Single-Fraction vs Multi-Fraction Radiotherapy in Palliative Bone Metastases Patients
Acknowledgements

GVSU Statistical Consulting Center for help with statistical analysis
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Overview

Introduction

Methods

Results

Discussion

Conclusion
Research Question

Is there a difference in the proportion of patients receiving single-fraction versus multi-fraction treatment based on:

- Primary Malignancy
- Age
- Gender
- Race
- Region
- Overall number of single versus multiple fraction treatments

Key issues- patterns of utilization
The Beginning

Why does this interest me?
Background

What is bone metastases?

- **Lytic lesions**
  - Osteoclasts
  - Break down the bone

- **Blastic lesions**
  - Osteoblasts
  - Extra growth

30-70% of cancer patients

http://www.medicine.luc.edu/lumen/meded/radio/curriculum/surgery/met_bone_list1.htm
Background

What do we treat?

- Multiple metastases
- CTV defined by pain & local tenderness (not radiological extent)
Background

Symptoms
- Severe pain
- Spinal cord compression
- Hypercalcemia
- Pathologic fracture

What does Radiation do?
- Clinically relevant outcome = control pain → Quality of Life

http://ispub.com/IJRA/14/1/14086
Background

Median Survival = < 1 year

Other treatment options
- Pharmacological interventions
- Chemotherapy
- Radiopharmaceuticals
Background

RT is effective: within 1-4 weeks post RT

- Partial Pain Relief: 60-80%
- Complete Pain Relief: 30-50%
Background

Common fractionations:

- 30 Gy in 10 fx  
- 24 Gy in 6 fx  
- 20 Gy in 5 fx  
- 8 Gy in 1 fx

Multi-Fraction

Single-Fraction
ASTRO Guidelines:

- Guidelines Subcommittee of the Clinical Affairs and Quality Committee of the ASTRO
- Provides guidance on the use of palliative RT for bone metastases to patients & physicians
Introduction

ASTRO Guidelines:
- Systemic Literature Review
  - “Radiotherapy bone metastases”
  - 4,287 articles
    - 25 randomized clinical trials, 20 prospective single-arm studies & 4 meta-analyses/systematic reviews
ASTRO Guidelines:

- Most patients 8 Gy in 1 fraction is a safe and effective treatment
  - Shorter acute radiation side effects
  - Retreatment rate: 8% versus 20%
  - Pain relief similar

Conclude that the US has shown a delay and suggests that a change in the dose regimen should occur.
Introduction

Multi-fraction Should be Considered in:
- Spinal cord compression, cauda equine compression or radicular pain
- Previous treatment to the spine
- Femoral axial cortical involvement > 3cm in length
- Surgical stabilization
- Retreatment would be problematic
Introduction

International
- Canada
  - 20 Gy in 5 fx
- United Kingdom
- Western Europe
- Australia
- New Zealand
- India

All more likely to prescribe a single fraction
Population

Retrospective study based on billing data

Research Data Assistance Center (ResDAC)

- Outpatient Medicare beneficiaries in 2014
  - Outpatient Limited Data Sets (LDS) and the Denominator file (which includes the demographic data)
  - 5% random selection from the total Medicare population = roughly 2.8 million beneficiaries (from the 55 million)
Population

- Medicare eligibility includes beneficiaries:
  - 65 or older
  - Permanently disabled
  - End-stage renal disease
  - Lou Gehrig’s disease.
Population

Data
- Final action, fee-for-service claims
- Medical institutional provider numbers
- Physician identifiers
- Ninth Revision (ICD-9) diagnosis codes
- HCPCS codes
- Dates of service
- Reimbursement amount
- Outpatient provider number
- Revenue center codes
- Beneficiary demographic information
Population

Outpatient Providers
- Hospital outpatient departments
- Rural health clinics
- Renal dialysis facilities
- Outpatient rehabilitation facilities
- Community mental health centers
Ethical Considerations

Data Use Agreement (DUA)
• Outlines the purpose, project methods, data management safeguards, key personnel and dissemination of the data but does not go through a privacy board review

Beneficiary level PHI, but exclude specified direct identifiers.
• Some variables are encrypted, blanked or ranged to ensure privacy.
  • IRB approval was not required
Population

Roughly 2.8 million beneficiaries

- Diagnosis and RT billing codes

Steps:

- 1) Diagnosis code 198.5: secondary malignant neoplasm of bone and bone marrow (5,987)
- 2) RT delivery CPT code: 77401-77416 (392 beneficiaries)
- 3) Exclusions: complicated treatments, brachytherapy treatments, or ≥ 16 fractions
- 4) CPT codes 77401-77416 counted to determine the number of fractions delivered
Population

The final sample population: **303 beneficiaries**
- 50 beneficiaries that were missing a primary malignancy diagnosis code

