Impact of Postoperative Daily Image-Guided Intensity-Modulated Radiotherapy on Overall and Local Progression-Free Survival in Patients with Oral Cavity Cancer

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Outline

- Introduction
- Purpose, Methods and Material
- Results and Discussion
- Conclusion
# RT in Far Eastern Memorial Hospital

| Radiation Therapy Type   | Date       |
|--------------------------|------------|
| Conventional RT         | 2001.11.01 |
| 3DCRT                   | 2002.02.01 |
| IMRT                    | 2002.08.01 |
| Tomo-IGRT               | 2006.12.12 |

> 5,000 cases

**Daily Tx:** 100 pts, 7:30am – 9:30pm, 90% IMRT; 45% IGRT

- **Elekta Versa HD**
- **TomoTherapy Hi ART® System to TomoHDA™ System**
- **TomoTherapy Hi ART® System**
Innovation of the TomoTherapy® System
Far Eastern Memorial Hospital

1st Global Experience, 2012
『Helical Irradiation of Total Skin』HITS
- Phantom study
  Biomed Res Int. 2013:108794
- Case Report
  Biomed Res Int. 2013:717589

1st Global Design, 2014
Lt Breast, Complete block
- Phantom Study
  Biomed Res Int. 2014:741326

1st Global Design, 2015
Esophageal Ca
Fan-shaped complete block
Biomed Res Int. 2015:959504

1st Asian Experience, 2008
『Total Marrow Irradiation』TMI
- Biomed Res Int. 2013;2013:321762.
- Technol Cancer Res Treat. 2009 Feb;8(1):29-38.
Head and Neck Cancer in Taiwan
The 4th Common Cancer in Male Taiwanese

- Oral cavity: 56%
- Nasopharynx: 14%
- Hypopharynx: 12%
- Oropharynx: 8%
- Larynx: 7%
- Salivary gland: 2%
- Nasal/sinus/Ear: 2%

Taiwan Cancer Registry, 2013
TomoTherapy® vs. 3DCRT, HNC of Korean study: better 2-y locoregional recurrence-free survival, but not OS

TomoTherapy® System vs. RapidArc, HNC of French prospective study: Benefits in 18-mo LR control and cancer-specific survival rate

Postop concurrent chemoradiation for oral cancer
TomoTherapy® System in FEMH

Hsieh CH et al, Radiat Oncol. 2010
Hsieh CH et al, BMC Cancer. 2016; 16:139
## Oral cancer: Acute Toxicity of Adjuvant Tomo +/- CT

| Institute          | Treatment | Fistula formation/or skin dehiscence | dermatitis | mucosistis | weight loss | Xerostomia | Anemia | Leukopenia | Thrombocytopenia |
|--------------------|-----------|--------------------------------------|------------|------------|-------------|------------|--------|------------|-----------------|
|                    |           |                                      |            |            |             |            |        |            |                 |
| RTOG 9501          | OP+RT +C/ T | -                                    | 8%         | 30%        | -           | 2%         |        | 38%        | (all of hematologic effects) |
| EORTC 22931        | OP+RT +C/ T | -                                    | -          | 41%        | -           | 14%        | -      | 16%        |                 |
| RTOG 0024          | OP+RT +C/ T | 11%                                  | 29%        | 60%        | -           | -          |        | 12%        | (all of hematologic effects) |
| Yu et al.          | OP+RT     | 8-29%                                | -          | -          | -           | -          | -      |            |                 |
| Jeremic et al      | RT+C/T    | -                                    | -          | -          | 29%         | -          | -      | -          |                 |
| Capuano et al      | RT+C/T    | -                                    | -          | -          | 17%         | -          | -      | -          |                 |
| FEMH, Taiwan       | OP+HT +C/T (84%) | 11%                          | 5%         | 42%        | 0%          | 0%         | 0%     | 5%         | 0%              |

BMC Cancer. 2011; 11: 3.
Oral Cancer

Postop RT+/-CT: TomoTherapy® vs. IMRT

- **Study interval**
  - 2006/12-2013/12 at FEMH

- **Patient selection**
  - Postop oral cavity cancer patients
  - Pathology proven SqCC with high risk factors

