Radiation Therapy Contraindications and Safety Panel: Re-irradiation, Novel Combination Therapies, and Hypofractionation

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Location: Hilton La Jolla Torrey Pines
Disclosures

• Associate Professor at University of Washington
• Medical Director of UW/SCCA Proton Therapy Center
• Apollo Oncology Group, member advisory board
• None relevant to this presentation
Learning Objectives

• To gain awareness of potential precautions and practical clinical considerations with re-irradiation, hypofractionation, and combination therapy with novel agents
The promise of targeted therapy

- Targeted therapies offer the promise of ‘selective’ systemic therapy
- Can result in dramatic responses in patients harboring the target mutation or receptor
Survival in Advanced NSCLC

- Move away toward histologically and biologically-directed therapies have resulted in significant gains in metastatic disease
- Consequence is that there is an emerging subset of patients with solid tumors in whom local progression (as opposed to distant spread) is a significant cause of death
- SBRT or SABR is currently our best weapon for providing local control in many solid tumors
Local Failure: Increasing Relevance as Survival Improves

- As survival improves local failures become increasingly clinically significant
Lung Cancer Targeted Therapy Landscape

Source: Compiled by Neeta Somalaih & George Simon.

 Courtesy of G. Simon

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Radiation Therapy Contraindications and Safety Panel

• How do these newly developed targeted agents interact with the radiation beam?
  • Are clinical trials the best mechanism to elucidate this?
  • The importance of case reports

• Hypofractionation/SBRT is associated with improved local control
  • What are the strengths and limitations of this approach?

• What is the clinical impact of improved systemic therapies on the patient profile of a radiation oncology clinic?
  • Significant increase in referrals for re-irradiation
  • How do we approach these high-risk patients?
Radiation and Targeted Therapies

Jing Zeng, MD
University of Washington
Disclosure

• I have no conflicts of interest to disclose.
Learning Objectives

• Review clinical data on combination of radiation therapy and targeted agents
  • Anti-angiogenic agents
  • Tyrosine kinase inhibitors
  • EGFR agents
  • ALK agents
  • Immunotherapy agents
  • HER-2
  • BRAF inhibitors
Bevacizumab & Tracheoesophageal Fistulas

- Recombinant, humanized monoclonal antibody against VEGF
- Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab

### Induction

<table>
<thead>
<tr>
<th>Week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8–12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16–18</th>
<th>Restage</th>
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<tbody>
<tr>
<td>Course</td>
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<td>2</td>
<td>3</td>
<td>4</td>
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<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
<td>11</td>
<td>12</td>
<td>Restage*</td>
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<td>ICB</td>
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</tbody>
</table>

MAINTENANCE

- Week 17 - Begin bevacizumab
- Continue until tumor progression or for a maximum of 6 months

- Progression
- Off study

### Break

<table>
<thead>
<tr>
<th>Week</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
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<tbody>
<tr>
<td>Break</td>
<td>BPC</td>
<td>BPC</td>
<td>RT</td>
<td>BPC</td>
<td>BPC</td>
<td>BPC</td>
<td>Restage</td>
</tr>
</tbody>
</table>

### Consolidation for CR, PR, Stable Disease

<table>
<thead>
<tr>
<th>Week</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25</th>
</tr>
</thead>
<tbody>
<tr>
<td>Break</td>
<td>BPC</td>
<td>BPC</td>
<td>RT</td>
<td>BPC</td>
<td>BPC</td>
<td>BPC</td>
<td>Restage</td>
</tr>
</tbody>
</table>

- Bevacizumab (B) 15 mg/kg IV, weeks 1 and 4 (2 courses)
- Pemetrexed (P) 500 mg/m² IV, weeks 1 and 4 (2 courses)
- Carboplatin (C) AUC 5 IV, weeks 1 and 4 (2 courses)
- Radiation (RT) 1.8 Gy single daily dose, Monday–Friday, to total dose 61.2 Gy

### Induction (weeks 1-7)

- Bevacizumab (B) 15 mg/kg IV, weeks 1 and 4 (2 courses)
- Pemetrexed (P) 500 mg/m² IV, weeks 1 and 4 (2 courses)
- Carboplatin (C) AUC 5 IV, weeks 1 and 4 (2 courses)
- Radiation (RT) 1.8 Gy single daily dose, Monday–Friday, to total dose 61.2 Gy

### Break (weeks 8-15)

- Bevacizumab (B) 15 mg/kg IV, weeks 16, 19, and 22 (3 courses)
- Pemetrexed (P) 500 mg/m² IV, weeks 16, 19, and 22 (3 courses)
- Carboplatin (C) AUC 5 IV, weeks 16, 19, and 22 (3 courses)

### Maintenance (weeks 25-51) for CR, PR, Stable Disease

- Week 25: Restaging was every 9 weeks. Off study for disease progression.

- Bevacizumab (B) 15 mg/kg IV every 3 weeks (weeks 25, 28, 31, 34, 37, 40, 43, 46, and 49; 9 courses)

Bevacizumab & Tracheoesophageal Fistulas

• Both trials stopped early due to toxicity (29 pts with SCLC, 5 with NSCLC)
  • SCLC:
    • 2 patients developed tracheoesophageal fistulae (1 resulting in death)
    • 3rd patient died from an aerodigestive hemorrhage (autopsy not performed)
    • 1 patient died from a treatment-related bowel perforation
  • NSCLC:
    • 2 patients developed tracheoesophageal fistulae
    • 1 patient developed bilateral pulmonary hemorrhage and left ventricular dysfunction during maintenance bevacizumab. Patient subsequently died.

Sunitinib & Bronchial Fistulas

- Multi-target tyrosine kinase inhibitor with antiangiogenic and anti-tumor activity
- 40 yo M with renal cell cancer treated by radical nephrectomy, then lung metastases 2 years later
  - Subcarinal tumor obstructing bronchus intermedius
    - 3D conformal RT, 30 Gy in 10 fractions
    - One week after RT, oral sunitinib started
  - Two months later, tumor shrinkage, associated with a bronchial fistula, confirmed by bronchoscopy
- Sunitinib stopped and antibiotic prophylaxis started. It was not possible to place an endobronchial stent

Bronchial fistula (black arrow) resulting from the dramatic reduction of the size of the subcarinal tumor. This fistula is localized into bronchus intermedius (white arrow).

Predicting Pulmonary Hemorrhage

- Panel of expert oncologists, pulmonologists and radiologists
- Patients with NSCLC are at an increased risk of PH due to underlying disease process
  - Squamous histology and/or grade ≥ 2 hemoptysis should not receive bevacizumab
  - No clinical or radiological features reliably predict severe PH
    - Major blood or bronchial vessel infiltration, encasement and abutting may predict PH, but standardized radiological criteria for defining infiltration have not been established
  - Not affected by patient age, performance status or anticoagulation or antiplatelet therapy

Anti-Angiogenic Agents & Pneumonitis

• Pulmonary toxicity after bevacizumab and concurrent thoracic radiotherapy observed in a phase I study for inoperable stage III non-small-cell lung cancer
  • Nonsquamous. 66 Gy+bevacizumab, after 2 cycles of chemo. V20 ≤ 36%
  • 6 patients enrolled before termination, 2 grade 2 RP, 2 grade 3 RP
• Early onset recall pneumonitis during targeted therapy with sunitinib
  • RCC and bone metastasis, RT to T5-8 to 24 Gy
  • Sunitinib (37.5 mg) started 14 days after RT
  • 14th day of sunitinib treatment, progressive fever with worsening of dyspnea and general weakness, resolved after steroids

Not all Gloom & Doom?

• A phase II trial of preoperative concurrent chemotherapy/radiation therapy plus bevacizumab/erlotinib in the treatment of localized esophageal cancer

• Treatment
  • Daily erlotinib (100 mg orally) on days 1-42
  • Bevacizumab (15 mg/kg IV) on days 1 and 22
  • Paclitaxel (200 mg/m2) and carboplatin (AUC 5.0) on days 1 and 22
  • 5-FU CI (225 mg/m2/day IV) on days 1-35
  • RT in 1.8-Gy single fractions to a total of 45 Gy

• 44/62 patients (71%) completed trimodality treatment
  • Eighteen patients (29%) achieved pCR
  • Common grade 3/4 toxicities: leukopenia (64%), neutropenia (44%), mucositis/stomatitis (42%), diarrhea (27%), and esophagitis (27%). 40 treatment-related hospitalization, and 2 postoperative deaths.