Is there a difference in the proportion of patients receiving single-fraction versus multi-fraction treatment based on:
- Primary Malignancy
- Age
- Gender
- Race
- Region
<table>
<thead>
<tr>
<th>Primary Malignancy</th>
<th>Age Group</th>
<th>Gender</th>
<th>Race</th>
<th>Geographic Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Under 65</td>
<td>Male</td>
<td>White</td>
<td>Northeast</td>
</tr>
<tr>
<td>Prostate</td>
<td>65 to 75</td>
<td></td>
<td>Black</td>
<td>Southeast</td>
</tr>
<tr>
<td>Lung</td>
<td>76 to 85</td>
<td>Female</td>
<td>Asian</td>
<td>Midwest</td>
</tr>
<tr>
<td>Kidney</td>
<td>Over 85</td>
<td></td>
<td>Hispanic</td>
<td>Southwest</td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td>North American Native</td>
<td>West</td>
</tr>
<tr>
<td>Melanoma</td>
<td></td>
<td></td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Other or Multiple</td>
<td></td>
<td></td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>
**Methods**

**Statistics**

- Chi-square test was done for each variable (primary malignancy, gender, race, region and age)
  - Fisher’s test when assumptions were not met
  - Significance level = 0.05
Results

- Multi-Fraction: 279 (92.1%)
- Single-Fraction: 24 (7.92%)
Results: Total Population

Primary Malignancy
- Lung most common (n=67; 26.5%)
  - Followed by Prostate (n=55; 21.7%) and Breast (n=49; 19.4%)

Age
- Majority were 65-75 years (n=129; 42.6%) and 76-85 years (n=106; 35%)

Gender
- Slightly more males than females
Results: Total Population

Race
• Majority were Caucasian (n=276; 91.1%)

Geographic Region
• Majority in the Southeast (n=123; 40.6%)
Results: Single-Fraction

*Primary Malignancy*
- Lung most common lung \( n=10; 55.6\% \)
- Prostate \( n=3; 16.7\% \)
- Kidney \( n=2; 11.1\% \)

*Age*
- Mean age = 74.5 years
- Most common age group 76-85 \( n=12; 50\% \)
- 65-75 year olds \( n =8; 33.3\% \)

*Gender*
- Equal
Results: Single-Fraction

Race
- All were Caucasian ($n=24; 100\%$)

Geographic Region
- Majority in the Southeast ($n=12; 50\%$)
Results: Multi-Fraction

Primary Malignancy
- Lung most common lung \((n=57; 24.3\%)\)
- Prostate \((n=52; 22.1\%)\)
- Breast \((n=48; 20.4\%)\)

Age
- Mean age = 73.6 years
- Majority were 65-75 years of age \((n=121; 43.4\%)\)
- 76-85 year olds \((n=94; 33.7\%)\)

Gender
- Equal
Results: Multi-Fraction

Race
* Majority were Caucasian ($n=252; 90.3\%$)

Geographic Region
* Majority in the Southeast ($n=111; 39.8\%$)
## Results

**Table 2**
Chi-square and Fisher’s exact test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Test Statistic</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>0.0141</td>
<td>0.9055</td>
</tr>
<tr>
<td>Primary Malignancy</td>
<td>n/a</td>
<td>0.0759</td>
</tr>
<tr>
<td>Race</td>
<td>n/a</td>
<td>0.67</td>
</tr>
<tr>
<td>Region</td>
<td>n/a</td>
<td>0.8239</td>
</tr>
<tr>
<td>Age Group</td>
<td>n/a</td>
<td>0.3688</td>
</tr>
</tbody>
</table>
## Results

Fisher’s exact test separated by gender for Primary Malignancy.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Primary Malignancy</th>
<th>Fractions</th>
<th>More than 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Less than 10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>Kidney</td>
<td>4 (33.3)</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>18 (50)</td>
<td>10 (27.8)</td>
</tr>
<tr>
<td></td>
<td>Prostate</td>
<td>20 (36.4)</td>
<td>16 (29.1)</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>2 (28.6)</td>
<td>3 (42.9)</td>
</tr>
<tr>
<td>Female</td>
<td>Lung</td>
<td>17 (54.8)</td>
<td>10 (32.3)</td>
</tr>
<tr>
<td></td>
<td>Breast</td>
<td>19 (38.8)</td>
<td>18 (36.7)</td>
</tr>
</tbody>
</table>

\( p = 0.5722 \)

\( p = 0.5009 \)

Not significant
Single Fraction Rate

Single-fraction rate = 7.92%

* No significant changes have been made since the recommendations were published in 2011.

Top three primary diagnoses:

* Lung 26.5%
* Prostate 21.7%
* Breast 19.4%

* Matches current literature
According to the Kaiser Family Foundation, in 2014:

- 76% white
- 10% black
- 8% Hispanic
- 5% were Other.