- **Stage**
  - AJCC 6th edition

Hsieh CH et al, BMC Cancer. 2016; 16:139
| Characteristics          | IMRT (No. = 79) | HT (No. = 73) | P value |
|--------------------------|-----------------|---------------|---------|
| No. of patients (%)     |                 |               |         |
| Age (years)              |                 |               |         |
| Median                   | 48              | 52            | 0.398   |
| Range                    | 29-78           | 24-78         |         |
| Subsite                  |                 |               |         |
| Oral tongue              | 25 (31.6%)      | 35 (47.9%)    |         |
| Buccal mucosa            | 34 (43.0%)      | 25 (34.2%)    |         |
| Alveolar ridge           | 8 (10.1%)       | 7 (9.6%)      | 0.348   |
| Retromolar trigone       | 5 (6.3%)        | 3 (4.1%)      |         |
| Floor of the mouth       | 2 (2.5%)        | 2 (2.7%)      |         |
| Hard palate              | 2 (2.5%)        | 1 (1.4%)      |         |
| Lip                      | 3 (3.8%)        | 0             |         |
| Tumor stage              |                 |               |         |
| I                        | 6 (7.6%)        | 8 (11.0%)     |         |
| II                       | 12 (15.2%)      | 12 (16.4%)    | 0.532   |
| III                      | 18 (22.8%)      | 15 (20.5%)    |         |
| IVA                      | 43 (54.4%)      | 38 (52.1%)    |         |
| Combined with chemotherapy|               |               |         |
| Yes                      | 67 (84.8%)      | 65 (89.0%)    | 0.442   |
| No                       | 12 (15.2%)      | 8 (11.0%)     |         |
| RT dose                  |                 |               |         |
| Median                   | 66 Gy           | 66 Gy         | 0.304   |
|                          | 17              |               |         |
Survival
Adjuvant TomoTherapy® System better than adjuvant IMRT

- Postop IGRT (TomoTherapy® System): better OS, better local PFS, less marginal failure and shorter overall treatment time than postoperative non-image-guided IMRT

Hsieh CH, et al. BMC Cancer. 2016
### Long-term Result

| Selected series | No. of postop patient | Postop Modality | FU (year) | OS   | DFS | LR PF | DMF |
|-----------------|-----------------------|-----------------|-----------|------|-----|-------|-----|
| Lin.            | 245                   | IMRT            | 5         | 54%  | 68% | 41%   | 66% |
| Hoffmann        | 18                    | IMRT            | 5         | 77%  | 72% | 78%   | 80% |
| EORTC 22931     | 41(167)               | CCRT            | 5         | 53%  |     |       |     |
| RTOG 9501       | 50(206)               | CCRT            | 5         | 46%  | 30% |       |     |
| FEMH (152 pts)  | 79                    | IMRT            | 5         | 48%  | 39% | 58%   | 83% |
|                 | 73                    | HT              | 5         | 87%  | 74% | 85%   | 80% |

Are these data compatible with previous published series?
Yes! IMRT’s data is compatible with other reports!

HT provides better results than IMRT: It could be believed probably....
More high-risk patients in IMRT group? No!

| Prognostic factors                      | IMRT | HT   | p value |
|----------------------------------------|------|------|---------|
| Resection-margin                       | 49%  | 58%  | 0.313   |
| ECE                                    | 17%  | 26%  | 0.148   |
| PNI                                    | 62%  | 82%  | 0.006   |
| LVSI                                   | 39%  | 62%  | 0.003   |
| Two or more positive lymph nodes       | 22%  | 30%  | 0.302   |
| T3, T4                                 | 54%  | 48%  | 0.768   |
| Adjuvant chemo                         | 85%  | 89%  | 0.442   |