# Anti-Angiogenic Agents & the Bowel

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Description</th>
<th>% of patients treated with anti-VEGF agent and SBRT</th>
<th>Radiation schedule</th>
<th>Anti-VEGF agent</th>
<th>Toxicity</th>
<th>In-field toxicity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peters et al (30)</td>
<td>1 patient with renal cell carcinoma</td>
<td>N/A</td>
<td>8 Gy in 1 fraction</td>
<td>Sorafenib 400 mg twice daily for 5 weeks before and 3 days after RT</td>
<td>Grade 5 colon perforations, 1 week after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td>Lordick et al (31)</td>
<td>1 patient with renal cell carcinoma</td>
<td>N/A</td>
<td>28 Gy in 7 fractions</td>
<td>Bevacizumab 10 mg/kg every other week, 4 months after RT</td>
<td>Grade 5 cecal perforation, 3.5 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td>Stephens et al (32)</td>
<td>2 patients with lung/liver tumors near esophagus</td>
<td>29%</td>
<td>50 Gy in 5 fractions</td>
<td>Not specified; received anti-VEGF agent within 2 months of completing SBRT</td>
<td>≥Grade 3 esophageal fistula at median time of 8.4 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td>Barney et al (33)</td>
<td>1 patient with hepatocellular carcinoma</td>
<td>35%</td>
<td>30 Gy in 3 fractions</td>
<td>Sorafenib 400 mg BID, 1.3 months after SBRT</td>
<td>Grade 3 gastric ulcer, 4.6 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with colorectal carcinoma</td>
<td></td>
<td>60 Gy in 5 fractions</td>
<td>Bevacizumab 5 mg/kg every 2 weeks, 0.5 months after SBRT</td>
<td>Grade 4 gastric perforation, 4.5 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with pancreas cancer</td>
<td></td>
<td>42 Gy in 5 fractions</td>
<td>Bevacizumab 15 mg/kg every 3 weeks, 7 months after SBRT</td>
<td>Grade 5 duodenal perforation, 10.4 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with melanoma</td>
<td></td>
<td>60 Gy in 3 fractions</td>
<td>Bevacizumab 15 mg/kg every 3 weeks, 2 months after SBRT</td>
<td>Grade 4 small bowel perforation, 5.1 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with renal cell carcinoma</td>
<td></td>
<td>40 Gy in 5 fractions</td>
<td>Bevacizumab 10 mg/kg every 2 weeks, 16.3 months after SBRT</td>
<td>Grade 3 duodenal ulcer, 17.2 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with melanoma</td>
<td></td>
<td>60 Gy in 3 fractions</td>
<td>Bevacizumab 10 mg/kg every 2 weeks, with SBRT</td>
<td>Grade 3 gastric ulcer, 3.1 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with melanoma</td>
<td></td>
<td>60 Gy in 5 fractions</td>
<td>Bevacizumab 10 mg/kg every 2 weeks, 2.3 months after SBRT</td>
<td>Grade 4 gastric ulcer, 2.7 months after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td>Dawson et al (34)</td>
<td>1 patient with hepatocellular carcinoma</td>
<td>12.5%</td>
<td>33 Gy in 6 fractions</td>
<td>Sorafenib 400 mg daily, with SBRT</td>
<td>Grade 4 acute on chronic small bowel obstruction, 27 days after SBRT</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>1 patient with hepatocellular carcinoma</td>
<td></td>
<td>30 Gy in 6 fractions</td>
<td>Sorafenib 400 mg daily, with SBRT</td>
<td>Grade 3 GI bleed, 51 days after SBRT</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Adapted from Pollom EL et al. IJROBP 2015 Jul 1;92(3):568-76.
Bevacizumab & Bowel

- Phase II study of bevacizumab with concurrent capecitabine and radiation followed by maintenance gemcitabine and bevacizumab for locally advanced pancreatic cancer: Radiation Therapy Oncology Group RTOG 0411.
  - 50.4 Gy in 1.8 Gy fractions
  - 82 pts, 35.4% ≥grade 3 GI toxicity; bleeding in 5 patients, GI perforation in 3 patients (grade 5/4/3)
- Phase II trial of full-dose gemcitabine and bevacizumab in combination with attenuated three dimensional conformal radiotherapy in patients with localized pancreatic cancer.
  - 36 Gy in 2.4 Gy fractions
- Phase II study of bevacizumab in combination with definitive radiotherapy and cisplatin chemotherapy in untreated patients with locally advanced cervical carcinoma: Preliminary results of RTOG 0417.
  - Standard RT: whole pelvis to 45 Gy plus brachy, boost side wall bulky disease to 65 Gy

Anti-Angiogenic Agents/TKI & the Liver

- RTOG 1112 Randomized Phase III Study of Sorafenib versus Stereotactic Body Radiation Therapy followed by Sorafenib in Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Registration</th>
<th>Stratify</th>
<th>Randomize</th>
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</thead>
<tbody>
<tr>
<td>Vascular involvement (IVC, main portal vein/right or left main branch portal vein vs. other vascular involvement vs. none)</td>
<td></td>
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<tr>
<td>Hepatitis B or B and C vs. C vs. other</td>
<td></td>
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<tr>
<td>North American site vs. Non-North American site</td>
<td></td>
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<tr>
<td>HCC volume/liver volume (&lt;10% vs. 10-40 vs. &gt;40%)</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm 1</th>
<th>Arm 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily sorafenib</td>
<td>SBRT alone (27.5 Gy – 50 Gy in 5 fractions) Followed by Sorafenib alone daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-liver OARs</th>
<th>per protocol</th>
<th>variation acceptable</th>
<th>deviation unacceptable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus max (to 0.5 cc):</td>
<td>32 Gy</td>
<td>&gt; 32 but ≤34 Gy</td>
<td>&gt; 34 Gy</td>
</tr>
<tr>
<td>Stomach max (to 0.5 cc):</td>
<td>30 Gy</td>
<td>&gt;30 but ≤32 Gy</td>
<td>&gt; 32 Gy</td>
</tr>
<tr>
<td>Duodenum max (to 0.5 cc):</td>
<td>30 Gy</td>
<td>&gt;30 but ≤32 Gy</td>
<td>&gt; 32 Gy</td>
</tr>
<tr>
<td>Small bowel max (to 0.5 cc):</td>
<td>30 Gy</td>
<td>&gt;30 but ≤32 Gy</td>
<td>&gt; 32 Gy</td>
</tr>
<tr>
<td>Large bowel max (to 0.5 cc):</td>
<td>32 Gy</td>
<td>&gt;32 but ≤34 Gy</td>
<td>&gt; 34 Gy</td>
</tr>
<tr>
<td>Cord + 5 mm max (0.5cc):</td>
<td>25 Gy</td>
<td>&gt;25 but ≤28 Gy</td>
<td>&gt; 28 Gy</td>
</tr>
<tr>
<td>Kidneys: Bilateral mean dose</td>
<td>≤10 Gy</td>
<td>&gt;10 but ≤12 Gy</td>
<td>&gt; 12 Gy</td>
</tr>
</tbody>
</table>

Dose values in these tables should be read as physical dose for photons, or RBE-weighted dose for protons (assuming RBE = 1.1).
Bevacizumab & the CNS

• Addition of bevacizumab to standard temozolomide–radiation does not improve survival in glioblastoma patients but does increase toxicity
  • AVAglio study: ≥grade 3 adverse events (66.8% vs. 51.3%): arterial thromboembolic events, bleeding, complications of wound healing, GI perforation, and CHF
  • RTOG 0825: hypertension (4.2% vs. 0.9%), thromboembolic disease (7.7% vs. 4.7%), wound dehiscence (1.5% vs. 0.9%), fatigue (13.1% vs. 9.0%), visceral perforation (1.2% vs. 0.4%), serious hemorrhage (1.5% vs. 0.9%), and serious neutropenia (10.0% vs. 5.1%)

