Quality Assurance of Radiotherapy in a Clinical Trial for Lymphoma: Individual Case Review

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Abstract. Background: A multi-institutional clinical trial was conducted for localized lymphoma. This study evaluated whether a quality assurance (QA) program could clarify the source of variation in radiotherapy treatment between the institutions. Materials and Methods: Two- or three-dimensional treatment planning is required to cover the target volumes adequately and to minimize doses to organs at risk. An original QA tool was used to compare pretreatment images with portal images and dose distribution, concurrently. Results: In two of the first 12 cases, there was a deviation in the delineation of planning target volume (PTV). The QA committee clarified that there were ambiguities in the definition of PTV. The study office distributed a memorandum outlining the definition of PTV in order to reduce deviations. Thereafter, a minor deviation was identified in one of the latter 11 cases. Conclusion: This QA program clarified the source of variation, and adapted the policy to reduce these problems.

However, there is still a need to establish standard care for elderly patients. Increased age at diagnosis is not only a poor prognostic factor in aggressive NHL, but is also associated with greater treatment-related toxicity such as severe infection and organ dysfunction (2, 3). It has been reported that an actual dose-intensity of doxorubicin of more than 75% is the single most important predictor of survival (4). Dose-reduction of chemotherapy for the elderly has led to poor treatment outcomes. In order to establish an appropriate treatment schedule for such cases, the Japan Radiation Oncology Group (JAROG) conducted a multi-institutional prospective study to evaluate the safety and efficacy of a three-course 80%-dose CHOP regimen followed by involved-field radiotherapy in patients over 70-years-old with localized disease (5).

To ensure that the trial results were not compromised by the use of inappropriate techniques, or large variation in the quality of the treatment techniques, the protocol prescribed the rules and regulations of chemotherapy and radiotherapy. Quality assurance (QA) procedures are important to guarantee a uniform quality of treatment among participating institutions. The European Organization for Research and Treatment of Cancer (EORTC) and other collaborative groups have developed effective systems for the application of valid QA procedures in radiation oncology trials (6-9). The JAROG QA committee employed an original QA tool and performed central individual case reviews to guarantee the quality of radiotherapy.

This study evaluated whether a QA program could clarify the source of variation in radiotherapy treatments between the participating institutions and could adapt the policy to reduce them.
Materials and Methods

The eligibility criteria, treatment schedule, and stopping rules have previously been reported in detail (5). The treatment consisted of an 80%-dose CHOP regimen for three cycles followed by involved-field radiotherapy of 30-50 Gy. The involved-field was defined as the area including the primary lesion and involved nodes determined by pretreatment evaluations and the adjacent uninvolved nodal area or region. The radiation dose was 30-30.6 Gy given in 15-20 fractions over 3-4 weeks for patients who achieved complete remission (CR), and 40-50 Gy in 20-28 fractions over 4-6 weeks for those who did not achieve CR. Response was assessed using the standard criteria (10). Two-dimensional or computed tomography (CT)-based three-dimensional treatment planning was required to adequately cover the target volumes and to minimize the doses to organs at risk such as the eyes, brain stem, spinal cord and visceral organs.

The gross tumor volume (GTV) was the gross palpable or visible extent and location of disease. The clinical target volume (CTV) was the volume that included demonstrable GTV and/or subclinical microscopic disease (at least 2 cm from GTV in any direction and the regional node area). The planning target volume (PTV) was a geometric concept and was defined to select the appropriate beam energy and beam arrangements, taking into consideration all possible geometric variations in order to ensure that the prescribed dose was actually administered.

The JAROG QA committee employed an original QA tool that was made using Microsoft PowerPoint, to compare pre-chemotherapy CT images and/or magnetic resonance images (MRI) with portal images and dose distribution, concurrently (Figures 1 and 2). Data from individual cases were sent to the review center using CD-ROMs. The following parameters of treatment records and charts were evaluated by the QA review board: pre- and post-chemotherapy CT and/or MRI; simulation images; portal images; dose distribution; prescribed dose; dose fractionation and overall treatment time, and dose to the risk organs. Compliance was defined as treatment in accordance with the protocol guidelines, while deviation was defined as treatment that differed from the protocol guidelines, but was not considered to compromise the clinical outcome, and violation was defined as treatment that was considered to have compromised the clinical outcome or induced severe adverse effects. Protocol violations included the incomplete coverage of the GTV, a dose to the reference point either less than 90% or more than 110% of the dose prescribed in the protocol or a fractional dose less than 1.5 Gy. Furthermore, more than 1 cm of difference between the simulation film and the portal film was also defined as a violation. The first QA review committee was held after enrollment of half of the planned number of cases was completed, and the second was held after termination of this study.

Results

Twenty-four cases were enrolled from eight Japanese institutions between December 2000 and February 2004. The primary sites and patient characteristics are shown in Table I. The study protocol was not completed in three patients, who each received only two cycles of chemotherapy. These three patients received radiotherapy after going off-protocol, and then all 24 enrolled cases received radiotherapy. Data from 23 cases were available for QA review, while the QA committee could not collect the data from one case.

