their thanks to the staff of the NIRS and AEC for their support of glass dosimeter irradiation and reading.

* **Corresponding author. Hideyuki Mizuno**, Research Center for Charged Particle Therapy, National Institute of Radiological Sciences, 4-9-1 Anagawa, Inage-ku, Chiba 263-8555, Japan. *E-mail address:* h_mizuno@nirs.go.jp

Received 16 August 2007; received in revised form 16 October 2007; accepted 17 October 2007; Available online 26 November 2007

References

[1] Aguirre JF, Tailor R, Ibbott G, Stovall M, Hanson, W. Thermoluminescence dosimetry as a tool for the remote verification of output for radiotherapy beams: 25 years of experience. In: Proceedings of the international symposium on standards and codes of practice in medical radiation dosimetry IAEA-CN-96/82. Vienna: IAEA; 2002. p. 191–99.

[2] Araki F, Ikegami T, Ishidoya T, Kubo HD. Measurements of Gamma-Knife helmet output factors using a radiophotoluminescent glass rod dosimeter and a diode detector. Med Phys 2003;30:1976–81.

[3] Araki F, Moribe N, Shimonobou T, Yamashita Y. Dosimetric properties of radiophotoluminescent glass rod detector in high-energy photon beams from linear accelerator and Cyber-Knife. Med Phys 2004;31:1980–6.

[4] Asahi Techno Glass Corporation. Explanation material of RPL glass dosimeter: small element System, Tokyo, Japan; 2000.

[5] Ferreira IH, Dutreix A, Bridier A, Chavaudra J, Svensson H. The ESTRO-QUALity assurance network (EQUAL). Radiother Oncol 2000;55:273–84.

[6] Kroutilíková D, Novotný J, Judas L. Thermoluminescent dosimeters (TLD) quality assurance network in the Czech Republic. Radiother Oncol 2003;66:235–44 .

[7] Hayami A, Inoue T, Kawagoe Y, Fuchihata H. Mailed TLD dose intercomparison at a reference point of high energy photon beams among 11 institutions in Japan. J Jpn Soc Ther Radiol Oncol 1997;9:139–45.

[8] Institute of Physical Science in Medicine (IPSM). Code of practice for high-energy photon therapy dosimetry based on the NPL absorbed dose calibration service. Phys Med Biol 1990;35:1355–60.

[9] Izewska J, Andreo P. The IAEA/WHO TLD postal programme for radiotherapy hospitals. Radiother Oncol 2000;54:65–72.

[10] Izewska J, Andreo P, Vatnitsky S, Shortt KR. The IAEA/WHO TLD postal dose quality audits for radiotherapy: a perspective of dosimetry practices at hospitals in developing countries. Radiother Oncol 2003;69:91–7.

[11] Izewska J, Georg D, Bera P, Thwaites D, Arib M, Saravi M, et al. A methodology for TLD postal dosimetry audit of high-energy radiotherapy photon beams in non-reference conditions. Radiother Oncol 2007;84:67–74.

[12] Kirby TH, Hanson WF, Johnston DA. Uncertainty analysis of absorbed dose calculations from thermoluminescence dosimeters. Med Phys 1992;19:1427–33.

[13] Mobit PN, Mayles P, Nahum AE. The quality dependence of LiF TLD in megavoltage photon beams: Monte Carlo simulation and experiments. Phys Med Biol 1996;41:387–98.

[14] National Institute of Standards and Technology (NIST). Tables of X-ray mass attenuation coefficients and mass energy-absorption coefficients from 1 keV to 20 MeV for elements $Z = 1$ to 92 and 48 additional substances of dosimetric interest. NISTIR 5632 (Version 1.4); 2004.

[15] Piesch E, Burgkhardt B, Vilgis M. Photoluminescence dosimetry: progress and present state of art. Radiat Prot Dosim 1990;33:215–26.

[16] Shimbo M, Nishio T, Ooyama M, et al. Report of the off-site dosimetry. Jpn J Med Phys 2003;23:25–6.

[17] Tsuda M. A few remarks on photoluminescence dosimetry with high energy X-rays. Jpn J Med 2000;20:131–9.

Jpn J Clin Oncol 2008;38(5)387–389
doi:10.1093/jjco/hyn025

Clinical Trial Note

Accelerated Fractionation versus Conventional Fractionation Radiation Therapy for Glottic Cancer of T1-2N0M0 Phase III Study: Japan Clinical Oncology Group Study (JCOG 0701)

Kenichi Nakamura[1], Takeshi Kodaira[2], Naoto Shikama[3], Yoshikazu Kagami[4], Satoshi Ishikura[1], Taro Shibata[1] and Masahiro Hiraoka[5]

[1]Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, [2]Department of Radiation Oncology, Aichi Cancer Center Hospital, Nagoya, [3]Department of Radiology, Shinshu University School of Medicine, Nagano, [4]Radiation Oncology Division, National Cancer Center Hospital, Tokyo and [5]Department of Radiation Oncology and Image-applied Therapy, Kyoto University Hospital, Kyoto, Japan

Received December 11, 2007; accepted March 1, 2008; published online April 3, 2008

A randomized Phase III study was started in Japan to demonstrate the non-inferiority of survival of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 glottic cancer. This study began in September 2007, and a total of 360 patients will be accrued from 22 institutions within 4 years. The primary endpoint is 3-year progression-free survival (PFS). The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Key words: laryngeal neoplasms – radiotherapy – dose fractionation – clinical trials – phase III

INTRODUCTION

Accelerated fractionation radiation therapy has considerable benefits in terms of treatment duration and cost compared with conventional fractionation methods. In addition, some reports suggest that increased single radiation dose and shortened treatment time may improve local control (1–7). However, no multi-institutional randomized study has been conducted to show that accelerated fractionation is equivalent to conventional fractionation in terms of efficacy and safety for early glottic cancer. Various types of fractionation methods are performed in clinical practice, and according to the guidelines of the Head and Neck Cancer Disease Site Group in Canada, an optimal fractionation protocol has not yet been established (8). We therefore designed a study, which investigates whether accelerated fractionation radiotherapy is suitable for T1-2N0M0 glottic cancer in terms of survival, feasibility, voice function and safety.

The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in August 2007 and the study was activated in September 2007. This trial was registered at the UMIN Clinical Trials Registry as UMIN000000819 [http://www.umin.ac.jp/ctr/index.htm].

For reprints and all correspondence: Takeshi Kodaira, Department of Radiation Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya, 464-8681, Japan. E-mail: 109103@aichi-cc.jp

PROTOCOL DIGEST OF THE JCOG 0701

Purpose

The aim of this study is to demonstrate the non-inferiority of the efficacy of accelerated fractionation radiation therapy (2.4 Gy/fr) with conventional fractionation radiation therapy (2 Gy/fr) in patients with T1-2N0M0 (UICC/TNM, 6th edition) glottic squamous cell carcinoma.