Compared to 91.1%
Retreatments

- 8% versus 20%
- Actual reason for retreatment is often not clear
- 4-6 weeks post RT
- Feasible, safe & effective
  - No conclusive statement on dosing & fractionation
  - Recent trial: re-irradiation to a previously treated skeletal site of bone pain can provide pain relief in 50% of patients
Retreatments

Patient and physician choice and bias

Price et al.

- More likely with 8 Gy/1fx schedule
- Increased painkiller use in 30 Gy /10 fx
Fractions

The chart shows the distribution of number of fractions. The highest frequency is 32.6% for 10 fractions. Other frequencies are: 7.9% for 1 fraction, 3.3% for 2 and 3 fractions, 3.9% for 4 fractions, 11.8% for 5 fractions, 3.3% for 6 and 7 fractions, 3.0% for 8 fractions, 4.9% for 9 fractions, 3.6% for 11, 12, 13, 14, and 4.9% for 15 fractions.
Long Term Side Effects

Task Group: no unacceptable rates of long term side effects

- Statistically insignificant or clinically insignificant
  - Example: Pathological fracture rate – small percentage but significant
    - 2004 Study: 1.6% vs 3%

- RTOG 97-14: spinal cord myelopathy
  - Re-evaluated: 0% risk
Palliative Radiation Objective

JAMA in 1964

“Overall treatment time must be short. Cost must be minimized. Convenience of treatment must be considered.”

Distinction between curative and palliative goals has become blurred
Prognosis

Overestimate survival by a factor of 3 or more

Prognostic tools

Shorter life expectancy:

- Patient: poor performance status, advanced age, significant weight loss, severe comorbid disease
- Cancer: metastatic disease, aggressive histology
- Treatment: poor response to systemic therapy, previous radiotherapy
## Prognosis

### Karnofsky Performance Status

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Normal; no complaints; no evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity; minor signs or symptoms of disease</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity with effort; some signs or symptoms of disease</td>
</tr>
<tr>
<td>70</td>
<td>Cares for self; unable to carry on normal activity or to do active work</td>
</tr>
<tr>
<td>60</td>
<td>Requires occasional assistance but is able to care for most personal needs</td>
</tr>
<tr>
<td>50</td>
<td>Requires considerable assistance and frequent medical care</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requires special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalisation is indicated, although death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Very sick; hospitalisation necessary; active support treatment is necessary</td>
</tr>
<tr>
<td>10</td>
<td>Moribund; fatal processes</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>
The selection of palliative radiotherapy dose depends not only on prognosis but also on:

- performance status
- comorbidities
- risk of acute toxicity
- prior treatment
- delivery of systemic therapy
- patient wishes
Hospice

Barriers
- Cost of treatment
- Transportation difficulties
- Short patient life expectancy
- Educational lapses between the specialties

3% of hospice patients receive radiation therapy
- cancer is the most common diagnosis in patients admitted to hospice
The disparity between radiotherapy costs and the hospice per diem of about $120 per day was limiting

Perceived unwillingness of radiation oncologists to offer single-fraction treatment to eligible patients with painful bone metastases.
## Barriers & Limitations

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>No formal palliative care training.</td>
</tr>
<tr>
<td></td>
<td>Minimal protected time at national meetings for palliative oncology</td>
</tr>
<tr>
<td>Research</td>
<td>Lack of federal funds dedicated to end-of-life studies</td>
</tr>
<tr>
<td>Financial</td>
<td>Increasing radiotherapy costs due to technological advances</td>
</tr>
</tbody>
</table>

National Hospice and Palliative Care Organization
Limitations

- Difficulty in finding data
- Large data in multiple files
  - SAS code on a standard PC - upwards of 40 minutes
  - Blade Server from the Engineering department – roughly 2-3 minutes
- CPT codes were under HCPCS column

Inexperience
Limitations

By hand review 303 beneficiaries treatments & count the number of fractions.

<table>
<thead>
<tr>
<th>HCPCS_CD</th>
<th>date_diff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>0</td>
</tr>
<tr>
<td>77416</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>1</td>
</tr>
</tbody>
</table>
Limitations

- No prescribing information (multiple courses)
- Not generalizable
- Only outpatient data
- Unable to determine if met the criteria for single-fraction
There is therefore overwhelming clinical trial evidence to show that a single dose of 8 Gy is adequate and for palliation optimal for the patient with localized metastatic bone pain. There is no role for multifraction treatment in uncomplicated bone metastasis.
Take Away...

No significant results
- Demographic data or primary malignancy was not associated with the prescribing habits
- Current prescribing practices

Roughly 41% of the population died within 2014
Take Away…

Always ask questions.

Continue to learn.

Have a good professional rapport with your physician.
References


-Lutz, S. (2014) Role of Radiation Therapy in Palliative Care of the Patient With Cancer