There were no protocol violations in the 23 cases. Deviations in delineation of the PTV were identified in three cases (13%). All cases complied with the prescribed dose, dose fractionation, overall treatment time, homogeneity of dose distribution at the iso-center plain (90–110% iso-dose line) and dose to the organs at risk including the eyes, brain stem and spinal cord (<40 Gy).

In two of the first 12 cases, there was a deviation in delineation of PTV. One case had stage II disease, which was located in the maxillary sinus with neck lymph node involvement, and another had a stage I paravertebral lesion. The QA committee investigated the sources of the deviations in delineation of the PTV and identified that there were ambiguities in the definition of the PTV in the protocol guidelines for cases demonstrating contiguous stage II disease or involvement in an unusual primary site. The QA committee concluded that these ambiguities of PTV definition in the protocol guideline might have led to these deviations. The study office proposed a memorandum regarding the definition of PTV to reduce the deviations. This memorandum demonstrated the definition of the PTV using graphic schemes. After the distribution of the memorandum, deviation of delineation of the PTV was identified in one case of the latter 11 cases. This case demonstrated stage II disease that included a primary lesion in Waldeyer’s ring and neck lymph node involvement. The protocol guideline recommended that the PTV should include the whole body.
Figure 1. JAROG original QA tool (pretreatment evaluation).

Figure 2. JAROG original QA tool (portal images and post-treatment evaluation).
pharyngeal space, but the upper border of the PTV extension in this case was smaller by approximately 5 mm than the protocol guideline.

Discussion

Clinical trials that include large inter-institutional variations in treatment technique might not correctly demonstrate the true clinical outcome. A QA committee should adopt a policy to reduce variation between participating institutions, as there will inevitably be a certain degree of difference arising in a multi-institutional setting. Central individual case review is an essential procedure for detecting deviations from the protocol guidelines. A QA program in multi-institutional trials must not only evaluate the individual quality of treatment delivered, but must also reduce inter-institutional variation by supplying immediate feedback to the participating institutions. The German Hodgkin Study Group conducted a prospective randomized trial to evaluate whether a total dose of 30 Gy was sufficient for treatment of Hodgkin’s disease compared to a 40 Gy total dose (11). The 5-year failure-free survival was significantly influenced by the quality of the radiotherapeutic procedures and resulted in 70% with protocol violations vs. 82% without violations. The QA program should guarantee the quality of radiotherapy to avoid compromising the clinical outcome by poor radiotherapy technique.

The Trans-Tasman Radiation Oncology Group conducted a prospective randomized control trial comparing a single 8 Gy dose with 20 Gy in five fractions as radiotherapy to treat neuropathic pain due to bone metastases, and the QA committee conducted independent audits to assess compliance with the eligibility criteria and the appropriateness of treatment of the index site for the first 234 cases (12). This study group concluded that QA auditing was an essential but time-consuming process in radiotherapy trials, and that the QA program using central individual case reviews should commence soon after study initiation. The present JAROG study conducted the first QA review after half of the planned enrollment was completed. In the future, quick identification of deviations and immediate feedback to the participating institutions should be realized.

In this study, a deviation from the definition of PTV was identified in three cases and two of these involved head and neck lesions. The head and neck region is the most irregularly shaped anatomical site in the human body. The presence of a highly sensitive structure such as the eye ball, optic nerve or spinal cord adjacent to the primary tumor and/or involved nodes, necessitates a high degree of irradiation conformity. Our study did not require high-dose radiotherapy or complex techniques and simple radiation techniques using two-opposed lateral fields or the three-field technique (two-opposed lateral fields plus an antero-posterior field) and moderate-dose radiotherapy were applied in most cases. There was no deviation or violation in the homogeneity of dose distribution and no violation of doses to organs at risk. However, clinical trials that include definitive radiotherapy, chemoradiotherapy and postoperative radiotherapy for locally advanced head and neck cancers require high-dose radiotherapy and complex techniques (13). Therefore, in clinical trials involving head and neck lesions, inter-institutional variations cannot be ignored and careful monitoring is required to ensure the quality of radiotherapy.

Ideally, a dummy run should be organized to test the compliance of participating institutions with the QA program’s protocol guidelines. A dummy run could highlight possible weaknesses in the study protocol guidelines (14). The EORTC QA team performed a dummy run before the commencement of a clinical trial that evaluated postoperative chemoradiotherapy for cases of locally advanced head and neck cancers and demonstrated a large inter-institutional variation in PTV extension and field arrangements (13). The importance of the QA program including the dummy run procedure to reduce inter-institutional variations was emphasized. The new radiation treatment techniques, which included three-dimensional radiotherapy, intensity-modulated radiotherapy and image-guided radiotherapy, have been established and new clinical trials might apply these new techniques. The complexity of the problem of defining an optimal plan indicates the need for a ‘second opinion’ from experts in the specific field using a tele-consultation system (14).

The JAROG QA program identified the deviations in PTV definition as resulting from ambiguities in the protocol guideline and enabled adaptation of the policy to reduce deviations among the participating institutions. However, variations among the participating institutions could not be completely eliminated. The monitoring system using the QA program should be continued to reduce variations in on-going trials. Especially for head and neck lesions, a dummy run before commencement of the study should be considered to improve the consistency of radiotherapy.

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