Study Setting

A multi-institutional randomized Phase III study.

Resources

Grants-in-Aid for Cancer Research (17-17, 16-12, 17S-5) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is the 3-year progression-free survival (PFS) proportion in all eligible patients. PFS is defined as days from randomization to first evidence of local progression, distant metastasis or death from any cause. In patients alive without events, PFS will be censored at the last visit. The secondary endpoints are overall survival, local progression-free survival, disease-free survival, survival with preserved voice function, complete response rate, proportion of treatment completion and adverse events.

Overall survival is defined as days from randomization to death from any cause. Local progression-free survival consists of time free from local disease progression or death from any cause, while disease-free survival is defined as duration free of local progression, distant metastasis, secondary cancer or death from any cause. Survival with preserved voice function is defined as days from randomization to first evidence of death from any cause or appearance of voice changes of Grade 3 or more as diagnosed by the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). The proportion of treatment completion denotes the percentage of patients whose treatment is completed within the recommended length of time: 51 days for T1 and 53 days for T2 in the conventional radiation arm, and 39 days for T1 and 43 days for T2 in the accelerated radiation arm.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill each of the following criteria: (i) primary tumor site lies within the vocal cords; (ii) the tumor consists of histologically proven squamous cell carcinoma; (iii) the extent of the primary tumor is evaluated as T1 or T2 without impaired cord mobility; (iv) the tumor is clinically staged as N0/M0; (v) radiation therapy can be completed within the recommended duration without interruption due to national holidays; (vi) age between 20 and 80 years; (vii) ECOG performance status of 0 or 1; (viii) no prior surgery or radiation therapy of the larynx; (ix) no prior chemotherapy for any malignancies within 5 years; (x) sufficient organ function; (xi) completed written informed consent.

Exclusion Criteria

Patients are excluded if they meet any of the following criteria: (i) active bacterial or fungous infection; (ii) simultaneous or metachronous (within 5 years) double cancers; (iii) women during pregnancy or breast-feeding; (iv) psychosis; (v) treatment with systemic steroids; (vi) history of collagen disease except for rheumatism; (vii) insulin-dependent or poorly controlled diabetes mellitus; (viii) poorly controlled hypertension; (ix) history of severe heart disease, heart failure; (x) myocardial infarction or angina pectoris within the past 6 months.

Randomization

After the confirmation of the inclusion and exclusion criteria by telephone or fax to the JCOG Data Center, the patients are randomized to either conventional radiation arm or accelerated radiation arm, by the minimization method of balancing the arms according to T factor (T1/T2 by UICC/TNM, 6th edition) and institution.

Treatment Method

In conventional radiation arm, conventional fractionation radiotherapy with 2 Gy/fr (1 fr/day and 5 fr/week) is performed 33 times for a total dose of 66 Gy in patients with T1 disease, and 35 times for a total dose of 70 Gy in patients with T2 disease. Irradiation twice daily is permitted, but the maximum number of irradiation sessions per week is limited to five. It is recommended that treatment using the conventional fractionation method is completed within 51 days for T1 disease and 53 days for T2 disease.

In accelerated radiation arm, accelerated fractionation radiotherapy with 2.4 Gy (1 fr/day and 5 fr/week) is delivered 25 times for a total dose of 60 Gy in patients with T1 disease, and 27 times for a total dose of 64.8 Gy in patients with T2 disease. Twice-daily irradiation is prohibited, as is irradiation six or more times per week. Recommended duration of accelerated fractionation radiotherapy is 39 days for T1 disease and 43 days for T2 disease.

In both study arms, the gross tumor volume (GTV) is defined as the GTV of the primary tumor. The clinical target volume (CTV) in T1 disease is the entirety of the vocal cords, while the CTV in T2 disease includes a 1-cm margin surrounding the tumor in addition to the vocal cords. The planning target volume (PTV) is defined as the CTV plus a margin of 0.5-1 cm in the craniocaudal direction and 0.5 cm in the posterioanterior direction.

Follow-up

All enrolled patients are followed-up at least every 6 weeks for the first 6 months and then every 3 months for a duration of 3 years. Laryngeal fiberscope and cervical lymph node exploration by manipulation are carried out at each visit.

Study Design and Statistical Method

This trial is designed to demonstrate that accelerated fractionation radiation therapy is not inferior to the conventional fractionation method in terms of 3-year PFS. If the non-inferiority of accelerated radiation arm is verified, the accelerated fractionation method will be the preferred treatment.

The planned sample size is 360 patients, with 180 cases per arm. We anticipate 3 years of follow-up after 4 years of accrual, ensuring at least 80% power with one-sided alpha of 5% and a non-inferiority margin of 5% for the primary endpoint. This assumes an expected 3-year PFS of 80% in patients treated with the conventional fractionation method, and 85% in those treated with the accelerated fractionation method.

Interim Analysis and Monitoring

We plan on conducting two interim analyses, considering multiplicity according to the method recommended by the Southwest Oncology Group (9). The Data and Safety Monitoring Committee of the JCOG will independently review the interim analysis reports and stop the trial early if necessary. In-house monitoring will be performed every 6 months by the Data Center to evaluate and improve study progress and quality.

Participating Institutions (From North To South)

Sapporo Medical University, Tohoku University, Saitama Cancer Center, National Cancer Center East, National Cancer Center, Tokyo Metropolitan Komagome Hospital, Tokyo Women's Medical University, Tokyo Medical Center, Keio University, Cancer Institute Hospital, University of Tokyo, Kitasato University, Niigata Cancer Center, Yamanashi University, Shinshu University, Aichi Cancer Center, Kyoto University, Osaka University, Kinki University, Osaka Medical Center for Cancer and Cardiovascular Diseases, Hiroshima University, Kyushu University.

Funding

This work is supported by Grant-in-Aid for Cancer Research (17-17, 16-12, 17S-5) from the Ministry of Health, Labour and Welfare of Japan.

Conflict of interest statement
None declared.

