Hypofractionation and the Oligometastatic paradigm

Jeff Ryckman

Outline

History of Hypofractionation
Recent advances: Radiation
Oligometastatic paradigm
Recent advances: Immunotherapy
Treatment Planning Tips

Hypofractionation: A Short History

1896 - First single fraction treatment to depigment a nevus=necrosis
Further attempts at single fraction radiation (1916 Friedrich, 1918 Seitz)


"The greatest cellkilling effect is obtained by single-dose fractionation; however, as a rule, the concomitant damage to normal tissues is not well tolerated...and we are forced to fractionate." Marcial V. Time-dose fractionation relationships in radiation therapy. Natl Cancer Inst Monogr 1967; 24: 187-203.

Because of the sparseness of long-term follow-up for SBRT, it should be recognized that the data in both Table III and the published reports represent, at best, a first approximation of normal tissue tolerance.

The Pace of Development - pre/post 2010

Other Developments Since 2010

- Immunotherapy and Systemic treatment
  - Since 2010, BRAF-directed therapy and immunotherapy were available on clinical trials, and after 2013-2015, use of these agents were more widely available.
  - Many other novel systemic agents available, such as Osimertinib for EGFR-mutated lung adenocarcinoma in 2018 (only ~10% of NSCLC).
- Imaging advancements improving sensitivity for mets

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Historic RT

- Extensive non-coplanar beams
- "Poor man's proton therapy"
- Giving up to 200-300 beams with couch rotations and kicks
- 4π optimization using group sparsity takes ~5 minutes
- Reduces R50 by 54%
- Heart, esophagus, trachea, bronchus, and spinal cord reduced by 44%, 74%, 40%, 42%, and 51%
Improving technology = more conformal plans

Comparison of SRS modalities

LINAC based SRS for multiple brain mets:
Guidance for clinical implementation

Brain Lab

Varian HyperArc:
4 non-coplanar beams
1 coplanar and 1 non-coplanar beam

What about protons?

Cost of a proton therapy center in 2010: $180 million
Cost of a proton therapy center in 2019: $50 million

Result: Sunk costs that need to be recouped in order to remain profitable

Theoretical benefit for pediatrics (decreased secondary malignancies) and central nervous system tumors (sparring of nearby organs at risk)

What about protons?

No difference in secondary malignancies for proton vs. photon [18]

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Conclusions

Proton Therapy vs. Photon Therapy

- Overall survival of all patients receiving proton therapy is comparable to previous reports of proton and photon treated metastasis patients.
- Our study also demonstrated no difference in the rate of SPM between proton and photon treated patients following radiotherapy for childhood metastasizations.
- In our study, proton treated patients demonstrated a higher rate of SPM in regions of the wall dose compared to photon patients.

● Actuarial SMN at 5y / 10y of 2.3→ 8.1%. MTTSMN of 6y.
What about protons?

Background: Proton beam therapy (PBT) is a radiotherapy platform that purportedly improves therapeutic ratio by way of a rapid dose fall off. Despite this technology being regarded significant capital and patient costs, the number of centres offering PBT is increasing exponentially. Consensus guidelines support PBT use in limited number of disease sites or on clinical trials. As patients frequently obtain information about PBT from hospital or cancer centre websites, the purpose of this study was to evaluate direct to consumer advertising (DTCA) content and claims made by proton therapy centre (PTC) websites.

Methods: English PTC websites were identified using the Particle Therapy Co-Operative Group website. Abstracts were performed independently by two investigators. Eight international guidelines were consulted to determine indications for PBT. Univariate and multivariate regression models were used to identify websites characteristics that were associated with claims that were not evidence based. Protons such as improved disease control or cure.

