Pancreatic Cancer – Treatment Approaches

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Disclosures

- Consultant or Advisory Role: Celgene, Cook Medical
Introduction

- This talk highlights clinical staging and treatment approaches for ‘pancreatic adenocarcinoma’

- I have used the term ‘pancreatic cancer’ synonymously with ‘pancreatic adenocarcinoma’

- The content of this talk is not applicable to neuroendocrine cancers of the pancreas and other histologic variants

Pancreas - Anatomy
Pancreatic Cancer – burden of disease

Estimated 46,420 new cases and 39,590 deaths due to pancreatic cancer in 2014

**Estimated Cancer Deaths by Sex in the United States, 2014**

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung and bronchus</td>
<td>86,930 (28%)</td>
<td>72,330 (26%)</td>
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<tr>
<td>Prostate</td>
<td>29,480 (10%)</td>
<td>40,000 (15%)</td>
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<tr>
<td>Colon and rectum</td>
<td>26,270 (8%)</td>
<td>24,040 (9%)</td>
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<tr>
<td>Pancreas</td>
<td>20,170 (7%)</td>
<td>19,420 (7%)</td>
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<tr>
<td>Liver</td>
<td>15,870 (5%)</td>
<td>14,270 (5%)</td>
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Pancreatic Cancer is projected to become a major problem

Rahib L et al, 2014

Siegel R et al, 2014

Estimated 46,420 new cases and 39,590 deaths due to pancreatic cancer in 2014
Evolution of Pancreatic Cancer

Iacobuzio-Donahue et al, 2012

Giovinazzo et al, Surgical Oncology, 2012
Pancreatic Cancer – Risk factors

- Cigarette smoking
- High body mass and lack of physical activity
  - Diabetes Mellitus
  - High Fat Diet
- Nonhereditary chronic pancreatitis
- Family History
- Hereditary pancreatitis
- Germ-line mutations
- Non-O blood group

Pancreatic Cancer – Symptoms and Signs

**Symptoms**
- Asthenia – 86 %
- Weight loss – 85 %
- Anorexia – 83 %
- Abdominal pain %
- Epigastric pain – 71 %
- Dark urine – 59 %
- Jaundice – 56 %
- Nausea – 51 %
- Back pain – 49 %
- Steatorrhea – 25 %

**Signs**
- Jaundice – 55 %
- Hepatomegaly- 39 %
- RUQ mass – 15 %
- Cachexia – 13 %
- Epigastric mass – 9 %
- Ascites – 5 %
Pancreatic Cancer Imaging

- Triple-phase contrast-enhanced thin-slice (multi-detector row) helical computed tomography (MDCT) with 3D reconstruction
- Endoscopic Ultrasound (EUS)
- Positron Emission Tomography (PET) scan
- Magnetic Resonance Imaging (MRI)

Pancreatic Cancer - Staging

- T – Tumor size
  - T0 – T4
- N – Lymph node status
  - N0-N1
- M – Metastases
  - M0-M1
- Stages
  - I – IV (based on T, N and M status)
Pancreatic Cancer Clinical Staging

- Resectable pancreatic cancer
  - Borderline resectable pancreatic cancer
    - Katz A
    - Katz B
    - Katz C
  - Locally advanced pancreatic cancer
  - Metastatic pancreatic cancer

Resectable pancreatic cancer
Borderline resectable pancreatic cancer

Locally advanced pancreatic cancer
Metastatic pancreatic cancer

Cancer Concepts/Terminology

- Resectable, borderline resectable, locally advanced and metastatic pancreatic cancer
- Synchronous/Metachronous
- Concept of metastases/micro-metastases
- Systemic therapy = Chemotherapy (cytotoxics) & biologic/targeted agents
- Adjuvant therapy/Neo-adjuvant therapy
- Response Rate (RR)
Principles of Cancer Therapy

- Goals of Therapy – Curative Intent or Palliative

- Treatment modalities offered are often locoregional and/or systemic

- Treatments offered depends on stage of cancer and patterns of recurrence/mode of metastases

- Disease recurrence can be a result of metachronous primary or locoregional/distant metastases

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Principles of Cancer Therapy