References

1. Mendenhall WM, Parsons JT, Million RR, Fletcher GH. T1-T2 squamous cell carcinoma of the glottic larynx treated with radiation therapy: relationship of dose-fractionation factors to local control and complications. *Int J Radiat Oncol Biol Phys* 1988;15(6):1267–73.
2. Rudoltz MS, Benammar A, Mohiuddin M. Prognostic factors for local control and survival in T1 squamous cell carcinoma of the glottis. *Int J Radiat Oncol Biol Phys* 1993;26(5):767–72.
3. Parsons JT, Cassisi NJ, Million RR. Results of twice-a-day irradiation of squamous cell carcinomas of the head and neck. *Int J Radiat Oncol Biol Phys* 1984;10(11):2041–51.
4. Van den Bogaert W, Van der Leest A, Rijnders A, Delaere P, Thames H, van der Schueren E. Does tumor control decrease by prolonging overall treatment time or interrupting treatment in laryngeal cancer? *Radiother Oncol* 1995;36(3):177–82.
5. Kim RY, Marks ME, Salter MM. Early-stage glottic cancer: importance of dose fractionation in radiation therapy. *Radiology* 1992;182(1): 273–5.
6. Robertson AG, Robertson C, Boyle P, Symonds RP, Wheldon TE. The effect of differing radiotherapeutic schedules on the response of glottic carcinoma of the larynx. *Eur J Cancer* 1993;29A(4):501–10.
7. Yu E, Shenouda G, Beaudet MP, Black MJ. Impact of radiation therapy fraction size on local control of early glottic carcinoma. *Int J Radiat Oncol Biol Phys* 1997;37(3):587–91.
8. Hodson D, Archibald S, Browman G, Johnston M, Cripps C, Davidson J, et al. Optimum radiation fractionation for T1 N0 glottic (vocal cord) carcinoma evidence summary report #5-4: program in evidence-based care a cancer care ontario program. www.cancercare.on.ca/accsessPEBC.htm.
9. Crowley J, Green S, Liu PY, Wolf M. Data Monitoring Committees and early stopping guidelines: the Southwest Oncology Group experience. *Stat Med* 1994;13(13–14):1391–9.

Jpn J Clin Oncol 2008;38(11)723–729
doi:10.1093/jjco/hyn112

Review Article

Quality Assurance of Radiotherapy in Cancer Treatment: Toward Improvement of Patient Safety and Quality of Care

Satoshi Ishikura

Outreach Radiation Oncology and Physics, Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Chuo-ku, Tokyo, Japan

Received August 29, 2008; accepted September 18, 2008

The process of radiotherapy (RT) is complex and involves understanding of the principles of medical physics, radiobiology, radiation safety, dosimetry, radiation treatment planning, simulation and interaction of radiation with other treatment modalities. Each step in the integrated process of RT needs quality control and quality assurance (QA) to prevent errors and to give high confidence that patients will receive the prescribed treatment correctly. Recent advances in RT, including intensity-modulated and image-guided RT, focus on the need for a systematic RTQA program that balances patient safety and quality with available resources. It is necessary to develop more formal error mitigation and process analysis methods, such as failure mode and effect analysis, to focus available QA resources optimally on process components. External audit programs are also effective. The International Atomic Energy Agency has operated both an on-site and off-site postal dosimetry audit to improve practice and to assure the dose from RT equipment. Several countries have adopted a similar approach for national clinical auditing. In addition, clinical trial QA has a significant role in enhancing the quality of care. The Advanced Technology Consortium has pioneered the development of an infrastructure and QA method for advanced technology clinical trials, including credentialing and individual case review. These activities have an impact not only on the treatment received by patients enrolled in clinical trials, but also on the quality of treatment administered to all patients treated in each institution, and have been adopted globally; by the USA, Europe and Japan also.

Key words: radiation therapy – quality assurance – radiation dosimetry – clinical audit – clinical trials

INTRODUCTION

Radiotherapy (RT) is one of the major options in cancer treatment. As a multimodality treatment combined with surgery and/or chemotherapy, it plays an important role in curing cancers. RT is also a very effective treatment option for palliation and symptom control in advanced or recurrent cancers. In Japan, only a quarter of patients receive RT (1,2), but 52% of patients should receive RT at least once during their treatment of cancer according to the best available evidence (3).

The process of RT is complex and involves understanding of the principles of medical physics, radiobiology, radiation safety, dosimetry, RT planning, simulation and interaction of RT with other treatment modalities. The professional team for RT includes radiation oncologists, medical physicists, radiation technologists and radiation nurses. These professionals work through an integrated process to plan and deliver RT to cancer patients. The sequential process is shown in Fig. 1 and each step needs quality control (QC) and quality assurance (QA) to prevent errors and to give high confidence that patients will receive the prescribed treatment correctly (4).

For reprints and all correspondence: Satoshi Ishikura, Outreach Radiation Oncology and Physics, Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: sishikur@ncc.go.jp

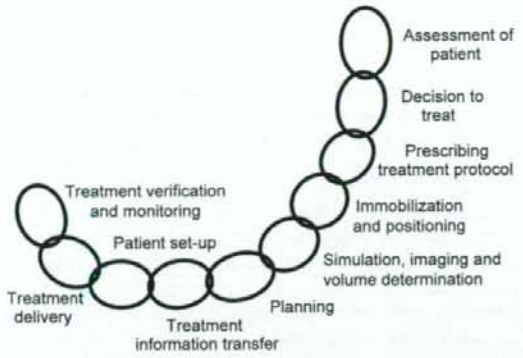

Figure 1. Sequential process of planning and delivering radiotherapy to patients.

The current paradigm of quality management (QM) in RT focuses on measuring the functional performance of RT equipment by measurable parameters with tolerances set at strict but achievable values. Guidelines for these have been provided by: the American Association of Physicists in Medicine (AAPM) in various documents, such as Task Group (TG) 40, 43, 53, 56, 59, 60 and 64 (5–11); the American College of Radiology and the American College of Medical Physics in reports on RTQA; the European Society for Therapeutic Radiology and Oncology (ESTRO) in a report on RTQA (12); the International Electrotechnical Commission publications on functional performance of RT equipment; and the International Organization for Standardization (ISO). The Japanese Society for Therapeutic Radiology and Oncology has also published guidelines in accordance with these for domestic RT institutions. Most of these reports recommend that every parameter that can be checked should be checked. This approach does not provide guidelines for optimally distributing resources for QA and QM activities to maximize the quality of patient care. This is a major problem, because almost no facility has the personnel to cover everything. The difficulty of this situation worsens as new advanced technologies, such as intensity-modulated radiation therapy (IMRT) and image-guided radiation therapy (IGRT) are introduced into the clinic. As new technologies are introduced, the number and sophistication of possible activities, tests and measurements required to maintain quality also increase.

Therefore, there is a keen need to develop a systematic RTQA program that balances patient safety and quality with available resources and also prescriptiveness with flexibility (13).

PROBLEMS WITH CURRENT RTQA PROGRAMS

The goal of an RTQA program is to deliver the best and safest RT to each patient to achieve cure or palliation. The quality of RT has been defined as the totality of features or characteristics of the RT service that bear on its ability to satisfy the stated or implied goal of effective patient care. The integrated nature of QA in RT makes it impossible to consider QA as limited to simply checking machine output or calibrating brachytherapy sources. QA activities cover a very broad range of areas in which the actions of radiation oncologists, radiation technologists, dosimetrists, accelerator engineers and medical physicists are important. With the increasing complexity of the equipment and processes required to deliver modern RT, the activities required to maintain and enhance quality are consuming ever more resources, and we need to re-examine the amount and distribution of resources committed to QA. In particular, we need to link QA activities to the expected benefit to the patient. In addition to re-examining current practice, the rapid introduction of new advanced technologies poses other challenges. The current process of developing consensus recommendations for prescriptive QA activities remains valid for many of the devices and software systems used in modern RT; however, for some technologies, QA guidance is incomplete or out of date. The formulation of QA guidance lags far behind the penetration of IMRT and IGRT into the community, leaving physicists and radiation oncologists without a clear strategy to maintain the quality and safety of treatment. In addition to leaving practitioners and patients at greater risk of catastrophic delivery errors, data from phantom testing have suggested that the quality of IMRT delivery has been much poorer than that expected (14). In such situations, physicists will be best served by guidance on how to approach the development of a QM system. Even before the availability of advanced technologies such as IMRT and IGRT, it was clear that the treatment preparation and the delivery equipment had such a wide range of possible configurations that both commissioning and routine QA activities could do no more than sample the performance of the equipment under selected conditions. There is a need to re-examine objectively those selected conditions and confirm that they are the most critical for modern RT (15,16).