• Bevacizumab used as treatment for radionecrosis

EGFR Inhibitors: Cetuximab

- Toxicity tolerable when given with radiation, no evidence of benefit in addition to chemoradiation
- Trials
  - H&N:
    - 0522 A Randomized Phase III Trial of Concurrent Accelerated Radiation and Cisplatin versus Concurrent Accelerated Radiation, Cisplatin, and Cetuximab (C225) for Stage III and IV Head and Neck Carcinomas
    - 0920 A Phase III Study of Postoperative Radiation Therapy (IMRT) +/- Cetuximab for Locally-Advanced Resected Head and Neck Cancer
    - 1016 Phase III Trial of Radiotherapy Plus Cetuximab Versus Chemoradiotherapy in HPV-Associated Oropharynx Cancer
    - 1216 Randomized Phase II/III Trial of Surgery and Postoperative Radiation Delivered with Concurrent Cisplatin versus Docetaxel versus Docetaxel and Cetuximab for High-Risk Squamous Cell Cancer of the Head and Neck
  - Esophageal Cancer: 0436 A Phase III Trial Evaluating the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation for Patients With Esophageal Cancer Who Are Treated Without Surgery
  - Lung Cancer: 0617 A Randomized Phase III Comparison of Standard- Dose (60 Gy) Versus Highdose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab in Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer
  - Rectal Cancer: EXPERT-C trial (Oxaliplatin, Capecitabine, and Radiation Therapy With or Without Cetuximab in Treating Patients Undergoing Surgery for High-Risk Rectal Cancer)
EGFR Inhibitors & the Thorax

- RTOG 1306: A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC)
- Well tolerated with thoracic RT
  - Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer.
  - Chemoradiotherapy and gefitinib in stage III non-small cell lung cancer with epidermal growth factor receptor and KRAS mutation analysis: cancer and leukemia group B (CALEB) 30106, a CALGB-stratified phase II trial.
  - Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer.

EGFR Inhibitors & Pneumonitis

• Unexpected high lung toxicity from radiation pneumonitis in a phase I/II trial of concurrent erlotinib with limited field radiation for intermediate prognosis patients with stage III or inoperable stage IIB non-small-cell lung cancer (NSCLC)
  • Erlotinib at 100 mg daily well tolerated, erlotinib at 150 mg daily caused RP in 2/5 pts, 1 fatal
• Single-agent gefitinib with concurrent radiotherapy for locally advanced non-small cell lung cancer harboring mutations of the epidermal growth factor receptor.
  • 2/7 patients unable to complete TRT due to pulmonary toxicity
• Radiation recall pneumonitis induced by erlotinib after palliative thoracic radiotherapy for lung cancer: Case report and literature review.
  • Palliative thoracic irradiation (30 Gy in 12 fractions) and erlotinib thereafter
  • RP 2 months. Lung V20 and the mean lung dose were 20.33% and 10.7 Gy

Awad R and Nott L. Asia Pac J Clin Oncol. 2016 Feb 5.
EGFR Inhibitors & the CNS

• WBRT concurrent with EGFR–TKI does not seem to increase neurotoxicity, although no firm conclusions can be made

• Caution: second and third generation TKI’s (EGFR: afatinib, ALK: ceritinib, alectinib) have better penetration in the CSF

<table>
<thead>
<tr>
<th>Trial, year</th>
<th>N</th>
<th>Arms</th>
<th>Neurological safety outcome</th>
<th>All other grade 3–5 toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sperduto et al. (2013)</td>
<td>126 (planned 381)</td>
<td>A: WBRT/SRS</td>
<td>Arm C: grade 3 confusion and ataxia (% not mentioned, grade 4 brain necrosis (2.4%), grade 5 stroke (2.4%)</td>
<td>Grade 3–5 toxicities arm A, B, C: 11%, 41%, and 49 Arm C: fatigue, acne, diarrhea, pneumonia, hyperkaliemia, muscle weakness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: WBRT/SRS + temozolomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C: WBRT/SRS + erlotinib</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lee et al. (2014)</td>
<td>80</td>
<td>A: WBRT + erlotinib</td>
<td>Arm A: grade 3/4 somnolence 2.5% Arm B: grade 3/4 headache 10%, seisure 5%, somnolence 2.5%</td>
<td>Grade 3/4 toxicities similar in both arms (70%) except for rash (erlotinib 20%, placebo 5%) and fatigue (erlotinib 17.5%, placebo 35%) QoL similar</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: WBRT + placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeng et al. (2012)</td>
<td>90</td>
<td>A: WBRT + gefitinib</td>
<td>“no significant differences although headache and vomiting occurred more often in the WBRT arm”</td>
<td>Alopecia significantly more in WBRT + TKI arm compared to TKI alone (73% vs 4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: gefitinib only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wang et al. (2014)</td>
<td>73</td>
<td>A: WBRT + gefitinib</td>
<td>None</td>
<td>For arm A (gefitinib) not well defined: 70% rash, grade not mentioned; Arm B: grade 3–4 hematological toxicities 41%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: WBRT + VMP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cai et al. (2013)</td>
<td>157</td>
<td>A: WBRT + TKI</td>
<td>No significant neurotoxicity differences between arm A and B.</td>
<td>Arm A: (grade not mentioned) rash 47.7%, interstitial pneumonia 7.7%, diarrhea 7.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B: WBRT only</td>
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EGFR Inhibitors & the GI Tract

• Chinese Trial: Concurrent Chemoradiotherapy Containing Paclitaxel & Cisplatin With/Without Tarceva in Locally Advanced Esophageal Cancer – tolerable toxicity

• RTOG 0848 A Phase IIR and A Phase III Trial Evaluating Both Erlotinib (Ph IIR) And Chemoradiation (Ph III) As Adjuvant Treatment For Patients With Resected Head Of Pancreas Adenocarcinoma

• Radiation recall gastritis secondary to erlotinib in a patient with pancreatic cancer
  • 7 cycles of FOLFIRINOX, followed by capecitabine with RT to 5,040 cGy, then erlotinib and capecitabine for 2 months before progression
  • Meds stopped, maroon colored stools, hct drop, EGD shows radiation gastritis with oozing
  • Tx argon plasma coagulation. Multiple admissions for transfusions and procedures

• Rectal Cancer: Infusional 5-fluorouracil and ZD1839 (Gefitinib-Iressa) in combination with preoperative radiotherapy in patients with locally advanced rectal cancer: a phase I and II Trial (1839IL/0092).
  • Gefitinib 250 mg more tolerable than 500 mg (41% Grade 3+ toxicity)
  • 30% pathologic complete response rate

Wu S et al. ESMO 2014.
EGFR Inhibitor: Panitumumab

• H&N: no benefit in addition to chemorads, probably cannot replace chemo
  - Chemoradiotherapy with or without panitumumab in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-1): a randomised, controlled, open-label phase 2 trial.
  - Panitumumab plus radiotherapy versus chemoradiotherapy in patients with unresected, locally advanced squamous-cell carcinoma of the head and neck (CONCERT-2): a randomised, controlled, open-label phase 2 trial.

• GI
  - Phase I Clinical Trial to Determine the Feasibility and Maximum Tolerated Dose of Panitumumab to Standard Gemcitabine-Based Chemoradiation in Locally Advanced Pancreatic Cancer. Manageable toxicity and potential clinical efficacy.
  - Preoperative chemoradiation therapy in combination with panitumumab for patients with resectable esophageal cancer: the PACT study. Safe and well tolerated but could not improve pCR rate to the preset criterion of 40%.
  - Phase II study of neoadjuvant therapy with docetaxel, cisplatin, panitumumab, and radiation therapy followed by surgery in patients with locally advanced adenocarcinoma of the distal esophagus (ACOSOG Z4051). 48.5% of pts had toxicity ≥grade 4.
  - FFCD also has an open phase I/II trial in anal cancer where patients receive 5-FU, mitomycin C, and panitumumab
  - Switzerland trial is examining the use of capecitabine, 5-FU, and panitumumab in this patient population

ALK/ROS1 Inhibitor: Crizotinib

- RTOG 1306: A Randomized Phase II Study of Individualized Combined Modality Therapy for Stage III Non-Small Cell Lung Cancer (NSCLC)
- Stereotactic Radiation Therapy can Safely and Durably Control Sites of Extra-Central Nervous System Oligoproggressive Disease in Anaplastic Lymphoma Kinase-Positive Lung Cancer Patients Receiving Crizotinib
  - 14 pts with ALK-positive NSCLC receiving crizotinib and manifesting ≤ 4 discrete sites of eCNS progression, suitable for radiotherapeutic LAT
  - Patients discontinued crizotinib only on the days they were to receive LAT
  - No acute or late grade >2 radiation therapy-related toxicities were observed

Immunotherapy: Ipilimumab & the CNS

- Ipilimumab administered concomitantly to whole brain irradiation seems to increase toxicity but tolerable
  - Dermatitis, brain radionecrosis – hypofractionation increases risk
  - 46 pts from MSKCC with met melanoma, on Ipi and underwent single-fraction SRS for BMs:
    - 113 BMs were treated with a median dose of 21 Gy (range, 15-24 Gy).
    - Ipi was given at 3 mg/kg (54%) or 10 mg/kg (46%) for a median of 4 doses (range, 1-21).

