Overall Quality Assurance and Review -- Clinical Perspective

Lester Peters
Professor of Radiation Oncology
Peter MacCallum Cancer Centre
Aims

Assuring accurate and safe delivery of radiotherapy to cancer patients through setting up a quality assurance/review system
Quality Assurance (QA)

Defined as:

All those planned and systematic actions necessary to provide adequate confidence that a product or service will satisfy the given requirements for quality

ISO 9000:1994
Quality Control (QC)

QC is one part of overall quality assurance and is defined as:

A regulatory process through which the actual quality performance is:

- Measured
- Compared with existing standards
Quality Assurance in radiotherapy

• All procedures that ensure
  – consistency of the delivered dose with the radiotherapy prescription
  – safe and effective treatment
• This includes
  – Optimal Dose to target volume
  – Minimal dose to normal tissue
  – Minimal exposure of personnel
  – Vigilant clinical assessment
  – Complete documentation, etc.
Components of a Comprehensive QA Program

- Quality Assurance Committee
- Policies and Procedures Manual
- Quality Assurance team
- Quality audits
- Appropriate Resources
QA Committee Members

- Must represent the many disciplines within the department
- Should be chaired by the Head of Department
- At a minimum, the committee members must include at least a radiation oncologist, a medical physicist and a radiotherapy technologist. Other professional groups like nursing, dosimetrists and an engineer responsible for service and maintenance, can be added as relevant.
- Must be appointed and supported by senior management
- Must have sufficient depth of experience to understand the implications of the process
- Must have the authority and access to the resources that are needed to initiate and support the QA process
Quality Assurance Team

• Includes all disciplines
• Well defined responsibility and reporting structure
• Each member of the team must
  – Know his/her responsibilities
  – Be trained to perform them
  – Know what actions are to be taken should a test or action be outside the preset “action levels”
## Responsibility Chart

<table>
<thead>
<tr>
<th>Area of Responsibility</th>
<th>Profession</th>
<th>Doctor</th>
<th>Head Technician</th>
<th>Physicist</th>
<th>Secretary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical</td>
<td></td>
<td>●</td>
<td>○</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Equipment</td>
<td>○</td>
<td>□</td>
<td>○</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>Availability of Technicians</td>
<td>●</td>
<td></td>
<td></td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>Stock</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>●</td>
</tr>
</tbody>
</table>
Quality Audit

A systematic and independent examination and evaluation to determine:

• whether quality of activities and results comply with planned arrangements
• whether the arrangements are implemented effectively and are suitable to achieve the objectives.”

“Quality assurance in radiotherapy.”, Radiother. Oncol., 1995

Do we do what we say we do?
Internal audit

• Carried out by staff members in the department who are appointed to:
  – Review results of all QC
  – Verify QC are effectively carried out at prescribed intervals
  – Verify results of QC are in line with tolerances and action levels
  – Identify trends for deviations
  – Propose improvements in QC technique
External Quality Audit

• Ideally performed by someone outside of the organisation (but with the same professional background): Peer review

• Examples
  – IAEA/WHO TLD programme for check of dose in radiotherapy units
  – QUATRO by IAEA
  – EQUAL programme for Europe
  – Audits as part of participation in clinical trials (eg RPC audit for RTOG)
QA should ensure every step in the treatment chain...

Eg: Hand calculation of treatment time
Eg: Check source activity

The treatment chain in radiotherapy
Treatment Verification

*Individual QA activities*

- Diagnostic Images
- Treatment Decision
- Prescription Implant
- Simulation
- Treatment Planning
- Preparation of sources
- Treatment

Treatment verification
QA in Radiotherapy

• Many documents exist that specify what QA activities should be performed in radiotherapy...
Documentation

• Internal
  – procedures
  – QA
  – forms

• External
  – reports
  – audits
  – publications
Treatment records

- Must contain all relevant information
- Should be compatible with international standards (e.g. ICRU reports 38, 50, 58, 62, 83)
- Can be in electronic format but should provide for electronic signatures according to local procedures.
Clinical QA