NEW PARADIGM FOR RTQA

To solve these problems, it is important to evaluate more formal error mitigation and process analysis methods of industrial engineering, such as aircraft accident analysis (17), to focus available QA resources more optimally on process components that have a significant likelihood of compromising patient safety or treatment outcomes.

The new possible approach is based on designing a framework for QM activities with the maximal impact being achieved when resource allocation reflects both the probability of an event and the severity should it occur; this requires quantitative knowledge of both probability and severity. To understand the new approach, new concepts, failure mode and effect analysis (FMEA) need to be

understood (18,19). This is a systematic method for documenting potential failure modes, determining effects, identifying causes of failures, developing plans, team concurrence and taking action. For each potential cause of failure, values are assigned in three categories: O, the probability that a specific cause will result in a failure mode; S, the severity of the effects resulting from a specific failure mode should it go undetected throughout treatment; and D, the probability that the failure mode resulting from the specific cause will go undetected. Convention uses numbers between 1 and 10. The product of these three indices forms the risk probability number ($RPN = O \times S \times D$). When designing a QM program based on the RPN values, resources should be allocated to failure modes with higher RPN values. TG 100 of the AAPM is now working to develop a consistent set of values for O, S and D, and a consistent set of terminology for describing the potential causes of failure and potential effects of failure. TG 100 also suggests that this approach could be a useful framework for the objective analysis of myriad emerging technologies. Adoption of a standard approach to QM would have clear advantages in developing new recommendations efficiently.

On the other hand, the WHO World Alliance for Patient Safety has taken an initiative to address high-risk areas in the RT process of care, complementary to the International Atomic Energy Agency (IAEA)-developed safety measures and other previously developed standards, to address non-equipment, non-system faults associated with RT delivery. An expert group facilitated by the WHO World Alliance for Patient Safety is in the process of developing a guide to identify high-risk practices in RT and to suggest specifically targeted interventions to improve patient safety. A literature review showed that, in the last three decades (1976–2007), >1700 patients were affected and ~2% of patients were reported to have died due to radiation overdose toxicity in middle- and high-income countries in the USA, Latin America, Europe and Asia. Most incidents (~98%) were reported to have occurred in the planning stage during the introduction of new systems and/or equipment. Of all incidents without any known adverse events to patients, 7% were related to the planning stage; 39% were related to information transfer and 19% to the treatment delivery stage. The remaining 35% of incidents occurred in the categories of prescription, simulation, patient positioning or in a combination of multiple stages (personal communication). The report will be published in the near future and will be useful to develop process-oriented RTQA programs.

EXTERNAL PEER REVIEW AUDIT

External audit programs for RTQA can serve to improve patient safety and quality of care. The international basic safety standards (20) require radiation centers to establish comprehensive QA programs for medical exposure, including external auditing for RT. Both regulatory authorities and professional societies have responded, producing similar end products. The Council Directive of the European Community 97/43/European Atomic Energy Community strengthened the need for clinical auditing in Europe. The regulatory authority of Finland (21,22) is pursuing a program to implement the European Union directive in all areas of radiation medicine. Norway's Radiation Protection Authority (23) has reported that 'Clinical audit/review involves mutual learning wherein colleagues evaluate completed work from the perspective of good clinical practice. This is essentially different from an authority's regulatory inspection where practice/activities are evaluated against laws and regulations.' The ESTRO has initiated a process to define comprehensive auditing (24). In all cases, the auditing team is composed of professionals; physician, medical physicist and radiation technologist. The IAEA also introduced its QA Team for Radiation Oncology (QUATRO) (25). The objective of QUATRO auditing is to review and evaluate the quality of the practice of RT at a cancer center to define how best to improve the practice. A guideline document (26) has defined how to conduct the audit. The IAEA has organized several workshops to train QUATRO auditors, and 17 missions were completed as of November 2006 in Europe and Asia. Individual RT centers received recommendations on quality improvement. In eastern European countries, most audited centers operate at a level requiring only minor improvements, except for the general shortage of well-qualified radiation technologists. Two centers were identified as operating at an internationally accepted level (27). Some countries, such as the Czech Republic (28), have adapted the QUATRO approach for national clinical auditing. In Asia, existing structural inadequacies were addressed.

In addition to an on-site audit, an off-site audit, such as a postal dosimetry audit program, is necessary to assure the dose from RT equipment. For more than three decades, the IAEA has operated a postal thermoluminescent dosimetry (TLD) dose-auditing program (29) for more than 1600 RT institutions in 120 countries. A global and steady improvement in the performance of dosimetry audits has been occurring so that ~95% of the participating institutions are within the 5% acceptance limit for beam calibration. Several countries have adopted the IAEA's method to establish their own national auditing networks (30–32). In Japan, a similar postal dosimetry audit program using a glass dosimeter was started on November 2007 (33,34). Further development is being considered to check not only the reference condition, i.e. beam calibration, but also non-reference conditions, such as irregularly shaped and wedged beams.

CLINICAL TRIAL QA

In the USA, RTQA programs have been developed mainly through clinical trial QA. The Radiological Physics Center (RPC) has been funded by the National Cancer Institute (NCI) continually since 1968 to provide quality auditing of

dosimetry practices at institutions participating in NCI cooperative clinical trials. The primary responsibility of the RPC is to assure the NCI and the cooperative clinical trial groups that all participating institutions have the equipment, personnel and procedures necessary to administer radiation doses that are clinically comparable and consistent. The monitoring tools used include on-site dosimetry reviews; remote auditing tools, including TLD and anthropomorphic phantoms; and reviews of both benchmark and actual protocol patient treatments. As of 2007, the RPC monitors nearly 1500 RT institutions. Discrepancies detected by the RPC are investigated to help the institution resolve them. The RPC overall RTQA program has an impact not only on the treatment received by patients enrolled in clinical trials, but also on the quality of treatment administered to all patients treated at the institution.