Kiess AP et al. IJROBP 2015 Jun 1;92(2):368-75.
Immunotherapy: Ipilimumab & the Non-CNS

- MSKCC performed a retrospective analysis of 29 patients who received extracranial radiation therapy during ipilimumab.

**Table 2. Grade ≥3 adverse events during radiotherapy and ipilimumab**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Ipilimumab treatment dose (mg/kg)</th>
<th>Cumulative ipilimumab dose (mg/kg)</th>
<th>Phase of ipilimumab radiotherapy given</th>
<th>RT dose (Gy)</th>
<th>Number of radiation therapy fractions</th>
<th>EOD2 (0.6)</th>
<th>Radiotherapy site</th>
<th>Grade ≥3 AE</th>
<th>Time from ipilimumab start to AE (days)</th>
<th>Time from radiotherapy start to AE (days)</th>
<th>AE Attribution</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>40</td>
<td>Induction</td>
<td>24</td>
<td>1</td>
<td>227</td>
<td>T12 Vertebral metastasis</td>
<td>Grade 3 cytokine release</td>
<td>7</td>
<td>3</td>
<td>ir and/or rr</td>
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<tr>
<td>3</td>
<td>3</td>
<td>40</td>
<td>Induction</td>
<td>20</td>
<td>0</td>
<td>75</td>
<td>Left base of skull tumor</td>
<td>Grade 3 cytokine release</td>
<td>7</td>
<td>2</td>
<td>ir and/or rr</td>
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<tr>
<td>6</td>
<td>10</td>
<td>40</td>
<td>Induction</td>
<td>25</td>
<td>30</td>
<td>300</td>
<td>Right lumbar metastasis</td>
<td>Grade 3 diarrhea</td>
<td>104</td>
<td>100</td>
<td>ir</td>
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<tr>
<td>7</td>
<td>10</td>
<td>20</td>
<td>Induction</td>
<td>62.5</td>
<td>25</td>
<td>75</td>
<td>Left axillary lymphadenopathy</td>
<td>Grade 3 transaminase elevation</td>
<td>63</td>
<td>94</td>
<td>ir</td>
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<tr>
<td>9</td>
<td>3</td>
<td>12</td>
<td>Induction</td>
<td>30</td>
<td>42</td>
<td>300</td>
<td>Conus medullaris metastasis</td>
<td>Grade 3 maculopapular rash</td>
<td>98</td>
<td>64</td>
<td>ir</td>
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<tr>
<td>13</td>
<td>3</td>
<td>12</td>
<td>Induction</td>
<td>28.5</td>
<td>3</td>
<td>111</td>
<td>Sacral metastasis</td>
<td>Grade 3 thrombocytopenia</td>
<td>50</td>
<td>22</td>
<td>rr</td>
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<tr>
<td>15</td>
<td>3</td>
<td>10</td>
<td>Induction</td>
<td>30</td>
<td>3</td>
<td>122</td>
<td>Right suboccipital lymphadenopathy</td>
<td>Grade 3 transaminase elevation</td>
<td>35</td>
<td>(Before radiotherapy)</td>
<td>ir</td>
</tr>
<tr>
<td>21</td>
<td>10</td>
<td>160</td>
<td>Induction</td>
<td>20</td>
<td>5</td>
<td>35</td>
<td>Base of skull metastasis</td>
<td>Grade 4 uveitis</td>
<td>1,186</td>
<td>1,156</td>
<td>ir and/or rr</td>
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<td>22</td>
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<td>110</td>
<td>Maintenance</td>
<td>28.5</td>
<td>3</td>
<td>111</td>
<td>T7 Vertebral metastasis</td>
<td>Grade 3 radiculitis</td>
<td>927</td>
<td>477</td>
<td>rr</td>
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<tr>
<td>24</td>
<td>10</td>
<td>170</td>
<td>Maintenance</td>
<td>30</td>
<td>10</td>
<td>42</td>
<td>Upper abdominal lymphadenopathy</td>
<td>Grade 3 pruritus</td>
<td>1,328</td>
<td>293</td>
<td>ir</td>
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<td>29</td>
<td>10</td>
<td>50</td>
<td>Maintenance</td>
<td>30</td>
<td>5</td>
<td>76</td>
<td>Right hilar lymphadenopathy</td>
<td>Grade 3 transaminase elevation</td>
<td>41</td>
<td>(Before radiotherapy)</td>
<td>ir</td>
</tr>
</tbody>
</table>

Abbreviations: EOD2, equivalent dose in 2 Gy fractions with $\alpha/\beta$ of 0.6; ir, immune related; rr, radiation related.

*Second course of radiotherapy to this site.

*Rash occurred outside radiotherapy field, after vemurafenib.

PD-1 Inhibitors: Nivolumab & the CNS

• Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy
  • 2 prospective nivolumab protocols enrolling 160 patients with melanoma
    • 26 patients with BMs treated with SRS within 6 months of nivolumab
    • Total of 73 BMs treated over 30 sessions
    • SRS administered before, during and after nivolumab in 45%/7%/48%
  • Toxicity
    • One patient with grade 2 headaches following SRS
    • No other treatment-related neurologic toxicities or scalp reactions reported
  • Local BM control at 6 and 12 months were 91% and 85%
  • Median OS 12.0 months

PD-1 Inhibitors: Pembrolizumab

• Acute skin reaction suggestive of pembrolizumab-induced radiosensitization.
  • Patient with met melanoma to left femoral and ipsilateral humeral bones
    • 30 Gy to both sites in 6 fractions over 2 weeks (AP/PA for elbow, IMRT for knee). Skin dose 18 Gy and 9 Gy, respectively. Well tolerated treatment.
  • 3 days after RT, pembrolizumab initiated as a single agent (2 mg/kg, every 2 weeks)
  • 3 days after pembrolizumab, well-defined square-shaped inflammatory erythematous eruption abruptly developed on left elbow, consistent with RT fields
    • Skin punch biopsy 10 days after onset of skin reaction showed inflammatory perivascular lymphocytic infiltrate in the dermis.
    • PD-1 receptor immunostaining showed a moderate expression of PD-1 receptors
  • Treated with topical corticosteroids and lesions regressed 3 weeks after onset, mild residual hyperpigmentation (Fig. 2)

PD-1 Inhibitors & Open/Pending Trials

• A Phase II Randomized Controlled Screening Trial of Nivolumab With Image Guided, Stereotactic Body Radiotherapy (SBRT) Versus Nivolumab Alone in Patients With Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)
• Phase Ib Study of Pembrolizumab in Combination With Chemo Radiotherapy (CRT) for Locally-advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN)
• A Feasibility Trial Evaluating Anti-PD1 Nivolumab Consolidation After Standard First-line Chemotherapy and Radiotherapy in Locally Advanced Stage IIIA/B NSCLC
• A Randomised Open-label Phase II Trial of Consolidation With Nivolumab and Ipilimumab in Limited-stage SCLC After Chemo-radiotherapy
• Moving PD-1 Blockade With Pembrolizumab Into Concurrent Chemoradiation for Locally Advanced Non-Small Cell Lung Cancer
• Pembrolizumab With Chemoradiotherapy as Treatment for Muscle Invasive Bladder Cancer
**Immunotherapy: IFNα & IL-2**

- IFNα and IL-2 have been combined with RT in small studies, with some evidence suggesting increased toxicity and/or efficacy
  - University of Utah:
    - 10 patients with melanoma (45-52.5 Gy in conventional fractionation in 9 patients, 36 Gy hypofractionated in 1 patient) and IFNα concurrently or within 1 month of RT
    - Severe complications in 50% of patients: peripheral neuropathy (n=2), brain radionecrosis (n=1), and subcutaneous necrosis (n=2)
  - University of Texas Southwestern:
    - 3 patients with melanoma (2 mucosal) treated with concurrent IFNα and RT
    - Grade 3 or 4 mucositis developed, and RT discontinued prematurely
  - Barcelona
    - 18 patients with melanoma (30-36 Gy hypofractionated in 16 patients, 50 Gy in conventional fractionation in 2 patients) and varying doses of IFNα concurrently (n=10), <30 days of RT (n=3), or ≥30 days after radiation therapy (n=5).
    - One case of grade 3 telangiectasia and 2 cases of grade 4 myelopathy were observed; all in patients who received hypofractionated radiation therapy to the cervical lymphatics