Hsieh CH et al, BMC Cancer. 2016; 16:139
| Prognostic factors | Modality   | 95% CI     | p value | Modality   | 95% CI     | p value |
|--------------------|------------|------------|---------|------------|------------|---------|
|                    | HT         | IMRT       |         | HT         | IMRT       |         |
| Resection-margin   | 84.0%      | 57.7%      | 0.52 to 0.68 | 0.008    | 92.5%      | 28.6%      | 0.51 to 0.77 | 0.006 |
| ECE                | 76.6%      | 31.7%      | 0.39 to 0.65 | 0.007    | 54.0%      | 64.1%      | 0.39 to 0.65 | 0.942 |
| PNI                | 79.3%      | 35.2%      | 0.15 to 0.97 | 0.005    | 82.3%      | 43.9%      | 0.28 to 0.85 | 0.003 |
| LVSI               | 77.0%      | 50.0%      | 0.49 to 0.64 | 0.012    | 78.8%      | 0.0%       | 0.54 to 0.74 | 0.001 |
| Two or more positive lymph nodes | 74.0% | 40.3% | 0.41 to 0.61 | 0.010 | 77.0% | 26.2% | 0.29 to 0.85 | 0.003 |
| T3,4               | 72.8%      | 38.7%      | 0.39 to 0.73 | 0.017    | 79.5%      | 39.8%      | 0.25 to 1.02 | 0.005 |

| Modality          | HT vs IMRT | Hazard ratio (HR)* | 95% CI     | P value | Hazard ratio (HR)* | 95% CI     | P value |
|-------------------|------------|---------------------|------------|---------|---------------------|------------|---------|
|                    |            | 0.32                | 0.15 to 0.67 | 0.002   | 0.21                | 0.08 to 0.59 | 0.003   |
IGRT may overcome the poor prognostic factors than IMRT potentially. why?
Better prognosis shorter POTT and OTTRT

OS

LPFS

POTT ≤ 13 weeks

OTTRT ≤ 8 weeks

Package of overall treatment time (POTT)

Overall treatment time of RT (OTTRT)

Hsieh CH et al, BMC Cancer. 2016; 16:139
Expansion of CTV to PTV margin for HN cancer
Higher incidence of complications: 5mm vs. 3mm

- Gastrostomy-tube dependence at 1 year
  ✓ 5 mm vs 3 mm
  10% vs 3%, p = 0.001

- Posttreatment esophageal stricture
  ✓ 5 mm vs 3 mm
  14% vs. 7%, p = 0.01

Small PTV margin difference
Make sense

Volume \( \frac{4}{3} \pi r^3 \)
V outer layer = V core of the orange

Chen AM et al. Head Neck. 2014;36:1766
Verellen D et al. Nat Rev Cancer;7:949
## More weight loss in adjuvant IMRT Group

| Weight loss | IMRT (No. = 79) | HT (No. = 73) | P value |
|-------------|-----------------|---------------|---------|
| Gr. 1       | 51 (64.6%)      | 62 (84.9%)    |         |
| Gr. 2       | 27 (34.2%)      | 11 (15.1%)    | 0.004   |
| Gr. 3       | 1 (1.3%)        | 0             |         |

## More pts with prolonged Tx time in adjuvant IMRT Group

| Tx time     | IMRT  | HT    | P value |
|-------------|-------|-------|---------|
| POTT ≤ 13 weeks | 58.0% | 83.4% | 0.001   |
| OTTRT ≤ 8 weeks | 68.0% | 89.0% | 0.002   |

Hsieh CH et al, BMC Cancer. 2016; 16:139
| Variable      | IMRT vs HT                                      |          |          | P value |          |          | P value |
|---------------|------------------------------------------------|----------|----------|---------|----------|----------|---------|
|               | Overall survival                               | P value  | Local    |         | progression-free survival |         |         |
| POTT ≤ 13 wks | 58.3% vs. 85.0%                                | 0.05     | 59.1%    |         | vs. 85.8%                  | 0.015   |         |
| OTTRT ≤ 8 wks | 58.3% vs. 85.0%                                | 0.05     | 56.2%    |         | vs. 88.0%                  | 0.025   |         |

Hsieh CH et al, BMC Cancer. 2016; 16:139

Why HT has better outcome than IMRT under the similar POTT or OTTRT?
Pattern of local failure

More local failure (esp. marginal failure) in IMRT group

| Local failure rate                  | IMRT (No. = 79) | HT (No. = 73) |
|-------------------------------------|-----------------|---------------|
| Total local failure                 | 24.0% (n = 19/79) | 6.8% (n = 5/73) |
| In-field failure                    | 31.6% (n = 6/19) | 80.0% (n = 4/5) |
| >95% recurrent volume in CTV        |                 |               |
| Marginal failure                    | 52.6% (n = 10/19) | 0 (n = 0) |
| 20-95% volume in CTV                |                 |               |
| Out-of-field failure                | 15.5% (n = 3/19) | 20% (n = 1/5) |
| <20% volume in CTV                  |                 |               |