The NCI-sponsored Advanced Technology QA Consortium (ATC), which consists of the Image-Guided Therapy QA Center (ITC), Radiation Therapy Oncology Group (RTOG), RPC, QA Review Center (QARC) and Resource Center for Emerging Technologies, has pioneered the development of an infrastructure and QA method for advanced technology clinical trials that requires volumetric digital data submission of a protocol patient's treatment plan and verification data. In particular, the ITC has nearly 15 years' experience in facilitating the QA review for RTOG advanced technology clinical trials. This QA process includes: (i) a data integrity review for completeness of protocol-required elements, the format of data, and possible data corruption, and recalculation of dose–volume histograms, (ii) a review of compliance with target volume and organ-at-risk contours by study chairs and (iii) a review of dose prescription and dose heterogeneity compliance by the RTOG Headquarters Dosimetry Group.

They also require institutions to obtain credentials before participating in clinical trials. The concepts pioneered by the ITC and RTOG include: (i) a facility questionnaire that documents the institution's technical capabilities and identifies the critical treatment team individuals and (ii) a series of tests that are protocol modality-specific, including an electronic data submission test and a dry-run test, to demonstrate understanding of the protocol planning and data submission requirements. New modalities such as IMRT and Stereotactic Body Radiation Therapy (SBRT) require additional credential tests. The RPC developed a postal anthropomorphic phantom (Fig. 2) that contains dosimeters to test the delivery capabilities of the institutions' IMRT systems (35) and a localization credential test has been implemented for SBRT protocols to test the reproducibility of the patient setup (36). The primary goal of credentials is to reduce the deviation rate for data submitted to clinical trials. Cooperative groups have experienced deviation rates that sometimes amount to as much as 17% of the cases submitted, according to a study conducted by the RPC (37). An elevated number of deviations reduce the quality of the study, and increased rates of major deviations may limit accrual to the trial. Credentialing evaluations result in feedback to the institution, to explain the results of the procedure and to give suggestions to improve those results in the future. Three protocols for which credentialing was required from all participants had rates of deviation between 0 and 4%, whereas two protocols that had limited credential requirements had rates of deviation of the order of 7–17% (37,38).

Figure 2. The Radiological Physics Center postal anthropomorphic phantom.

These activities have also been adopted in Europe and Japan. As early as in 1982, the European Organization for Research and Treatment of Cancer RT Group (EORTC) established RTQA programs. In the course of 25 years, QA procedures have become a vast and important part of the activities of the group. The radiation dosimetry QA program demonstrated the disappearance of large deviations of photon and electron beam calibrations after two successive audits (39). This methodology has now become a standard procedure in RT routine practice in Europe. In Japan, following the results of a phase III trial that revealed poor protocol compliance (40%), the Japan Clinical Oncology Group (JCOG) started clinical trial RTQA programs in 2002 (40,41). The QA scores of the first trial (JCOG 0202) that required on-going RTQA have been reported recently and showed good protocol compliance (42). The JCOG is also collaborating with the ATC and EORTC to establish a global standard in advanced technology clinical trial QA. A phase II SBRT trial for stage I non-small cell lung cancer (JCOG 0403) is supported by the ATC (43) and individual case reviews are being performed using a web-based remote review tool (Fig. 3).

CONCLUSIONS

Recent advances in RT focus on the need for a systematic RTQA program that balances patient safety and quality with

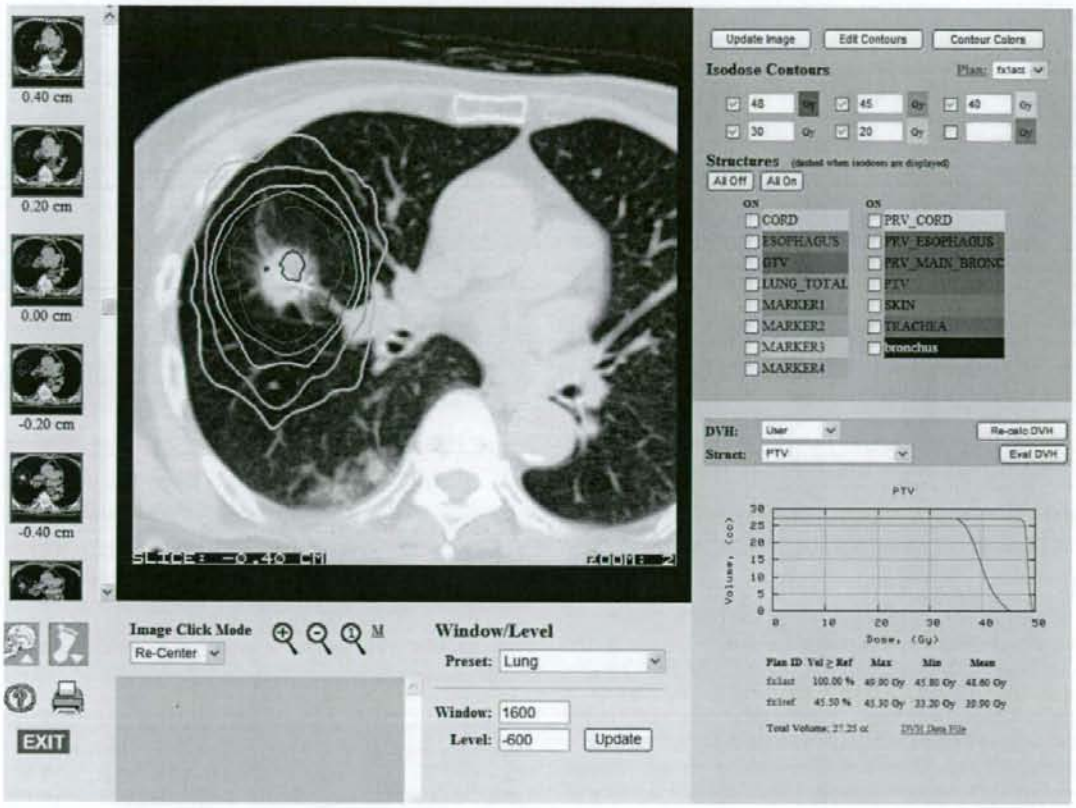

Figure 3. Advanced Technology Quality Assurance Consortium remote review tool.

available resources. It is necessary to develop more formal error mitigation and process analysis methods such as FMEA to focus available QA resources more optimally on process components to avoid catastrophic delivery errors. External audit programs for RTQA are also effective. Both postal dosimetry audit and clinical trial RTQA, especially for advanced technologies, in collaboration with global networks, will serve to enhance patient safety and quality of care.

Conflict of interest statement

None declared.