Trastuzumab: HER-2/neu

- Breast Cancer
  - NSABP B-43: A Phase III Clinical Trial Comparing Trastuzumab Given Concurrently with Radiation Therapy and Radiation Therapy Alone for Women with HER2-Positive Ductal Carcinoma In Situ Resected by Lumpectomy
  - NSABP B-47: A Randomized Phase III Trial of Adjuvant Therapy Comparing Chemotherapy Alone (Six Cycles of Docetaxel Plus Cyclophosphamide or Four Cycles of Doxorubicin Plus Cyclophosphamide Followed by Weekly Paclitaxel) to Chemotherapy Plus Trastuzumab in Women with Node-Positive or High-Risk Node-Negative HER2-Low Invasive Breast Cancer
  - Early phase II data from a multicenter French study suggested the potential for cardiac toxicity with concurrent administration of trastuzumab and radiation, but a subsequent phase II study did not reproduce such toxicity and indicated potential for radio sensitization
- Bladder Cancer: RTOG 0524 A Phase I/II Trial of a Combination of Paclitaxel and Trastuzumab With Daily Irradiation or Paclitaxel Alone With Daily Irradiation Following Transurethral Surgery for Non-Cystectomy Candidates With Muscle-Invasive Bladder. Response rate for HER2/neu-targeted therapy is encouraging but may increase certain adverse events including marrow suppression
- Esophageal Cancer: RTOF 1010 A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of Her2-Overexpressing Esophageal Adenocarcinoma

BRAF Inhibitors

- Reports of unusually severe radiodermatitis
  - Left image: 47 yo man with met melanoma, 4 months of dabrafenib with progressive T12 met. Treated to 36 Gy in 12 fractions. Grade 3 dermatitis, images at 10 days after termination of radiation therapy.
  - Multicenter analysis in 161 melanoma patients receiving RT with concomitant BRAF inhibitor therapy: acute radiodermatitis ≥2 36%, and follicular cystic proliferation was seen in 13% of all patients.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study</th>
<th>TRT</th>
<th>N</th>
<th>Type of lesions</th>
<th>RT dose</th>
<th>Adverse effects</th>
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</thead>
<tbody>
<tr>
<td>Satzger et al. (2013)</td>
<td>Case report</td>
<td>Non brain RT + BRAF inhibitor</td>
<td>4</td>
<td>Stage III/IV melanoma</td>
<td>36–60 Gy</td>
<td>Radio-dermatitis</td>
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<tr>
<td>Schulze et al. (2014)</td>
<td>Case report</td>
<td>Brain RT + BRAF inhibitor</td>
<td>2</td>
<td>Stage III/IV melanoma</td>
<td>30 Gy</td>
<td>Radio-dermatitis</td>
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<tr>
<td>Ducassou et al. (2013)</td>
<td>Case report</td>
<td>Non brain RT + BRAF inhibitor</td>
<td>1</td>
<td>Stage III/IV melanoma</td>
<td>30 Gy</td>
<td>Radio-dermatitis</td>
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<td>Peuvrel et al. (2013)</td>
<td>Case report</td>
<td>Non brain RT + BRAF inhibitor</td>
<td>2</td>
<td>Stage III/IV melanoma</td>
<td>20–30 Gy</td>
<td>Radio-necrosis and anorectitis</td>
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<tr>
<td>Boussemart et al. (2013)</td>
<td>Case report</td>
<td>Non brain RT + BRAF inhibitor</td>
<td>2</td>
<td>Stage III/IV melanoma</td>
<td>18–20 Gy</td>
<td>Radio-dermatitis</td>
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<td>Narayana et al. (2013)</td>
<td>Retrospective</td>
<td>Brain or stereotactic RT + BRAF inhibitor</td>
<td>12</td>
<td>Stage III/IV melanoma</td>
<td>20–30 Gy</td>
<td>Radio-necrosis and oedemas</td>
</tr>
<tr>
<td>Hecht et al. (2015)</td>
<td>Retrospective</td>
<td>RT + BRAF inhibitor</td>
<td>161</td>
<td>Stage III/IV melanoma</td>
<td>NC</td>
<td>Radio-dermatitis</td>
</tr>
</tbody>
</table>

Key Points to Take Home

• Anti-angiogenic agents and RT to the chest: HIGH RISK
• Anti-angiogenic agents and RT to the abdomen/pelvis: MODERATE/HIGH RISK
• BRAF inhibitors and RT: HIGH RISK
• IFNα and IL-2 concurrently with RT: HIGH RISK
• Erlotinib and RT: LOW/MODERATE RISK
• PD-1 inhibitors and non-CNS RT: LOW/MODERATE RISK
• Ipilimumab and RT: LOW RISK
• PD-1 inhibitors and CNS RT: LOW RISK
• Cetuximab, Panitumumab, Trastuzumab and RT: LOW RISK
SBRT/SABR for Locally Advanced Pancreatic Cancer

Albert Koong, MD, PhD
Sue and Bob McCollum Professor
Department of Radiation Oncology
Stanford University
Disclosures

• None
Learning Objectives

• To understand various treatment options for locally advanced pancreatic cancer

• To understand relevant normal tissue dose constraints to use in SBRT/SABR for locally advanced pancreatic cancer
• 65 yo previously healthy woman presents with jaundice, abdominal pain, and 20 lb weight loss
• CT scan reveals mass in the head of the pancreas. Mass involves celiac axis and SMV.
Question #1
What do you recommend as initial treatment?

1) Surgery.
2) Chemotherapy.
3) Chemoradiotherapy.
4) SBRT/SABR.
5) Clinical Trial.
6) Observation.
• Multidisciplinary tumor board evaluation
  • Locally advanced, unresectable
    • Celiac and SMV involvement

• Initial treatment recommendation is chemotherapy
Question #2
Which chemotherapy?

1) Gemcitabine alone.
2) Gemcitabine and Abraxane.
3) Gemcitabine and Erlotinib.
4) FOLFIRINOX.
5) 5FU.
6) Other.
Metastatic Pancreatic Cancer: Gem vs. FOLFIRINOX, n=342

Conroy et al, NEJM 2011
Metastatic Pancreatic Cancer: Gem-Abraxane vs. Gem Alone, n=861

Von Hoff et al, NEJM 2013
ECOG 4201: Locally Advanced Pancreatic Cancer

**Stratify:**
- PS (0 vs 1)
- Weight loss >10% vs ≤10%

**ARM A: INDUCTION**
- GEMCITABINE 1000mg/M2
  - Once weekly x 6 weeks

**ARM A: CONSOLIDATION**
- GEMCITABINE 1000mg/M2
  - Once weekly x 3 weeks
  - Followed by 1 week rest x 5 cycles
    - 1 cycle = 4 weeks

**ARM B: INDUCTION**
- GEMCITABINE 600mg/M2
  - Once weekly x 6 weeks
- CONCURRENT RT 180 cGy/day
  - 5 days a week x 6 weeks
  - Total dose 50.4 Gy

**ARM B: CONSOLIDATION**
- GEMCITABINE 1000mg/M2
  - Once weekly x 3 weeks
  - Followed by 1 week rest x 5 cycles
    - 1 cycle = 4 weeks

Loehrer et al JCO 2011
Radiation Therapy

- 50.4 Gy at 1.8 Gy/fraction
- 3D conformal RT used – no IMRT
- 39.6 Gy initially to tumor plus regional elective nodes
- 10.8 Gy boost to GTV + 2 cm margin
- Concurrent Gemcitabine 600 mg/m2

Loehrer et al JCO 2011
ECOG 4201: Locally Advanced Pancreatic Cancer, n=71

- Median OS
  - Gem: 9.2 mos
  - CRT: 11.1 mos

Loehrer et al JCO 2011
LAP07 Conclusions

- Chemo-RT is not superior to continuing chemo alone in locally advanced pancreas cancer with tumor controlled after 4 months of chemo.
- Erlotinib is not beneficial in locally advanced pancreas cancer and increases toxicity significantly.
- Improved local control with chemoXRT.
- Other schemas of RT (SBRT?) and/or chemo (FOLFIRINOX, nab-paclitaxel/gemcitabine) should be tested in locally advanced pancreas cancer.
Patient Enrolled on Randomized Clinical Trial of FOLFIRINOX +/- SBRT

• Patient received 4 cycles of mFOLFIRINOX.

• Repeat CT scan revealed stable disease.