• QA extends to everyone - not just the technical aspects
• A good way to do this are ‘chart rounds’ or ‘grand rounds’
• Film review
• New patient planning conferences
Chart Rounds

• Regular review of patients

• Can be all patients or randomly selected patients

• Should include all patients with unexpected severe complications
Outcome Monitoring

• At the regional or national level: Cancer Registry (incidence and mortality)

• At the department level:
  – Serious adverse events registry
  – Survival of cancer patients
  – Morbidity and mortality conferences
The Cost of QA

• Dedicated staff - qualifications, training and numbers
• Equipment - include allowance for redundancy
• Time - commissioning, QA, reports, meetings, training
• Benefit of QA comes at a cost
• Are these the true shapes of curves?
• Balance between too little and too much
The benefits of QA

• Benefits for the department
  – improved management system
  – improved communication
  – improved safety
  – less duplication and waste

• Benefits to patients
  – Better chance of safe and effective treatment
  – optimized procedure
  – re-assurance
Additional benefits

• Credibility
• Potential to attract funding (and account for it…)
• Participation in clinical trials
• Regular updates and audits continue improvements
• Pride and confidence of staff
QA is not a threat, it is an opportunity

- It is essential in a QA program that all staff feel free to report errors
- A non threatening environment must exist
- Reward honesty with encouragement
- Education is the key
- It is not punishment
Key points

- Quality assurance is an essential part of radiotherapy.
- It affects all aspects including the radiation protection program.
- There are many different standards and guidelines for specific QA activities - it requires a qualified expert to choose the most appropriate for a particular center.
- QA requires and encourages regular external audits.
- QA is a continuous process - it is aimed at achieving improvements not laying blame.
Illustration of Importance of Quality in Determining Treatment Outcome

Critical impact of radiotherapy protocol compliance and plan quality in the treatment of advanced head and neck squamous cell carcinoma: Results from TROG 02.02


*J Clin Oncol* 28:2996-3001, 2010
Objective

- To analyse the effect of radiotherapy quality on the outcome of treatment in patients with loco-regionally advanced HNSCC treated with chemoradiotherapy

Database

- International phase III registration trial TROG 02.02 “HeadSTART” designed to test the efficacy of adding the hypoxic cell cytotoxin tirapazamine (TPZ) to cisplatin-based chemoradiotherapy

- 853 eligible patients from 81 sites in 16 countries enrolled Sep 02 - Apr 05
- Median potential FU at cut-off date - 2.3 yrs
Treatment regimens

Radiotherapy:
RT common to both arms: 70 Gy in 35 Fx over 7 weeks to gross disease; 50 Gy in 25 Fx over 5 weeks to electively treated areas

Chemotherapy:
Arm A: Cisplatin 100mg/m² weeks 1,4,7
Arm B: Cisplatin 75 mg/m² weeks 1,4,7 plus
   Tirapazamine 290 mg/m² with cisplatin weeks 1,4,7 and
   Tirapazamine alone 160 mg/m² x 3 in weeks 2 and 3

Trial powered at 90% to detect 10% improvement in survival at 2 years
(60% Arm A vs 70% Arm B)
# Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CIS</th>
<th>TPZ/CIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>88%</td>
<td>86%</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Stage IV</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>T4 and/or N3</td>
<td>54%</td>
<td>51%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>53%</td>
<td>56%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Larynx</td>
<td>18%</td>
<td>17%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>16%</td>
<td>14%</td>
</tr>
<tr>
<td>ECOG PS 0, 1, 2 (%)</td>
<td>62, 35, 3</td>
<td>61, 36, 3</td>
</tr>
</tbody>
</table>
Overall results

• In contrast to the randomized Phase II trial (TROG 98.02) on which it was based, this trial showed essentially no differences between the arms in any of the key endpoints:
  - Overall survival
  - Disease-free survival and
  - Freedom from locoregional failure

