 22% were alive at 2 years later**

Summary

- Combined treatment with radiation and CT increases median survival for pts with locally advanced cancers to approximately 10 to 13 months, but rarely increases long-term survival

Metastatic disease

Kindler et al. Proc Am Soc Clin Oncol 2003

Bruns et al. CancerRes 2000

- *Single Agent CT* mainstay of treatment for patients with mets, but see high refractory rate (?inactivating mutations that inhibit p16 protein function
- Gemcitabine – standard of care in 2004
- 5FU
- Capecitabine
- Gemcitabine vs. dose-rate infusion
- Anthracyclines
- Taxanes
- Streptozocin
- *Combination CT* have been associated with higher response rates, but NO clear survival benefit with advanced disease – multiple phase III trials failed to showed improvement in survival
- 5FU + Gemcitabine
- Gemcitabine + Capecitabine
- Gemcitabine + Cisplatin
- *Hormone Therapy* – tamoxifen, octreotide
- *Monoclonal antibodies directed against antibodies* – Bevacizumab, cetuximab

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