• Chemotherapy was poorly tolerated.
  • Patient required dose reductions for neutropenia.
  • Profound fatigue.
Question #3
Which SBRT/SABR dose would you recommend?

1) 25 Gy x 1
2) 10-12 Gy x 3
3) 6.6-8 Gy x 5
4) Other
Moffitt Experience: FOLFIRINOX+SBRT (median dose 30-40 Gy, 5 fractions)

Retrospective review of 159 pts

Log Rank p=0.402

Mellon et al, Acta Oncologica 2015
Stanford Pancreatic Cancer SABR Experience

- Median OS: 13.6 months
- N=167

Pollom et al, IJROBP 2014
Less GI Toxicity with Multi-Fraction SABR

- 12-month ≥ grade 2 GI toxicity rates
  - Single-fraction: 26.1%
  - Multi-fraction: 7.8%

*No significant difference in ≥G3 GI toxicity in single (12.3%) vs. multi-fraction (5.6%) SABR

Pollom et al., IJROBP 2014
Phase 2 Multi-institutional Trial Evaluating Gemcitabine and Stereotactic Body Radiotherapy for Patients With Locally Advanced Unresectable Pancreatic Adenocarcinoma

Joseph M. Herman, MD; Daniel T. Chang, MD; Karyn A. Goodman, MD; Avani S. Dholakia, MD; Siva P. Raman, MD; Amy Hacker-Prietz, PA-C; Christine A. Iacobuzio-Donahue, MD; Mary E. Griffith, RN; Timothy M. Pawlik, MD; Jonathan S. Pai, BA; Eileen O’Reilly, MD; George A. Fisher, MD; Aaron T. Wild, MD; Lauren M. Rosati, BS; Lei Zheng, MD; Christopher L. Wolfgang, MD; Daniel A. Laper, MD; Laurie A. Colombo, RN; Elizabeth A. Sugar, PhD;

Figure 2. Kaplan-Meier estimates of the survival function for (A) overall survival and (B) progression-free survival are shown. The 95% confidence intervals are included as dotted lines.
Patient received 8 Gy x 5 fractions

• Dose constraints:
  • Stomach/duodenum/small bowel
    • 40 Gy<1 cc, 30 Gy<10cc, 20 Gy<30cc

• Respiratory Gated VMAT
Contouring: GTV, ITV, PTV
Relationship Between Duodenal Volume and Toxicity

V10
One Minus Survival Functions

V20
One Minus Survival Functions

V15
One Minus Survival Functions

V25
One Minus Survival Functions

Murphy et al, IJROBP 2010
DVH Analysis: Duodenum

V30 = 2.3 cc
V20 = 14.0 cc
V40 = 0 cc

Duodenum
Stomach
Rapid Dose Fall Off

40 Gy

30 Gy

20 Gy
Rapid Dose Fall Off

40 Gy  30 Gy  20 Gy
Rapid Dose Fall Off

40 Gy

30 Gy

20 Gy
Take Home Points

• Chemotherapy is an essential component of the treatment of locally advanced pancreatic cancer.

• Duodenum is the radiation dose limiting structure in the upper abdomen.

• Multi-fraction SABR/SBRT results in less toxicity than single fraction SABR/SBRT.
Thoracic Reirradiation for Locally Recurrent NSCLC: Using Current Evidence to Define a Treatment Approach

Daniel Gomez, M.D.
Associate Professor, Radiation Oncology
MD Anderson Cancer Center

ASTRO Reirradiation Panel
October 21, 2015
Disclosures

• I have no conflicts of interest to disclose.
Learning Objectives

• 1) Discuss difficulties with selection of patients for conventionally fractionated reirradiation and reported outcomes

• 2) Propose algorithms and treatment approaches for patients who may be candidates for reirradiation in context of current data
A Tale of Two Patients

• Patient #1
  • 71 year-old woman who presented with stage T3N1 adenocarcinoma of the lung in 05/2011
  • Treated with chemoradiation, RT to 50 Gy at OSH
  • Underwent attempted resection but was deemed to be unresectable
  • Received postoperative carboplatin/paclitaxel x 6 cycles
  • 9/11 – redo thoracotomy and removal of most of disease, but with small amount of gross disease.
  • Referred for further radiation therapy after surgery
RT Course 1 – 50 Gy in 25 fractions
RT Course 2 – 50 Gy in 25 fractions with 10 Gy cone-down in region of residual disease
Patient 2

- 74 y/o woman with h/o R hilar mass, SCC. No other evidence of disease. TXN1M0.

- Not surgical candidate, received definitive chemoradiation to dose of 70 Gy in 35 fractions, completed in 7/2011

- Tolerated treatment well, 2 years later found to have recurrent disease

- Still medically inoperable, high PS, so referred for definitive chemoradiation
Patient 2

Course 1

Course 2
A Tale of Two Patients

• Both patients were NED after reRT
• Patient 1 – Composite Rx dose 110 Gy
  • Tolerated both courses of RT well
  • Currently doing well, high quality of life
A Tale of Two Patients

• Patient 2 – Composite Rx dose 130 Gy
  • Tolerated RT well with no acute side effects
  • In early 2014, developed locally recurrent disease, bronchoscopy also demonstrated evidence of tracheal necrosis
  • Died in May 2014

Why the different outcomes, and who should we select for reirradiation?
Introduction

• Locoregional disease recurrence of NSCLC remains a dominant cause of death.
  • Many pts w/ LRR are not surgical candidates
  • Low responses to second-line chemo have prompted increased interest in reRT
What patients do we currently select for thoracic reirradiation in NSCLC?

Less controversial indications

• Peripheral lesions – SBRT is an option
• High performance status
• Limited sites of disease (treating could achieve long-term control)
• Longer disease-free interval
• Not reirradiating critical structures of esophagus, spinal cord, and tracheobronchial tree
• Patient understands risks of reirradiation
What patients do we currently select for thoracic reirradiation in NSCLC?

More Controversial Indications/Open Questions

• Role of histology
• When is appropriate time interval cutoff?
• What are best dose constraints, and how is time factored?
• What is chance of local control with reRT, and is it better than palliative chemotherapy?

Need more data to answer these questions.
Limitations of Current Data

• Studies small, retrospective
• Heterogenous dose prescriptions
  • Many include patients with palliative or non-therapeutic doses
• Collected over long time periods, techniques antiquated
• Many confounding factors difficult to control
Scenario #1 – ReRT with Lesion Amenable to SABR

• Premise – additional lung being radiated is small, so prior dose less of an issue
• “Can’t kill dead lung twice,” so even if near or overlapping prior lung field, consequences will be modest
• Hypofractionation should allow for high levels of local control
• Is this premise supported by the data?
## Re-Irradiation with SABR

<table>
<thead>
<tr>
<th>Study</th>
<th># Patients</th>
<th>Dose Regimen</th>
<th>Safety</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Mayo Clinic, 2015 (Oliver et al.)</td>
<td>18</td>
<td>48/4, 54/3, 50/5</td>
<td>No Grade 3 Toxicity</td>
<td>OS 21 months</td>
</tr>
<tr>
<td>Stanford, 2012 (Trakul et al.)</td>
<td>15</td>
<td>1-5 fraction regimens</td>
<td>No high grade toxicity</td>
<td>12-month LC 65%, worse if treatment time &lt;6 months</td>
</tr>
<tr>
<td>Temple U, 2013 (Valakh et al.)</td>
<td>9</td>
<td>3-5 fraction regimens</td>
<td>1 patient with chest wall pain</td>
<td>2-year LRFS 69%, OS 75%</td>
</tr>
<tr>
<td>MDACC, 2010 (Kelly et al.)</td>
<td>36</td>
<td>12.5 Gy x 4</td>
<td>50% with worsening dyspnea, 30% with chest wall pain</td>
<td>92% in-field local control</td>
</tr>
<tr>
<td>Riferimento Oncologico/Italy, 2014 (Trovo et al.)</td>
<td>17</td>
<td>30/5 or 30/6</td>
<td>23% with grade 3 RP, 1 with fatal RP, one patient with fatal hemoptysis</td>
<td>86% local failure at 1 year</td>
</tr>
</tbody>
</table>
ReRT with SABR – Special Considerations

• When low patient numbers and short follow-up, tolerated well and with good local control

• With higher patient numbers, local control still good, but more toxicity elucidated
  • Chest wall toxicity
  • High-grade pneumonitis

• Even with small volumes and peripherally located lesion, not a “free ride” and more data needed.
Scenario #2 – Patient not Candidate for SABR