• The trial did demonstrate however, a major impact of radiotherapy quality which compromised interpretation of the results of the trial in relation to TPZ
Results – Final analysis by ITT

Overall Survival By Arm

- CIS
- CIS/TPZ

2P = 0.65

Estimated percentage surviving

Years following randomisation

Hazard ratio 95% CI

CIS/TPZ : CIS
Results – Final analysis by ITT

Failur-Free Survival By Arm

- Estimated percentage surviving and failure-free

2P = 0.96

Years following randomisation

Hazard ratio 95% CI

CIS/TPZ : CIS
Results – Final analysis by ITT

Time to Locoregional Failure By Arm (Kaplan-Meier)

![Diagram showing time to locoregional failure by arm with Kaplan-Meier estimation. The graph illustrates the estimated percentage of locoregional failure-free patients over time, with two arms: CIS and CIS/TPZ. The hazard ratio with 95% CI is indicated for CIS/TPZ vs. CIS. The log-rank test with p-value 0.44 is shown.](image)
What role did radiotherapy quality play in yielding these results?

The protocol placed high emphasis on RT compliance with obligatory interventional review by the Quality Assurance Review Center (QARC).

Analysis of the effect of radiotherapy compliance was a planned secondary objective of the trial.
Timeline for radiotherapy quality assessment

Review of plan by QARC in week 1 of RT
Modifications recommended if non-compliant

Review of modified plan
Further modifications if required

Post-treatment assessment of plan by TMC for protocol compliance

Non-compliant plans – independently reviewed to assess whether acceptable according to ‘reasonable standard of care’

All reviews performed blinded to treatment arm
Protocol-specified criteria for significant deviations

- **Tumour**
  - Dose at 2 Gy/fraction delivered to tumour volumes*
  - All gross disease (except nodes <2cm) must receive at least 66.5 Gy
  - No more than 10% of the PTV enclosing gross disease must receive <66.5 Gy (<57Gy for small nodes) or >75 Gy, excluding volumes within the GTV or air cavities
  - No more than 10% of PTV defining electively treated areas must receive <40Gy
    - *If volumes are incorrectly drawn deviation assessments will be made on corrected volumes

**Treatment Prolongation**
- Overall treatment time must not exceed 9 weeks

**Normal tissues**
- Maximum dose to spinal cord must not >50 Gy
- Volumes and doses to uninvolved normal tissues must not be excessive
Overall results of TMC review
(of 853 eligible and evaluable patients)

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reviewed</td>
<td>33</td>
</tr>
<tr>
<td>No RT given</td>
<td>10</td>
</tr>
<tr>
<td>Plan unevaluable (inadequate data)</td>
<td>23</td>
</tr>
<tr>
<td>Number of plans reviewed by TMC</td>
<td>820</td>
</tr>
<tr>
<td>Number compliant</td>
<td>612</td>
</tr>
<tr>
<td>Number non-compliant</td>
<td>208</td>
</tr>
<tr>
<td>Number non-compliant (%)</td>
<td>25.4%</td>
</tr>
<tr>
<td>Non-compliant because of tumour (+/- normal tissue) criteria</td>
<td>162</td>
</tr>
<tr>
<td>Non-compliant because of normal tissue criteria only</td>
<td>46</td>
</tr>
</tbody>
</table>
## Results of interventional review

<table>
<thead>
<tr>
<th>QARC review category</th>
<th>TMC Compliance status</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Compliant</td>
<td>Non-compliant</td>
</tr>
<tr>
<td>No plan submitted</td>
<td>109</td>
<td>32</td>
</tr>
<tr>
<td>Modification(s) not required</td>
<td>402</td>
<td>12</td>
</tr>
<tr>
<td>Modification(s) required and made</td>
<td>89</td>
<td>0</td>
</tr>
<tr>
<td>Modification(s) required and not made</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>Deviation subsequent to QARC review*</td>
<td>69</td>
<td>69</td>
</tr>
<tr>
<td>Total</td>
<td>612</td>
<td>208</td>
</tr>
</tbody>
</table>