Results: From the 48 PTCs with 46 English websites, most (58%) did not provide any references for claims made regarding PBT. The most common conditions treated were prostate (87%), head and neck (87%), and pediatric (83%) and less common sites not endorsed in any consensus guidelines were pancreatobiliary (52%), breast (50%) and esophageal (44%). Prostate (87%) and pediatric (83%) cancers were most frequently listed PBT disease sites, consistent with international guidelines. However, pancreatobiliary (52%), breast (50%) and esophageal (44%) cancers were frequently advertised despite not being endorsed in any consensus guidelines. On multivariate analysis, an increasing number of listed disease sites and claims of being a regional PTC leader were associated with indicating that PBT offers greater disease control or cure. The availability of PBT through a clinical trial was mentioned on 57% of websites.

Conclusions: PTC websites often contain information and DTCA claims inconsistent with international consensus guidelines. As online marketing information may have significant influence on patient decision making, alignment of such information with accepted guidelines and consensus opinion should be adopted by PBT providers.

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Oligometastatic disease: The gardener analogy
Detecting Metastases from Prostate Cancer

Restaging with PSA < 0.5 after surgery:
- Limited data for restaging at PSA < 0.2 and moderate to slow doubling time. Most data for PSA >
- Bone scan has close to 0% positivity.
- CT ~ 5% positivity.
- MRI ~10% positivity.
- Axumin and Choline ~20% positivity.
- PSMA ~40% positivity. [Fendler JAMA Onc '19]

This is a very low PSA!

Detecting the "weeds"

Axumin PET/CT is FDA approved for prostate cancer, but is far inferior to PSMA PET which will have PET approval within 1-2 years.

UCLA [Calais Lancet Onc '19]: Prospective. PSMA accuracy in localizing recurrent prostate cancer.

Endpoint: PPV, detection rate, inter-reader reproducibility, and safety.
- 635 patients with PSA recurrence ≥ 0.2 after RP or nadir + 2 after RT (24%). Median PSA 2.1.
- For PSA < 0.5 / 1 / 2 / 5 of 38→ 57→ 84→ 86%.
- PET-directed therapy alone led to PSA drop of 50% or more in 31 of 39 patients (80%).

In patients with PSA >1, disease more often spread to multiple regions and less often confined to the pelvis.

This is not a very high number!
Which "gardener" to use?

Surgery preferred if: Need for pathology, outpatient procedure with quick recovery time, organ or node confined disease, mechanical instability, low volume metastatic disease, and/or younger patients.

Definition of Oligometastatic Prostate Cancer

Simplified: ≤ 5 bone or nodal mets (Per STOPCAP meta (although < 5), JHH data)

Variable definition: Essentially all definitions exclude patients with visceral mets.

CHAARTED/STAMPEDE H: < 4 bone-only mets anywhere or any number of spine/pelvis mets.

LATITUDE: < 3 bone metastases.

HORRAD: GS < 9, < 5 bony lesions, and PSA ≤ 142 (did not report non-bony mets).

Definition of Oligometastatic Lung Cancer

Patients with NSCLC with 5 or fewer metastases in 3 or fewer organs can be considered oligometastatic after staging with PET/CT and MRI brain.

Definition of synchronous oligometastatic NSCLC [Dingemans JTO '19]: A European consensus statement on the definition of synchronous oligometastatic NSCLC.

Bottom Line: A European consensus statement on the definition of synchronous oligometastatic NSCLC has been created, which will potentially inform future clinical trial design, appropriate patient selection for local therapy, and American payer definitions.

We need American definitions of oligometastatic disease for payor coverage!

10/7/2019
Colorectal → Liver resection

**EORTC 40004** [Ruers JNCI '17]: Phase II. Systemic ± LCT (RFA ± resection).

The first study to demonstrate aggressive local treatment improves OS for patients with unresectable liver metastasis.

In the LCT arm, 2/3 had any progression in liver, while in systemic arm 4/5 had any progression in liver.

More pts w less liver dz burden in LCT group.

- 152 pts. Unresectable liver-only CRC mets, primary resected. < 10 lesions, each < 4 cm. MFU 10y.
  - Systemic therapy: FOLFOX ± bevacizumab.
  - Nearly 50% of pts req'd combined surgery and RFA to obtain complete tumor treatment.