References

1. Matsuda T, Marugame T, Kamo K, Katanoda K, Ajiki W, Sobue T, et al. Cancer incidence and incidence rates in Japan in 2002: based on data from 11 population-based cancer registries. Jpn J Clin Oncol 2008; 38:641–8.
2. JASTRO database committee. Present status of radiotherapy in Japan: the regular structure survey in 2003. J Jpn Soc Ther Radiol Oncol 2005;15:115–21 (in Japanese).
3. Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005;104: 1129–37.
4. Tripartite committee - The Faculty of Radiation Oncology, The Australian Institute of Radiography, The Australasian College of Physical Scientists and Engineers in Medicine. Developing standards for radiation treatment services in Australia. Sydney: RANZCR 2005. Available at: http://www.ranzcr.edu.au/documents/download.cfm/Discussion%20Paper%20-%20Final.pdf?txtLibraryID=ranzcr&txtFileName=ACF4E02.pdf (Accessed 18 August 2008).
5. Kutcher GJ, Coia L, Gillin M, Hanson WF, Leibel S, Morton RJ, et al. Comprehensive QA for radiation oncology: Report of AAPM Radiation Therapy Committee Task Group 40. Med Phys 1994;21: 581–618.
6. Rivard MJ, Coursey BM, DeWerd LA, Hanson WF, Huq MS, Ibbott GS, et al. Update of AAPM Task Group No. 43 report: a revised AAPM protocol for brachytherapy dose calculations. Med Phys 2004;31:633–74.
7. Fraass B, Doppke K, Hunt M, Kutcher G, Starkschall G, Stern R, et al. American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53: quality assurance for clinical radiotherapy treatment planning. Med Phys 1998;25:1773–829.

8. Nath R, Anderson LL, Meli JA, Olch AJ, Stitt JA, Williamson JF. Code of practice for brachytherapy physics: Report of the AAPM Radiation Therapy Committee Task Group No. 56. American Association of Physicists in Medicine. Med Phys 1997;24:1557–98.
9. Kubo HD, Glasgow GP, Pethel TD, Thomadsen BR, Williamson JF. High dose-rate brachytherapy treatment delivery: Report on the AAPM Radiation Therapy Committee Task Group no. 59. Med Phys 1998;25:375–403.
10. Nath R, Amols H, Coffey C, Duggan D, Jani S, Li Z, et al. Intravascular brachytherapy physics: Report of the AAPM Radiation Therapy Committee Task Group no. 60. American Association of Physicists in Medicine. Med Phys 1999;26:119–52.
11. Yu Y, Anderson LL, Li Z, Mellenberg DE, Nath R, Schell MC, et al. Permanent prostate seed implant brachytherapy: Report of the American Association of Physicists in Medicine Task Group No. 64. Med Phys 1999;26:2054–76.
12. Thwaites D, Scalliet P, Leer JW, Overgaard J. Quality assurance in radiotherapy. ESTRO advisory report to the Commission of the European Union for the 'Europe Against Cancer Programme'. Radiother Oncol 1995;35:61–73.
13. Williamson JF, Dunscombe PB, Sharpe MB, Thomadsen BR, Purdy JA, Deye JA. Quality assurance needs for modern image-based radiotherapy: recommendations from 2007 interorganizational symposium on "quality assurance of radiation therapy: challenges of advanced technology". Int J Radiat Oncol Biol Phys 2008;71:S2–12.
14. Ibbott GS, Followill DS, Molineu HA, Lowenstein JR, Alvarez PE, Roll JE. Challenges in credentialing institutions and participants in advanced technology multi-institutional clinical trials. Int J Radiat Oncol Biol Phys 2008;71:S71–5.
15. Palta JR, Liu C, Li JG. Current external beam radiation therapy quality assurance guidance: Does it meet the challenges of emerging image-guided technologies? Int J Radiat Oncol Biol Phys 2008;71: S13–7.
16. Huq MS, Fraass BA, Dunscombe PB, Gibbons JP, Ibbott GS, Medin PM, et al. A method for evaluation quality assurance needs in radiation therapy. Int J Radiat Oncol Biol Phys 2008;71: S170–3.
17. Logan T. Error prevention as developed in airlines. Int J Radiat Oncol Biol Phys 2008;71:S178–81.
18. Stamatis DH. Failure mode and effect analysis: FMEA from theory to execution. Milwaukee, WI: ASQC Quality Press 1995.
19. Rath F. Tools for developing a QM program: proactive tools (process mapping, value stream mapping, fault tree analysis and Failure Mode and Effects Analysis (FMEA). Int J Radiat Oncol Biol Phys 2008; 71:S187–90.
20. International Atomic Energy Agency. International Basic Safety Standards for Protection Against Ionizing Radiation and for the Safety of Radiation Sources. IAEA Safety Series No. 115. Vienna: IAEA 1996.
21. Soimakallioa S, Järvinen H, Ahonen A, Wigren T, Lyyra-Laitinen T. Impact of clinical audit on the quality of radiological practices—experiences from a national audit programme supported by a national steering committee. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/038. Vienna: IAEA 2006;104–5.
22. Parkkinen R, Järvinen H. Implementation of QA in medical radiological practices: a national cooperation model. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/139P. Vienna: IAEA 2006,114–5.
23. Norwegian Radiation Protection Authority Bulletin. Quality assurance in radiotherapy. Østera's: Norwegian Radiation Protection Authority 2005.
24. Malicki J, Järvinen H, Scalliet P, Stankusová H, Leer JW. Clinical audit guidelines in radiotherapy -Preliminary results of the ESTRO working group. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/039. Vienna: IAEA 2006,106–7.
25. Izewska J, Scalliet P, Levin V, Järvinen H, Lartigau E. QA team for radiation oncology (QUATRO). In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/036. Vienna: IAEA 2006,100–1.
26. International Atomic Energy Agency. Comprehensive Audits of Radiotherapy Practice: A Tool for Quality Improvement. STI/PUB/ 1297. Vienna: IAEA 2007.
27. International Atomic Energy Agency. Setting up a Radiotherapy Programme: Clinical, Medical Physics, Radiation Protection and Safety Aspects. STI/PUB/1296. Vienna: IAEA 2008.
28. Horáková I, Pavliková I, Valenta J, Petera J, Šlampa P, Stankusová H. Components of QA of radiotherapy process—setup in the Czech Republic. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/138P. Vienna: IAEA 2006,112–3.
29. Izewska J, Georg D, Bera P, Thwaites DI, Arib M. Development of a methodology for TLD postal dosimetry audit of high-energy radiotherapy photon beams in non-reference conditions: an IAEA coordinated research project. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/088. Vienna: IAEA 2006,408–9.
30. Sergieva KM, Buchakliev Z, Ivanov G, Dimitrova V, Staykova V, Gesheva N. The results from external TLD audit in reference and non-reference conditions in Bulgarian radiotherapy centres. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEACN-146/227P. Vienna: IAEA 2006,416–7.
31. Viamonte A, Viegas CCB, Rosa LAR, Campos de Araujo AM, Souza RS. Postal audit in reference and non-reference conditions in Brazil. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/229P. Vienna: IAEA 2006,420–1.
32. Vatnitsky S, Izewska J, Bera P, Shortt KR. The IAEA/WHO TLD postal dose audits as a tool for evaluating the status of dosimetry practices in radiotherapy hospitals in developing countries. In: Shortt KR editor. Book of Extended Synopses. International Conference on Quality Assurance and New Techniques in Radiation Medicine. IAEA-CN-146/234P. Vienna: IAEA 2006,430–1.
33. Mizuno H, Kanai T, Kusano Y, Ko S, Ono M, Fukumura A, et al. Feasibility study of glass dosimeter postal dosimetry audit of high-energy radiotherapy photon beams. Radiother Oncol 2008;86:258–63.
34. Cancer Control and Information Services, National Cancer Center. Remote and on-site radiotherapy audit program. Available at: http:// www.ncc.go.jp/jp/cis/divisions/01clinical/clinicaltest05_en.html (Accessed 18 August 2008).
35. Molineu A, Followill DS, Balter PA, Hanson WF, Gillin MT, Huq MS, et al. Design and implementation of an anthropomorphic quality assurance phantom for intensity-modulated radiation therapy for the Radiation Therapy Oncology Group. Int J Radiat Oncol Biol Phys 2005;63:577–83.
36. Radiation Therapy Oncology Group. RTOG 0236: a phase II trial of stereotactic body radiation therapy (SBRT) in the treatment of patients with medically inoperable stage I/II non-small cell lung cancer. 2002. Available at: http://www.rtog.org/members/protocols/0236/0236.pdf (Accessed 18 August 2008).
37. Leif J, Roll J, Followill D, Ibbott G. The value of credentialing. Int J Radiat Oncol Biol Phys 2006;66:S716.
38. Ibbott GS, Hanson WF, O'Meara E, Kuske RR, Arthur D, Rabinovitch R, et al. Dose specification and quality assurance of Radiation Therapy Oncology Group protocol 95-17: A cooperative group study of 192Ir breast implants as sole therapy. Int J Radiat Oncol Biol Phys 2007;69:1572–8.
39. Bernier J, Horiot JC, Poortmans P. Quality assurance in radiotherapy: from radiation physics to patient and trial-oriented control procedures. Eur J Cancer 2002;38:S155–8.
40. Atagi S, Kawahara M, Tamura T, Noda K, Watanabe K, Yokoyama A, et al. Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced non-small cell lung cancer: a phase III trial of the Japan Clinical Oncology Group (JCOG9812). Jpn J Clin Oncol 2005;35:195–201.
41. Ishikura S, Teshima T, Ikeda H, Hayakawa K, Hiraoka M, Atagi S, et al. Initial experience of quality assurance in radiotherapy within the