• Much more complex case due to involvement of central structures receiving high cumulative dose
  • Esophagus, airways, vessels, lung
• Many times these patients don’t have option for surgery, even if “local only” problem
• Do these patients have an option for reRT?
Thoracic reirradiation for lung cancer: a literature review and practical guide

C. Suzanne Drodge¹, Sunita Ghosh², Alysa Fairchild¹

Table 1 Patient population

<table>
<thead>
<tr>
<th></th>
<th>%, squamous/ SCLC adeno</th>
<th>Initial stage III/IV</th>
<th>Distant metastases present at ReRT</th>
<th>%, new primary</th>
<th>%, without pathologic confirmation at ReRT</th>
<th>PS at ReRT</th>
<th>Minimum median time to ReRT (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green</td>
<td>65.5/13.8</td>
<td>2/29</td>
<td>NR</td>
<td>NR</td>
<td>72.4 (21/29)</td>
<td>14/29 good, 11/29 poor, 4/29 NE</td>
<td>3/10</td>
</tr>
<tr>
<td>Jackson</td>
<td>47.8/34.8</td>
<td>0/22</td>
<td>NR</td>
<td>NR</td>
<td>47.8 (11/23)</td>
<td>NR</td>
<td>5.7/15</td>
</tr>
<tr>
<td>Montebello</td>
<td>53.3/26.7</td>
<td>1/30</td>
<td>76.7%/0</td>
<td>NR</td>
<td>73.3 (22/30)</td>
<td>Median KPS 60 [40-100]</td>
<td>8.1/NR</td>
</tr>
<tr>
<td>Gressen</td>
<td>34.8/30.4</td>
<td>2/23</td>
<td>NR/NR</td>
<td>NR</td>
<td>Not specified</td>
<td>NR</td>
<td>3/15</td>
</tr>
<tr>
<td>Okamoto</td>
<td>50.0/17.6</td>
<td>6/34</td>
<td>82.4%/6.8%</td>
<td>38.2%</td>
<td>0</td>
<td>NR</td>
<td>WHO 0-3/34; 1-11/34; 2-10/34; 5-7/34; 4-3/34</td>
</tr>
<tr>
<td>Wu</td>
<td>39.1/30.4</td>
<td>7/23</td>
<td>68.5%/0</td>
<td>Not permitted</td>
<td>34.8 (6/23)</td>
<td>KPS ≥70-23/23</td>
<td>6/13</td>
</tr>
<tr>
<td>Kramer</td>
<td>NR/NR</td>
<td>0/28</td>
<td>NR/NR</td>
<td>NR</td>
<td>32.1 (9/28)</td>
<td>Median KPS 60 [40-90]</td>
<td>6/17</td>
</tr>
<tr>
<td>Tada</td>
<td>73.7/21.1</td>
<td>0/19</td>
<td>100%/0</td>
<td>Not permitted</td>
<td>0</td>
<td>ECOG 0-1-8/19; 2-8/19; 3-5/19</td>
<td>5/16</td>
</tr>
<tr>
<td>Pottinikov</td>
<td>35.3/33.0</td>
<td>0/17</td>
<td>NR/NR</td>
<td>NR</td>
<td>0</td>
<td>NR</td>
<td>Median KPS 60 [60-90]</td>
</tr>
<tr>
<td>Ebara</td>
<td>43.2/25.0</td>
<td>0/44</td>
<td>NR/NR</td>
<td>NR</td>
<td>81.8 (36/44)</td>
<td>ECOG 0-1-8/44</td>
<td>5.8/12.6</td>
</tr>
<tr>
<td>Cetingoz</td>
<td>60.5/13.2</td>
<td>0/38</td>
<td>94.7%/0</td>
<td>15.8%</td>
<td>0</td>
<td>5.3* (2/38)</td>
<td>1/8.8</td>
</tr>
<tr>
<td>Krucer</td>
<td>35.4/NR</td>
<td>11/48</td>
<td>41.7%/25.0%</td>
<td>37.5%</td>
<td>0</td>
<td>75 (30/48)</td>
<td>NR</td>
</tr>
<tr>
<td>Griffen</td>
<td>41.7/20.0</td>
<td>4/24</td>
<td>62.6%/3.3%</td>
<td>16.7%</td>
<td>54.2 (11/24)</td>
<td>10.7 (4/24)</td>
<td>Median ECOG 1 [0-3]</td>
</tr>
</tbody>
</table>

* minimum time to recurrence required; **, initial diagnosis; †, includes two extensive stage small cell lung cancer patients. Abbreviations: adeno, adenocarcinoma; NE, not evaluable; NR, not reported; PS, performance status; ReRT, reirradiation; SCLC, small cell lung cancer.
Safety and Palliative Efficacy of Single-Dose 8-Gy Reirradiation for Painful Local Failure in Patients With Stage IV Non-Small Cell Lung Cancer Previously Treated With Radical Chemoradiation Therapy

Erkan Topkan, MD, * Berna Akkus Yildirim, MD, * Ozan Cem Guler, MD, * Cem Parlak, MD, * Berrin Pehlivan, MD, † and Ugur Seleni, MD ‡
Defining Treatment Based on Intent

Topkan et al., IJROBP 2014
Reirradiation for Locoregionally Recurrent Lung Cancer Outcomes in Small Cell and Non–Small Cell Lung Carcinoma

Tim J. Kruser, MD,* Bradley P. McCabe, MS,† Minesh P. Mehta, MD,‡ Deepak Khuntia, MD,§ Toby C. Campbell, MD,∥ Heather M. Geye, MS,* and George M. Cannon, MD*

### TABLE 2. Initial Radiation Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>NSCLC Patients (n = 37)</th>
<th>SCLC Patients (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Range</td>
</tr>
<tr>
<td>Radiation dose (Gy)</td>
<td>57</td>
<td>30-80.5</td>
</tr>
<tr>
<td>No. fractions</td>
<td>25</td>
<td>10-37</td>
</tr>
<tr>
<td>N (%)</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Initial radiation intent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitive</td>
<td>24</td>
<td>65</td>
</tr>
<tr>
<td>Preoperative/adjuvant</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Palliative</td>
<td>9</td>
<td>24</td>
</tr>
<tr>
<td>Initial radiation delivery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 dimensional-CRT</td>
<td>25</td>
<td>68</td>
</tr>
<tr>
<td>IMRT</td>
<td>12</td>
<td>32</td>
</tr>
<tr>
<td>Concurrent chemotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td>No</td>
<td>34</td>
<td>65</td>
</tr>
</tbody>
</table>

*Palliative radiation (12 Gy) for superior vena cava syndrome, no concurrent chemotherapy.

CRT indicates conformal radiotherapy; IMRT, intensity-modulated radiotherapy; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer.
Toxicity

• 9 patients with grade $\geq 2$ toxicity
• Toxicity not associated with dose
• No reported Grade 4 or Grade 5 toxicity
Factors Associated with Survival in NSCLC (n=37)

• Higher initial RT dose (58.3 Gy(2))
• Interval to recurrence (cutoff 1 year)
• Extrathoracic disease at or before RT
• Radical reRT intent
• KPS at time of reRT
Interval to hospice:

2.6 months for NSCLC

1.6 months for SCLC

Kruser et al., AJCO 2014
High-dose, conventionally fractionated thoracic reirradiation for lung tumors

Gwendolyn H.M.J. Griffioen a,*, Max Dahele a, Patricia F. de Haan a, Peter M. van de Ven b, Ben J. Slotman a, Suresh Senan a

a Department of Radiation Oncology, VU University Medical Center, Amsterdam, The Netherlands
b Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

Griffioen et al., Lung Cancer 2014
Patient Outcomes

• 24 total patients
• 4 with SCLC
• 54% with recurrence, 46% with primary tumor
• Three patients died with Grade 5 bleeding
• PTV at reRT (300 cc) most significant prognostic factor

Griffioen et al., Lung Cancer 2014
Median time between reirradiation and local progression 6.7 months

Median time between reirradiation and distant progression 11.8 months

Griffioen et al., *Lung Cancer* 2014
MDACC Retrospective Trial of PBT Thoracic ReRT

• Retrospective study (n=33) with locally recurrent NSCLC treated with PBT.
  • Patient Characteristics
    • Median age 69 at reRT
    • Primary histology adenocarcinoma (n=15)
    • 67% with ECOG PS 0 or 1
    • 24% received concurrent chemotherapy

McAvoy et al., Radiother Oncol 2013
Proton Outcomes Results

• Median follow up 11 months.