- 3y OS 55→ 57%, 5y OS 30→ 43%, 8y OS 9→ 36%, nearly all die from progressive dz. MS 41→ 46 mo.
  - MPFS 10→ 17 mo. 8y PFS 2→ 22%.
  - Progression in liver 80→ 67%.
  - Liver as first site of progression 80→ 50%. For RFA, only 15% LF.
  - Extrahepatic progression as first site of progression 14→ 25%.

It's not just Radiation that can improve survival in metastatic disease.

Local Consolidative Treatment

- Gomez [Lancet '16, JCO '19]: Phase II. Maintenance/Obs vs. Local Consolidative Therapy (Surgery, RT or CMT).

**Bottom Line**

Low-volume metastatic NSCLC that passes the stress test of not progressing on initial systemic therapy deserves consolidative treatment, and that might include conventional treatment of the primary lung disease.

This trial closed early due to PFS benefit with LCT. There is suggestion of inferior OS with delayed LCT in those who crossed over.

- 49 pts. Stage IV NSCLC with ≤ 3 mets after front line chemo. ECOG 0-2. Primary endpoint PFS. MFU 39 mo.
  - Front line chemo: 4c plt doublet chemo or 3 mo EGFR/ALK targeted therapy.
  - Required no progression after at least 4c of front line chemo.

- MT/O: Standard maintenance tx or surveillance. Crossover allowed at time of progression in MT/O group.

- LCT: Patients with a CR in metastatic sites and a persistent primary were allowed in the study (0 mets).
  - Treatment of lung primary: CCRT (n=6, 60-66 Gy), 45-60/15 (n=7), Surgery (n=3, two rec'd PORT).

- Patient characteristics: Around 2/3 had 0-1 sites of metastasis. Nearly all synchronous. Few CNS or EGFR.
  - MPFS 4→ 14 mo. MTT new lesions of 6→ 14 mo (p=0.11). MS 17→ 41 mo.
  - Survival after progression 9→ 38 mo.
  - Of the 20 pts who experienced progression in MT/O, 9 rec'd LCT to all lesions after progression w MS 17 mo.

- Suggestion of inf OS with crossover to complete LCT after PD/toxicity with standard maintenance.
  - No additional G3+ in either arm!

Don't delay local therapy!! Translation: Kill the Weeds, then Spray Weed-Gone

SBRT for oligo

SABR-COMET [Chung IJROBP '18]: Phase II. Standard of care ± SABR.

- Oligo vs standard ablative care & the PFS benefit is intriguing!
  - Oligo: Controlled primary w maximum 5 sites. No recurrence allowed. Median 3 mos. SABR by:
    - 2 wk after bevacizumab IRR syndrome cancer.
  - Median follow-up 3 mos.
  - SBRT ± Radiotherapy as per normal clinical practice.
  - PTV (uncensored clinical target volume).
  - 1 patient excluded due to fatal disease progression within 6 mos.
  - 6 patients excluded due to IRR syndrome after SBRT (4) or bevacizumab (2).

- Treatment of oligometastatic lesions may double overall survival!
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Immuno for oligo

Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial

**KEYNOTE-042** [ASCO abstract '18, Mok Lancet '19]:

- **Platinum chemo vs. Pembro** 200 q3w. PD-L1 ≥ 1%.
- **Pembro alone can be first line for PD-L1 ≥ 1%!** [Not in NCCN yet]

- **1,274 pts. SqCC or AC, treatment naive LA or metastatic NSCLC without EGFR or ALK. MFU 1y.**
  - **PDL1 ≥ 20% in 64%; PDL1 ≥ 50% in 47%.
  - **Carbo/paclitaxel or carbo/pemetrexed ≤ 6 cycles.**
  - **Still taking drug at 1y of 5→ 14%.**
  - **MS improved by 4-8 mo!**
  - **PDL1 ≥ 1%: MS 12.1→ 16.7 mo, HR 0.81.**
  - **PDL1 ≥ 20%: MS 13→ 17.7 mo, HR 0.77.**
  - **PDL1 ≥ 50%: MS 12.2→ 20 mo, HR 0.61.**

- **G3+ toxicity 41→ 18%.**

Recall: Last slide demonstrated a potential double-digit benefit in median survival with SBRT to oligometastases. There appears to be a greater benefit with SBRT alone vs. immunotherapy alone.

