Intensity modulated radiotherapy versus conventional 2D radiotherapy in oropharyngeal & hypopharyngeal cancer: the outcome & the pattern of recurrence

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Aim

1- To compare the early\& late side effects (grade 2 or more) associated with treatment with IMRT\& conventional 2D radiotherapy (2DRT) in patients with oropharyngeal\& hypopharyngeal cancer

(as a primary outcome measure).

2- To compare the loco-regional control in patients with oropharyngeal \& hypopharyngeal cancer treated with IMRT with those treated with conventional 2D radiotherapy (as a secondary outcome measure).

3- To compare the pattern of recurrence after treatment using IMRT with that seen after treatment using conventional 2D radiotherapy.
Methods and materials

Study design:

This is a matched case - control study. Matching has been done by the T.N.M stage. Cases were chosen to be patients who were treated using IMRT while the control group included patients who had been treated using conventional 2D radiotherapy.

Review of the medical records of patients diagnosed with; oropharyngeal& hypopharyngeal squamous cell carcinoma histopathology as well as the data base at our institution in the period between 1993&2010 has been done with emphasis on the toxicity profile, locoregional control & the pattern of tumour recurrence after radiotherapy.

Patients in both groups:

The review included patients with oropharyngeal & hypopharyngeal SCCA who were treated with curative intent except those with carcinoma of the base of tongue (due wide individual variability in target volume delineation & inaccurate assessment of the extent of recurrence on CT scan ) as well as those with concurrent primary tumour &/or those receiving biological therapy.

Staging, response evaluation & side effects grading:

Staging was done according to the AJCC staging manual 2002.

Evaluation of the response to treatment was done using the (WHO criteria).

Grading of side effects was performed according to the (NCIC common toxicity criteria).

Review of the radiotherapy plans was done by reviewing the charts for patients treated with IMRT & on the planning system while in conventional 2D radiotherapy, it was done by reviewing the patients radiotherapy charts together with the x-ray check films.

Determination of the volume & site of tumour recurrence in the conventional radiotherapy group was done by reviewing the CT scans/MRI showing it by a Radiologist. The patients in both groups were immobilized using the thermoplastic head & neck mask.

Intensity-Modulated Radiotherapy (IMRT):
Virtual simulation was done using a multislice CT simulator with slice thickness from 2 to 5 mm.

**Treatment planning**

(The inverse planning system)

Delineation of the target volumes & the organs at risk (OAR) was done according to the ICRU 50&62 reports definitions. In definitive radiotherapy, delineation of the gross tumour volume (GTV) was done based on the imaging & clinical examination.

The high risk clinical target volume (CTV) included the GTV primary & nodal plus a margin of 0.7 - 1cm. In N0 lymph nodes, CTV low risk was delineated according to the DAHANCA, EORTC, GORTEC, RTOG consensus guidelines.

The planning target volume (PTV) was delineated by adding a margin of (0.3 - 0.5cm) to the corresponding CTV. The radiotherapy doses were prescribed to the PTVs.

**The organs at risk (OARs):**

Doses to (OARs) were kept within the tolerance limits:

In most cases a margin around the organ at risk (PRV) of 0.3 cm was added around the spinal cord & the brain stem.

**Treatment delivery:**

IMRT treatment delivery was done in the corvus unit using 6MV linear accelerators by (3 - 7) angled beams using the Simultaneous Integrated Boost (SIB) technique with a fraction size ranging from 2.12 Gy to 2.25Gy.

**Chemotherapy:**

Concurrent weekly cisplatin was used in most patients.
**Recurrence after IMRT:**

On recurrence, fusion of the new CT/MRI or PET scan with the CT scan which was initially used for delineation of target volumes has been performed.

The recurrence was considered (in field) if 95% or less of its volume was located in the high dose region, borderline&marginal, if 25% (or less)&5% (or less) of its volume lies in the high dose region respectively.

**Conventional 2D radiotherapy (2DRT):**

Conventional radiotherapy had been planned using the conventional simulator using two lateral opposing fields matched with the low anterior neck field.