Japan Clinical Oncology Group (JCOG). Radiother Oncol 2002;64: S224.
42. Sanuki-Fujimoto N, Ishikura S, Kubota K, Nishiwaki Y, Tamura T. Radiotherapy quality assurance review in the multi-center randomized trial for limited-disease small cell lung cancer: the Japan Clinical Oncology Group (JCOG) trial 0202. Int J Radiat Oncol Biol Phys 2008;72:S449.
43. Advanced Technology Consortium. ATC ASTRO 2008 Brochure. Available at: http://atc.wustl.edu/publications/ASTRO2008/ATC_Brochure_ASTRO2008.pdf (Accessed 10 October 2008).

特集：がん対策の新たな展開　―がん対策基本法に基づく総合的・計画的な推進に向けて

放射線治療の推進：現状と課題

石倉聡

国立がんセンターがん対策情報センター
多施設臨床試験・診療支援部がん治療品質管理推進室

Developing a High Quality Radiotherapy Service: Current Status and Future Perspectives

Satoshi ISHIKURA

Outreach Radiation Oncology and Physics Section, Clinical Trials and Practice Support Division
Center for Cancer Control and Information Services National Cancer Center

抄録

放射線治療はがん治療における重要な治療法の一つであるが，我が国では十分に活用できていない．2007年に策定された我が国の「がん対策基本計画」においては，「放射線療法及び化学療法の推進並びにこれらを専門的に行う医師等の育成」が謳われ，「全てのがん診療連携拠点病院において放射線療法を実施すること」が5年以内の達成目標としてあげられている．

我が国の現状として，人材が絶対的に不足している．2007年度の全国のがん診療連携拠点病院353施設に対して，放射線治療実施施設は340施設，放射線治療専従の常勤医がいる施設は，1名：144施設（42%），2名以上：112施設（33%）であり，84施設（25%）は常勤医が不在であり，国際原子力機関（IAEA）等によるガイドラインに遙かに及ばない状況にある．

今後は新たな人材育成と同時に，都道府県がん診療連携拠点病院等への集約化・効率化ならびに小規模施設への診療支援体制の構築が必要になると思われる．

また，がん診療連携拠点病院で提供すべき各種放射線治療にも格差がある．がん診療連携拠点病院における定位照射（SRT）と強度変調放射線治療（IMRT）の実施割合は高くなく，SRTは148施設（44%），IMRTは44施設（13%）に止まっている．また小線源治療においても前立腺シード治療は63施設（19%）であり，高線量率ラルスの実施も限られている．今後，がん診療連携拠点病院として必要な治療が実施できるよう，人材の確保ならびに診療報酬面による支援など，早急な対策が必要である．

さらに，放射線治療は誤って使用すれば死亡にもつながる障害を引き起こす危険もあり，放射線治療の実施にあたっては，一連の過程に対して品質管理（QC）/品質保証（QA）プログラムを行うことにより治療の質を保つことが必須となる．近年ではSRT，IMRTなどの先進的技術を安全に臨床導入するためにも各技術に応じた人材の確保とともに適切なQC/QAプログラムの実施が求められている．わが国においても，リニアック等の治療装置の線量管理を行なう物理技術的QC/QAおよび放射線治療の内容に関する臨床的QC/QAを全国規模で体系的に実施するシステムがようやく動き出した．

今後，種々の対策が実を結び，先進的放射線治療技術の臨床導入が安全かつ効果的に行われ，放射線治療の均てん化とともにがんの治療成績向上に寄与することを期待したい．

キーワード：　放射線治療，施設間格差，医療資源，品質保証，人材育成

〒104-0045　東京都中央区築地5-1-1
TEL：03-3542-2511（内線2457）　FAX：03-3547-5013
E-Mail：sishikur@ncc.go.jp

Abstract

Radiotherapy is one of the important options in cancer treatment, but is not utilized sufficiently in Japan. In "The Basic Plans to Promote Anti-Cancer Measures" in Japan introduced in 2007, "promotion of radiotherapy and chemotherapy as well as training for these professionals" was proposed along with "installation of radiotherapy in all designated cancer centers" within a target date of less than 5 years.

Currently in Japan, there is an absolute shortage of radiotherapy professionals. Of 340 designated cancer centers that provide radiotherapy, 144 institutions (42%) have only one full-time radiation oncologist, 112 (33%) have 2 or more, but 84 (25%) have none. This situation is markedly inferior to the guidelines proposed by the International Atomic Energy Commission (IAEA). Together with education for professionals, it will be necessary to centralize radiotherapy institutions effectively and to develop a practical support system for relatively small radiotherapy centers in the near future.