*Incomplete plan submitted in week 1
Secondary review of non-compliant plans by reasonable standard of care criterion

<table>
<thead>
<tr>
<th>Total non-compliant plans reviewed</th>
<th>Predicted major adverse impact on tumour control</th>
<th>No major predicted adverse impact on tumour control</th>
</tr>
</thead>
<tbody>
<tr>
<td>206 (of 208)</td>
<td>97</td>
<td>109</td>
</tr>
</tbody>
</table>

97/818 (11.9%) of plans had predicted major adverse impact on tumour control
Categories of non-compliance predicted to have major adverse impact on tumour control on secondary review

- **Target definition:** Gross disease was not properly defined and therefore inadequately covered $N=24$
- **Planning:** Dose distribution was inadequate to cover correctly defined gross disease to protocol specifications $N=41$
- **Dose:** The prescribed dose (or fractionation) was inappropriate $N=25$
- **Time:** Treatment protracted > 9 weeks $N=7$

NB Categories not mutually exclusive
Target definition error

R sided adenopathy not contoured and not fully included in boost volume
The L-sided node is too deep to be treated by 7 MeV electrons.

There is a cold area in nodal GTV at the photon-electron match on the R planning error.
Factors analysed for adverse impact on TCP after secondary review  

1. Disease factors

<table>
<thead>
<tr>
<th>Primary Site</th>
<th>Number of patients</th>
<th>Number with major adverse impact</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cavity</td>
<td>105</td>
<td>11</td>
<td>10.5%</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>449</td>
<td>54</td>
<td>12.0%</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>120</td>
<td>16</td>
<td>13.3%</td>
</tr>
<tr>
<td>Larynx</td>
<td>144</td>
<td>16</td>
<td>11.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodal Stage</th>
<th>Number of patients</th>
<th>Number with major adverse impact</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>121</td>
<td>3</td>
<td>2.5%</td>
</tr>
<tr>
<td>N1, N2A</td>
<td>167</td>
<td>25</td>
<td>15%</td>
</tr>
<tr>
<td>N2B, N2C, N3</td>
<td>530</td>
<td>69</td>
<td>13%</td>
</tr>
</tbody>
</table>
Factors analysed for adverse impact on TCP after secondary review  

2. Investigator factors

<table>
<thead>
<tr>
<th>Country</th>
<th>Number of patients</th>
<th>Number with major adverse impact</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>W Europe C</td>
<td>39</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Oceania A</td>
<td>154</td>
<td>8</td>
<td>5.2%</td>
</tr>
<tr>
<td>N America A</td>
<td>101</td>
<td>6</td>
<td>5.9%</td>
</tr>
<tr>
<td>E Europe A</td>
<td>48</td>
<td>5</td>
<td>10.4%</td>
</tr>
<tr>
<td>S America A</td>
<td>54</td>
<td>6</td>
<td>11.1%</td>
</tr>
<tr>
<td>W Europe B</td>
<td>67</td>
<td>8</td>
<td>11.9%</td>
</tr>
<tr>
<td>W Europe E</td>
<td>25</td>
<td>3</td>
<td>12.0%</td>
</tr>
<tr>
<td>Oceania B</td>
<td>16</td>
<td>2</td>
<td>12.5%</td>
</tr>
<tr>
<td>W Europe A</td>
<td>127</td>
<td>17</td>
<td>13.4%</td>
</tr>
<tr>
<td>S America B</td>
<td>42</td>
<td>6</td>
<td>14.3%</td>
</tr>
<tr>
<td>E Europe B</td>
<td>28</td>
<td>4</td>
<td>14.3%</td>
</tr>
<tr>
<td>N America B</td>
<td>63</td>
<td>10</td>
<td>15.9%</td>
</tr>
<tr>
<td>W Europe D</td>
<td>30</td>
<td>5</td>
<td>16.7%</td>
</tr>
<tr>
<td>W Europe F</td>
<td>6</td>
<td>2</td>
<td>33.3%</td>
</tr>
<tr>
<td>W Europe G</td>
<td>4</td>
<td>2</td>
<td>50.0%</td>
</tr>
<tr>
<td>E Europe C</td>
<td>14</td>
<td>13</td>
<td>92.9%</td>
</tr>
</tbody>
</table>
Factors analysed for adverse impact on TCP after secondary review  