Treatment delivery had been performed using the cobalt unit & 6 MV linear accelerators. Patients had been treated up to 45 Gy to the lateral opposing fields to the neck then off-cord. Patients with residual lymph nodes in the posterior neck had been boosted by a 9 Mev electron beam.

**Recurrence after conventional 2D radiotherapy (2DRT):**

Localization of the site recurrence either in the high dose region (60 Gy or more) or low dose region (< 60 Gy) or both has been done using the CT data describing the site of recurrence & its maximal 3D diameters then multiplying them to obtain the volume of recurrence (in cm$$^3$$) & correlating that volume to the conventional 2D radiotherapy fields (on the x-ray check films) in relation to a bonny landmark (e.g. the hyoid bone) by a Radiologist.
Fig. 1: Isodose lines on a sagittal CT slice for an IMRT plan of adjuvant radiotherapy for pyriform sinus carcinoma.

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Fig. 2: DVH for an IMRT plan of adjuvant radiotherapy for pyriform sinus carcinoma

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Results

This study included 100 patients. Fifty patients were treated using IMRT & the other 50 patients had been treated using conventional radiotherapy (2DRT).

Cases had a median age of 62 years & with a median follow up of 18 months while, the control group had had a median age of 58 years, & a median follow up of 22.6 months. In the cases, 45 patients received definitive radiotherapy & 5 patients received adjuvant radiotherapy while in the control group, 38 patients & 12 patients received definitive & adjuvant radiotherapy respectively. The median radiotherapy dose in cases was 67.5 Gy while in the control group, it was 66 Gy.

Chemotherapy (cisplatin) was received by 38 patients in cases while 5 patients had received it in the control group. The response rate was 93% in cases while it had been 89% in the control.

(I) Side effects:

(A) Early side effects:

1- Xerostomia

Early xerostomia of grade II (moderate) was reported in 8 patients in cases while in the control, grade II & III xerostomia had been reported in 32 patients.

Xerostomia odds ratio = 0.10

2- Mucositis was reported in 35 patients in cases while, it had been reported in 37 patients in the control.

Mucositis odds ratio = 0.61

3- Dermatitis was reported in 22 patients in cases but, it had been reported in 14 patients in the control.

Dermatitis odds ratio = 2.02
4.-**Dyphagia, laryngitis & weight loss:**

Dyphagia was reported in 7 patients (14%) in cases but it had been reported in one patient (2%) in the control. It is to be noted that 2 patients of those who developed dyphagia in the IMRT group had oesophageal stenosis & underwent endoscopic dilatations.

Laryngitis (grade III) was reported in one patient (2%) in cases but in three (6%) patients in the control.

Weight loss was reported in 9 patients (18%) in cases but in 23 patients (46%) in the control.

Also, **Otitis media** was reported in one patient (2%) in the control.

Desquamation (dry & moist) was reported in one patient (2%) in cases but in 6 patients (12%) in the control.

**(B) Late side effects:**

1.- **Late Xerostomia** was reported in 8 patients (16%) (grade II) in cases while it had been reported in 32 patients (64%) (28 grade II & 4 grade III) in the control.

2.- **Other late side effects:**

Pharyngeal/esophageal Stenosis was reported in 2 patients (4%) in cases.

**Osteonecrosis & mandibular fracture** had been reported in one patient (2%) in the control.

**Late skin reactions:**

**Fibrosis** was reported in one patient (2%) in cases while **Fibrosis, telangiectasia, hyper & hypopigmentation** had been reported in two (4%), 5 (10%) & 9 (18%) patients respectively in the control.
Hypothyroidism was reported in 8 patients (16%) in the control group but unfortunately thyroid function tests were not requested on routine basis in cases.

(II) Locoregional control & survival

The 5 years actuarial locoregional control was 89.54% in cases (IMRT) versus 62.48% in the control (P<0.0001) & multivariate analysis revealed that IMRT is an independent factor for improving the locoregional control (P<0.0001).

The 5 years actuarial relapse free survival was 92.3% in cases versus 78.75% in the control.

(III) The pattern of recurrence

In the IMRT group/cases 3 patients recurred while in the control 10 patients recurred.

The recurrence odds ratio =0.25

Recurrence after IMRT

Two patients (66.7%) recurred in the high dose PTV (in field recurrence) and the 3rd patient’s recurrence (33.3%) was borderline.