- Cancer stage usually correlates with survival
  - Biology trumps everything else

- Clinical staging may or may not be equal to pathologic staging
  - clinical staging has limitations

- Scans don’t tell the complete story

- Stage IV = metastases = palliative intent therapy with rare exceptions

- Not all stage IV cancers are equal
Principles of treatment

- Resectable and borderline resectable pancreatic cancer patients are treated with a curative intent
- Locally advanced and metastatic pancreatic cancer patients are treated with a palliative intent
- Surgery offers the only chance for cure but only 15 to 20% of patients have resectable disease at initial diagnosis
- Reported 5-yr survival rates following surgery (PD) for node-negative and node-positive disease are 25-30% and 10%, respectively
- Therefore, surgery is essential but not sufficient for cure

Pancreatic Cancer – components of treatment

- Surgery
- Chemotherapy (CT) – systemic treatment
  - Offers local/regional benefit and systemic benefit
- Radiotherapy (RT)
  - Offers local/regional benefit
- Surgery, chemotherapy and radiotherapy are essential for curing pancreatic cancer
- The optimal sequence of these treatment modalities is still evolving
Curative Intent Treatment

Resectable and Borderline Resectable Pancreatic Cancer

Surgery for pancreatic cancer
A complex surgery

Surgery-first:
~50% do not receive adjuvant therapy

~30% do not receive surgery
Neoadjuvant Treatment Sequencing

Resectable

- EUS/FNA Diagnosis
- Neoadjuvant CT/RT
- Surgery
- Adjuvant CT

BL Resectable

- EUS/FNA Diagnosis
- Neoadjuvant CT
- Neoadjuvant CT/RT
- Surgery
- Adjuvant CT

Palliative Treatment

Locally Advanced & Metastatic Pancreatic Cancer
Metastatic Pancreatic Cancer (MPC): Landmarks

- **1996**: Gemcitabine improved survival compared to 5-FU
- **2005**: Gemcitabine + Erlotinib improved survival compared to Gemcitabine
- **2010**: FOLFIRINOX (FFX) improved survival compared to Gemcitabine
- **2013**: nab-Paclitaxel + Gemcitabine (Nab-P/G) improved survival compared to Gemcitabine

Principles of treatment

- Locally advanced pancreatic cancer
  - 4 months of chemotherapy → Chemo-radiotherapy
- Metastatic pancreatic cancer
  - Chemotherapy
- Role of Clinical Trials cannot be emphasized enough
Supportive Care

- Venous thromboembolism (VTE)
  - Low molecular weight heparin/warfarin

- Biliary Obstruction
  - Plastic/Metal stent
  - Percutaneous Drain

- Exocrine Pancreatic Insufficiency

- Cancer related Cachexia

- Diabetes Management

Treatment of Pancreatic Cancer

What are the challenges?
Challenges - evolution

Yachida et al., 2010

![Diagram showing the evolution of tumors with subclones and metastatic capacity.]

Michl et al., Gut, 2012

- Targeting downstream survival pathways: e.g., IGFR, MEK, Akt, PI3K, mTOR, Notch inhibitors.
- Targeting stromal response: e.g., Hedgehog, TGFβ inhibitors, PEGPH20 hyaluronidase.
- Targeting tumor vasculature: e.g., (nab)-paclitaxel.
- Targeting immune response: e.g., CTLA4 antibodies, L19-IL2 fusion product.
# Multidisciplinary Team

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<thead>
<tr>
<th>Clinical Team</th>
<th>Supportive Team</th>
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<tr>
<td>Surgical Oncology</td>
<td>Nutrition</td>
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<tr>
<td>Medical Oncology</td>
<td>Diabetes management team</td>
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<tr>
<td>Radiation Oncology</td>
<td>Psychosocial support</td>
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<td>Gastroenterology</td>
<td>Genetic Counseling</td>
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<td>Radiology</td>
<td>Oncology Nursing</td>
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<td>Interventional Radiology</td>
<td>Physical/Occupational Therapy</td>
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<td>Pathology</td>
<td></td>
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<tr>
<td>Palliative Care/Pain Clinic</td>
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