• 1 year disease outcomes:
  • Overall survival: 47%
    • Median OS 11.1 months
  • Progression free survival: 28%
  • Locoregional control: 54%
  • Distant metastasis-free survival: 39%

McAvoy et al., *Radiother Oncol* 2013
Proton Outcomes Results

A. OS

B. PFS

C. LRC

D. DMFS
Proton Toxicity Results

• Toxicity (Grade ≥3)
  • Esophageal: 9%
  • Pulmonary: 21%
  • Cardiac: 3%

• Toxicity Grade 4:
  • 1 pt w/ TE fistula, composite max esophagus dose 135.7 Gy. TE fistula developed 2 yrs 5 mo post RT.
  • 2 pts with tracheal necrosis. Max composite trachea dose 147.37 Gy (BED 220 Gy₄)

• Factors predicting for grade ≥3 toxicity:
  • Interval between RT 44 vs 36 months NS (p=0.15)
  • Peripheral vs central less cardiac toxicity (p=0.02) trend towards less pulmonary toxicity (p=0.08) no difference esophageal (p>0.05)
  • iGTV size not significant
  • Concurrent chemo not associate with toxicity

McAvoy et al., Radiother Oncol 2013
Proton Toxicity (Grade ≥2)

A. All

B. Pulmonary

C. Esophageal

D. Cardiac
PBT conclusions

• Rates of toxicity similar to conventional RT
  • Pulmonary most common and associated with centrally located tumors.
  • Esophageal toxicity high in comparison to up-front treatment but similar to other reRT studies.
    • Note majority of pts central & did not qualify for SBRT
  • High composite doses related to increased toxicity
• Outcomes remain poor: LRR at one year 46%
IMRT & Proton

• Goal of study:
  • Report toxicity and outcomes after reRT in a larger patient cohort using highly conformal techniques
    • Many of patients from prospective registry trial at MDACC
  • Define dose constraints
  • Guidance on what patients are optimal candidates
Key Characteristics

• Initial Radiation:
  • Median Dose: 70 EQD2 Gy (range 33–276 EQD2 Gy)
    • 117 Gy\( _3 \) and 80.5 Gy\( _{10} \)
  • Time to tumor recurrence 11 months
  • Majority underwent RT for in-field failure
    • In-Field 57.5%, Marginal 6%, Out of field failure 36%

• Reirradiation:
  • Interval to reRT 17 months
  • Median dose: 60.5 EQD2 Gy (range 25.2–155 EQD2 Gy)
    • 100.8 Gy\( _3 \) and 74.3 Gy\( _{10} \)
  • iGTV 27.1 cm\(^3\) and ITV 94.2 cm\(^3\)
  • Composite plans in 64% of pts.
  • Median follow-up 6.5 months (range >1-72)

McAvo et al., IJROBP 2014
IMRT & Proton Toxicity

• Rates of grade ≥3 toxicity:
  • Esophageal 7%
  • Pulmonary 10%

• Factors affecting risk of grade ≥2
  • Esophageal
    • Increased toxicity: Concurrent chemo (p=0.029), high max point dose (p=0.001) increased esophageal $V_{60}$ ($P<0.001$)
    • NS: EQD2, time to reRT, iGTV, ITV, central vs. peripheral
  • Pulmonary
    • Increased toxicity: larger $V_{10}$ ($P=0.025$), $V_{20}$ ($P=0.025$), MLD ($P=0.032$), and composite MLD ($P=0.024$)
    • NS: smoking status, concurrent chemo, central vs. peripheral, time to reirradiation, iGTV, ITV, EQD2

McAvoy et al., *IJROBP* 2014
IMRT & Proton Outcomes

- OS: median 14.7 months
- DMFS: median 11.4 months
- Local failure free survival: median 11.4 months

McAvoy et al., *IJROBP* 2014
Concurrent Chemotherapy

Histology

Reirradiation EQD 66

Time to ReRT 6 months

reRT GTV Volume 27

ECOG PS
# Patterns of Failure

<table>
<thead>
<tr>
<th>Site of Failure</th>
<th>Value or No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LRR after original radiation</strong></td>
<td></td>
</tr>
<tr>
<td>Same lobe</td>
<td>38 (37)</td>
</tr>
<tr>
<td>Ipsilateral lung, different lobe</td>
<td>16 (16)</td>
</tr>
<tr>
<td>Contralateral lung</td>
<td>17 (17)</td>
</tr>
<tr>
<td>Failure in radiation field</td>
<td>41 (40)</td>
</tr>
<tr>
<td>Marginal failure</td>
<td>13 (13)</td>
</tr>
<tr>
<td><strong>LRR after reirradiation</strong></td>
<td></td>
</tr>
<tr>
<td>Failure in field (either reirradiation or original)</td>
<td>37 (88)</td>
</tr>
<tr>
<td>Failure in reirradiation field</td>
<td>29 (69)</td>
</tr>
<tr>
<td>Failure in original field</td>
<td>23 (55)</td>
</tr>
<tr>
<td>Marginal failure</td>
<td>6 (14)</td>
</tr>
</tbody>
</table>

*Abbreviation: LRR, local-regional recurrence*
IMRT & Proton Key Points

- ReRT well tolerated
  - Rates of grade ≥3 toxicity: Esophageal 7%, pulmonary 10%
- LRC remains suboptimal (1 yr 49.2%)
- OS poor with median OS 14.7 months
- Patient selection is crucial & best candidates:
  - ECOG PS ≤1, T1-T3 disease, small volume recurrence, concurrent chemo, >6 months between RT
Patient selection factors associated with improved outcomes.

<table>
<thead>
<tr>
<th>Patient Factor</th>
<th>Low risk of Toxicity ≥ Grade 2 (esophagus or lung)</th>
<th>High probability of improved local control</th>
<th>High probability of improved OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG performance status 0</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Concurrent Chemotherapy</td>
<td>-</td>
<td>ns</td>
<td>+</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>ns</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>T4 disease at diagnosis</td>
<td>ns</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased EQD2 at reirradiation</td>
<td>ns</td>
<td>ns</td>
<td>+</td>
</tr>
<tr>
<td>Small volume iGTV (&lt;27 cm³)</td>
<td>ns</td>
<td>ns</td>
<td>+</td>
</tr>
<tr>
<td>Recurrence outside original RT field</td>
<td>ns</td>
<td>+</td>
<td>ns</td>
</tr>
<tr>
<td>Time to reirradiation &gt;6 months</td>
<td>ns</td>
<td>+</td>
<td>+ (marginal)</td>
</tr>
</tbody>
</table>

(+) designates variable has a positive impact on outcome;
(-) variable has a negative impact on outcome;
(ns) variable has no significant impact on outcome.
Can we create an algorithm for reirradiation in NSCLC?

• First decision point – candidate for SABR?
  • RT often more straightforward if can receive SABR
  • Within SABR, high-risk groups are chest wall involvement, centrally located lesions

• Second decision point – if not candidate for SABR, can patient be treated for definitive intent or is this palliative?
  • Use ECOG PS, number of sites, time to recurrence

• Third decision point – if non-SABR, what dose/fractionation regimen to use, chemo?
Overall Themes:

1) Attempt to find surgical option.

2) Severe RP is higher risk in all patients.

3) Most appropriate treatment for majority of patients is on clinical trial!
Designing Future Trials with Reirradiation

• Pertinent Issues:
  • 1) What dose constraints should be used?
  • 2) What should standard arm be?
  • 3) How aggressive should doses be?
  • 4) Fractionation regimen to be used?
  • 5) Relevant endpoint?
  • 6) Incorporate new agents?
Randomized Phase II Study of Concurrent Chemotherapy/Reirradiation + Adjuvant Nivolumab vs. Nivolumab Alone in Patients with Locoregionally Recurrent NSCLC

PI: Daniel Gomez, M.D.
Co-PI, Medical Oncology: Corey Langer, M.D.
Co-PI, Radiation Oncology: Charles Simone, M.D.
Translational Collaborator: Bo Lu, M.D., Ph.D.
Other core collaborators: Inga Grills, M.D., Spring Kong, M.D., Billy Loo, M.D., Jeff Bradley, M.D.
Overall Conclusions/Take Home Points

• Reirradiation for NSCLC still “black box,” with limited information to guide clinicians on appropriate patient selection or dose constraints
• More conformal methods will limit toxicity, but some increased risk for high-grade events will always be unavoidable
• Appropriate design of clinical trials will be critical in establishing role