Recurrence after conventional 2D radiotherapy

In the control group (2DRT) the 10 patients whose tumours recurred, 6 patients (60%) had infield & 4 patients (40%) had borderline recurrences.

Distant metastases in both groups

Distant metastases were reported in 6 patients in cases while they had been reported in 7 patients in the control group (P-value=0.76).
Fig. 3: Early & late xerostomia in both groups

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Fig. 4: Mucositis in both groups

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**Fig. 5:** Dermatitis in both groups

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![Table 2-1](image)

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Conventional Radiotherapy</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 years actuarial</td>
<td>89.54%</td>
<td>62.48%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Locoregional Control</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 years Overall</td>
<td>74.03%</td>
<td>60%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years actuarial</td>
<td>58.08%</td>
<td>47.72%</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Overall survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 years actuarial</td>
<td>92.03</td>
<td>78.75</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Relapse free survival</td>
<td></td>
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</tbody>
</table>

**Fig. 6:** The locoregional control & survival

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![Table 2-2](image)

<table>
<thead>
<tr>
<th>Variable</th>
<th>95% confidence interval</th>
<th>Test statistic</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td>1.06 - 7.38</td>
<td>2.625</td>
<td>0.0102</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>0.66 - 1.68</td>
<td>4.511</td>
<td>0.0001</td>
</tr>
<tr>
<td>Surgery</td>
<td>-0.35 - 0.30</td>
<td>-0.170</td>
<td>0.7560</td>
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</tbody>
</table>

**Fig. 7:** The multivariate analysis for locoregional control

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Table (2-3) Recurrence in both groups

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>Conventional radiotherapy</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>0</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Loco-regional</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>10</td>
<td>0.0377</td>
</tr>
</tbody>
</table>

**Fig. 8:** Recurrence in both groups

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Table (2-4) The observed recurrence odds ratio:

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>No</td>
<td>47</td>
</tr>
<tr>
<td>2D RT</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
</tr>
<tr>
<td>No</td>
<td>40</td>
</tr>
<tr>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>87</td>
</tr>
</tbody>
</table>

Odds ratio = 0.25

**Fig. 9:** The recurrence odds ratio

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Table 2.5: The Site & volume of recurrence in relation to the conventional radiotherapy fields

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>High dose field (%)</th>
<th>Low dose field (%)</th>
<th>Number</th>
<th>Localization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>100</td>
<td>0</td>
<td>6</td>
<td>In field</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>55</td>
<td>45</td>
<td>1</td>
<td>Borderline</td>
</tr>
<tr>
<td>Regional</td>
<td>60</td>
<td>40</td>
<td>1</td>
<td>Borderline</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>65</td>
<td>35</td>
<td>1</td>
<td>Borderline</td>
</tr>
<tr>
<td>Loco-regional</td>
<td>83</td>
<td>17</td>
<td>1</td>
<td>Borderline</td>
</tr>
</tbody>
</table>

**Fig. 10:** The site of recurrence in 2DRT relative to the conventional radiotherapy fields

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**Fig. 11:** The overall survival

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Fig. 12: The relapse free survival

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Conclusion

Treatment with Intensity Modulated Radiotherapy (IMRT) improved the early side effects except for dermatitis & dysphagia meanwhile, the late side effects were not compromised, most side effects decreased. Thus, it improved the therapeutic ratio.

Using IMRT, markedly decreased the proportion of patients who developed xerostomia during treatment of oropharyngeal & hypopharyngeal cancer with radiotherapy.

The use of IMRT allowed dose escalation & it added an improvement to the locoregional control in oropharyngeal & hypopharyngeal cancer patients.

In other words, Intensity Modulated Radiotherapy (IMRT) improved the treatment outcome in oropharyngeal & hypopharyngeal cancer patients.

The pattern of recurrence after treatment with Intensity Modulated Radiotherapy (IMRT) is almost like that seen after treatment with conventional 2D radiotherapy in oropharyngeal & hypopharyngeal cancer patients.
Personal information

Radiation Oncology Fellow, McGill University, Canada
(Head & Neck cancer unit).

References