**Pembro-RT Trial** [Theelen ASCO '18, JAMA Onc '19]: Phase II + SBRT→ Pembro within 7d after end of SBRT.

- **Bottom Line**
  - **QS**: Inserting a quick shot of SBRT prior to pembrolizumab for refractory NSCLC is clearly safe and may double response rates, suggesting it is more practical than not to extrapolate Gomez data in the setting of pembrolizumab.

- **76 pts. ≥ 2nd line chemo for advanced NSCLC. Bx of tumor at baseline and after 2c pembrolizumab.**
  - **Pembro 200 q3w.**
  - **SBRT 24/8 within 7 days prior to first cycle.**

- **12w ORR 18→ 36%. MPFS 1.9→ 6.6 mo, MS 7.6→ 15.9 mo.**
  - **Improvements in ORR with SBRT are most marked with PD-L1 of 0%.**

- **G3+ in ~20%. Most commonly fatigue, nausea, fever, hypothyroidism.**

Immuno + RT?

**July 11, 2019**

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small-Cell Lung Cancer: Results of the PEMBROL亍 R1 Phase 2 Randomized Clinical Trial

- Pembrolizumab or pembrolizumab with stereotactic body radiotherapy (SBRT) for patients with advanced NSCLC who have failed first or second-line treatment.

- **SBRT and Immunotherapy work hand in hand!**
Harnessing the Immune System with SBRT

RT may promote immune-mediated killing by:

- Release of Damage-associated molecular patterns (DAMPs)
- Increased tumor-specific antigen presentation
- Upregulation of MHCs
- Decreased expression of PD-L1
- Upregulation of proteins that support T-cell adhesion.

Translation:

- Radiation causes irritation in an area of interest, jump-starting the immune system there!
- Radiation works hand in hand with immunotherapy.

Current research: 10/7/19

- 299 active trials investigating immunotherapy for metastatic disease
- 157 active trials investigating stereotactic radiation techniques for metastatic disease
- 23 studies investigating stereotactic radiation in combination with immunotherapy for metastatic disease

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Planning tips: Beware (?) of Immunotherapy

**Pembro with RT**

- Pembro within 7 days after end of RT.
- This toxicity isn’t really different than Pembro alone, but seems to correlate to area irradiated.

**73 pts, SBRT to 2 sites in 69/73 pts.**
- Target volumes < 65 mL (5 cm tumor).
- MFU 5.5 mo.
- 30/3 for bone/spinal.
- 45/3 for peripheral lung/liver/abd/pelvis.
- 50/5 for central lung/mediastinal/cervical.

**6 G3 toxicity (3 pneumonitis, 2 colitis, 1 hepatitis). 10% dose limiting toxicity.**

**Objective response 13.5% (2 CR, 8 PR, 21 SD, 38 PD).**

**Issue:** Toxicity from RT may lead to discontinuation of immunotherapy. Tread carefully!

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**Table 1:** Treatment Related, Spontaneous, and Clinical Toxicity to Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Toxicity Score</th>
<th>Spontaneous</th>
<th>Clinical</th>
<th>Treatment Related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>50%</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>25%</td>
<td>25%</td>
<td>5%</td>
</tr>
<tr>
<td>Grade 3</td>
<td>25%</td>
<td>25%</td>
<td>5%</td>
</tr>
</tbody>
</table>

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The final cohort included ninety-three patients with 103 treated lesions; eight of whom developed symptomatic RILD (63%). The use of total mean lung dose (MLD) 5–5 Gy captured five of the eight patients who developed symptomatic RILD, while only two of these patients demonstrated a total lung V20 > 10%. Only one patient died potentially as a result of treatment [3.2%] with a V10% of 9% and an MLD of 5.9 Gy, with 50% delivered to the MLD.
Thank you!