2. Investigator factors

Number of patients enrolled

<table>
<thead>
<tr>
<th>Enrolment bracket</th>
<th>Number of patients</th>
<th>Number with major adverse impact</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-4 (26 centres)</td>
<td>57</td>
<td>17</td>
<td>29.8%</td>
</tr>
<tr>
<td>5-9 (22 centres)</td>
<td>130</td>
<td>28</td>
<td>21.5%</td>
</tr>
<tr>
<td>10-19 (22 centres)</td>
<td>279</td>
<td>33</td>
<td>11.8%</td>
</tr>
<tr>
<td>≥ 20 (11 centres)</td>
<td>352</td>
<td>19</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

2P<0.0001
Outcome analysis by deviation status

To minimise bias, these analyses were restricted to 780 patients with evaluable plans who completed at least 6 weeks of treatment (60Gy to gross disease)

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMC compliant <em>ab initio</em></td>
<td>502</td>
</tr>
<tr>
<td>2</td>
<td>TMC compliant after QARC interventional review</td>
<td>86</td>
</tr>
<tr>
<td>3</td>
<td>TMC non-compliant without predicted major adverse impact on TCP at secondary review</td>
<td>105</td>
</tr>
<tr>
<td>4</td>
<td>TMC non-compliant with predicted major adverse impact on TCP at secondary review</td>
<td>87</td>
</tr>
</tbody>
</table>

No sig diff in OPC p16+ status between groups
Overall survival by deviation status

Patients who had received at least 60 Gy to PTV2

- Compliant/No mod
- Compliant/Mod
- Non-compliant/No TCP dev
- Non-compliant/TCP dev

P < 0.001
Patients who had received at least 60 Gy to PTV2

% alive and failure-free

0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0

Years from end of RT

Compliant/No mod
Compliant/Mod
Non-compliant/No TCP dev
Non-compliant/TCP dev

P < 0.001

Failure-free survival by deviation status
Time to LRF by deviation status

Patients who had received at least 60 Gy to PTV2

% locoregional failure-free
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Years from end of RT
Compliant/No mod
Compliant/Mod
Non-compliant/No TCP dev
Non-compliant/TCP dev

P < 0.001

Patients who had received at least 60 Gy to PTV2

% locoregional failure-free
0 0.5 1.0 1.5 2.0 2.5 3.0 3.5 4.0
Years from end of RT
Compliant/No mod
Compliant/Mod
Non-compliant/No TCP dev
Non-compliant/TCP dev

P < 0.001
Time to LRF by treatment arm in patients without predicted adverse impact on TCP

Patients who had received at least 60 Gy to PTV2

Hazard ratio 95% CI

P = 0.067
Time to LRF by treatment arm in patients with predicted adverse impact on TCP

Patients who had received at least 60 Gy to PTV2

% locoregional failure-free

Years from end of RT

CIS

CIS/TPZ

P = 0.42

Hazard ratio 95% CI

Patients who had received at least 60 Gy to PTV2
Main Conclusions

- Effect of poor quality RT was much greater than the hypothesised treatment effect of TPZ

- RT quality was significantly better in centres enrolling larger numbers of patients (surrogate for experience)

- In patients receiving good quality RT, overall results were excellent and there was a borderline significant beneficial effect of TPZ on locoregional control
Lessons re radiotherapy quality learnt from the HeadSTART trial

- Poor quality RT can compromise the evaluation of agents that interact with radiotherapy

- Interventional review is able to correct many RT planning errors but is of limited value overall in ensuring protocol compliance

- Centres enrolling only a few patients are the largest source of quality problems

- At the community level, doing well what we already know is more important than seeking incremental gains through new drugs/biologicals