Hsieh CH et al, BMC Cancer. 2016; 16:139
Marginal Failure is an issue
Postop IMRT ± concurrent chemo

| Institution                      | Modality | Pt. No. | No. of oral cancer (%) | PTV margin | No. of marginal failure / local failure | marginal failure (%) |
|---------------------------------|----------|---------|------------------------|------------|----------------------------------------|----------------------|
| Bern University Hospital, Switzerland[1] | IMRT     | 53      | 100%                   | 3 mm       | 10/12                                  | 83%                  |
| Iowa, USA[2]                    | IMRT     | 49      | 100%                   | 5 mm       | 4/9                                    | 44%                  |
| Toronto, Canada [3]             | IMRT     | 180     | 100%                   | -----      | 12/38                                  | 32%                  |
| UC Davis [4]                    | IMRT     | 90      | 48%                    | 3-5 mm     | 6/17                                   | 35%                  |
| UC Davis [5]                    | IMRT     | 52      | 48%                    | 3-5 mm     | 4/13                                   | 31%                  |
| Stanford [6]                    | IMRT     | 30      | 100%                   | 3-5 mm     | 2/11                                   | 18%                  |
| Kashiwa, Japan [7]              | IMRT     | 122     | 48%                    | 5 mm       | 5/32                                   | 16%                  |
| FEMH [8]                        | IMRT     | 79      | 100%                   | 5 mm       | 10/19                                  | 53%                  |
## Postop daily IGRT decrease marginal miss

| Modality               | Pt. No. | oral cancer (%) | PTV margin | No. of marginal failure /local failure | marginal failure (%) |
|------------------------|---------|-----------------|------------|----------------------------------------|----------------------|
| UC Davis [9]           | IG-IMRT | 103             | 31%        | 5 mm                                   | 5/76                 | 7%                   |
|                        |         | 264             | 21%        | 3 mm                                   | 4/76                 | 5%                   |
| FEMH [8]               | IG-IMRT daily Tomo | 73           | 100%       | 3 mm                                   | 0                    | 0%                   |

1. Geretschläger A et al. Radiat Oncol. 2012;7:175
2. Yao M et al. Int J Radiat Oncol Biol Phys. 2007;67:1332
3. Chan AK et al. Oral Oncol. 2013;49:255
4. Chen AM et al. Int J Radiat Oncol Biol Phys. 2011;80:1423
5. Chen AM et al. Head Neck. 2010;32:1452
6. Daly ME et al. Int J Radiat Oncol Biol Phys. 2011;80:1412
7. Ooishi M et al. Jpn J Clin Oncol. 2016;46:919
8. Hsieh CH et al, BMC Cancer. 2016; 16:139
9. Chen AM et al. Head Neck. 2014;36:1766
Bigger PTV of IMRT vs. Tomo

Margin for primary PTV
- IMRT: 5 mm
- HT: 3 mm

But

Setup Error of Postop oral cancer by Tomo MVCT

| Axis                      | Variation       |
|---------------------------|-----------------|
| X-axis (right and left)   | 6.4 – 8.7 mm    |
| Y-axis (craniocaudal)     | 4.7 – 9.7 mm    |

Hsieh CH et al, BMC Cancer. 2016; 16:139
Less-than-daily image-guided RT strategies: UCSF
- high incidence of potential miss at 3-mm PTV margin
- Recommend: at least 5-mm PTV margin

Different IGRT protocol and margin size

Geometric miss: observed setup error with axial component greater than the margin size

Yu Y. et al. Head Neck, 2014
Geometric miss detected by TomoTherapy®-MVCT

Be careful:
Weight loss/gain, tumor shrinkage/progression, edema!

Weight loss / motion related missing target, esp at lower neck

What’s wrong?

CT-sim, 53Kg & MVCT, 56Kg
Daily IGRT using TomoTherapy® System may increase OS and local control rate!
Prospective and randomized study is warranted.