In addition, there are disparities in the capability of providing various type of radiotherapy in designated cancer centers. The availability of stereotactic radiotherapy (SRT) and intensity modulation radiation therapy (IMRT) is not high; SRT, 148 institutions (44%), and IMRT, 44 institutions (13%). With regard to brachytherapy, the availability of prostate seed therapy is limited to 63 institutions (19%), and a high dose-rate (HDR) Remote After-loading System (RALS) also has a limited availability. Immediate measures such as maintaining the level of radiotherapy professionals and raising the re-imbursement for radiotherapy will be necessary to make designated cancer centers capable of providing radiotherapy,

Furthermore, there is a risk of causing a fatal accident if the radiotherapy is performed incorrectly, thus it is essential to maintain the quality by performing a quality control (QC) and quality assurance (QA) program for the sequential process of radiotherapy. Currently, it is also necessary to install advanced technologies such as SRT and IMRT to prepare capable professionals and develop an adequate QC/QA program. In Japan, nationwide physics QC/QA programs, such as dosimetry audit, and clinical QC/QA program in treatment planning have recently been initiated.

We expect that various measures will be realized, and clinical introduction of advanced technology for radiotherapy will be achieved safely and effectively, so that disparity in the availability of radiotherapy will be resolved leading to improved outcomes in the near future.

Keywords: radiotherapy, healthcare disparities, health resources, quality assurance, professional education

I. はじめに

放射線治療はがん治療における重要な治療法の一つである．手術や化学療法との併用による集学的治療が，がんを治癒させるための有力な手段である一方，進行したがんに対する症状緩和にも効果的な方法として使用される．また，身体侵襲が少なく形態・機能温存を図れること，社会の高齢化と Quality of Life の視点からも放射線治療を必要とする患者数が増加している．それでも我が国ではがん治療における放射線治療の施行割合が約25% と先進諸国の60% 前後に比べて低い[1]．エビデンスに基づく試算では，52% のがん患者が経過中に少なくとも一度は放射線治療を受ける必要があると報告されている[2]．

2007年に策定された我が国の「がん対策基本計画」においては，「放射線療法及び化学療法の推進並びにこれらを専門的に行う医師等の育成」が謳われ，「全てのがん診療連携拠点病院において放射線療法を実施すること」および「都道府県拠点病院及び特定機能病院において放射線療法部門を設置すること」が5年以内の達成目標としてあげられている．厚生労働省ではこれらに基づき「がん診療連携拠点病院の整備に関する指針」の改訂，「がんに係る放射線治療機器緊急整備事業」ならびに国立がんセンターによる「放射線治療計画にかかる指導者研修」および「がん診療連携拠点病院に対する放射線治療品質管理（Quality Control: QC）/ 品質保証（Quality Assurance: QA）に関する現地研修会」（図1）などを実施しており，文部科学省では「がんプロフェッショナル養成プラン」として各大学が連携した人材育成プログラムを実施している．

今回，国立がんセンターがん対策情報センターで，がん診療連携拠点病院の機能強化を支援する視点から，放射線治療の推進における現状と課題について考察する．

II. 今何が不足しているのか

我が国の現状として，まず人材の絶対的不足がある．厚生労働省がん研究助成金指定研究「がん専門医療施設を活用したがん診療の標準化に関する共同研究」班（主任研究者：吉田茂昭）が実施したアンケート調査によると，2007年度の全国のがん診療連携拠点病院353施設に対して，放射線治療実施施設は340施設，放射線治療専従の常勤医がいる施設は，1名のみ：144施設（42%），2名以上：112施設（33%）であり，84施設（25%）は常勤医が不在であった．日本医学放射線学会認定の医学物理士にいたっては僅か93施設（27%）で採用しているのみであった．また，年間治療患者数は100名以下：27施設（8%），

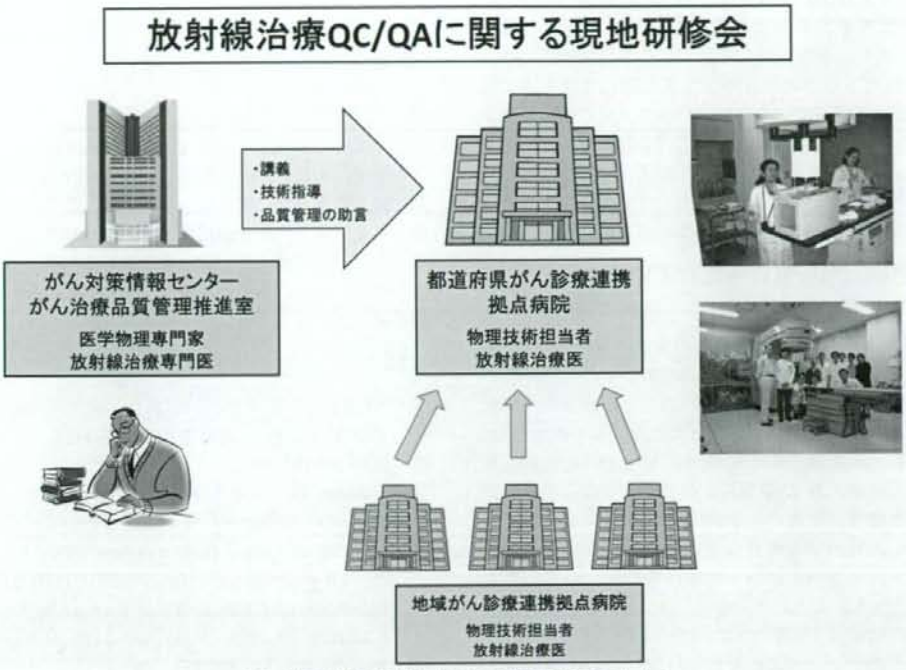

図1 放射線治療 QC/QA に関する現地研修会のスキーマ

100-300名：172施設（51%），300-500名：79施設（23%），500-1000名：49施設（14%），1000名以上：13施設（4%）であった．

一方，国際原子力機関（IAEA）をはじめとする国際機関によるガイドライン[3]では，放射線治療部長1名に加え，年間患者200-250名毎に放射線治療医1名の追加が必要であり，放射線治療医1名の担当患者は1日当たり25-30名を超えないこととされている．すなわち，少なくとも患者数200名以上の施設には最低2名の放射線治療医が必要であり，300-500名の施設では3名，500-1000名の施設では4-5名，1000名以上の施設では6名以上の放射線治療医が必要となる．また医学物理士は患者数400名毎に1名，診療放射線技師は技師長1名に加えて，リニアック1台につき1日の治療患者25名までは2名，25名を超えて50名までは4名，また患者数500名毎に治療計画担当技師2名が必要であり，放射線治療看護師も患者数300名毎に1名が必要とされている．しかしながらアンケート結果を見ると，がん診療連携拠点病院の現状はガイドラインに遙かに及ばない状況といえる．

放射線治療医不足に対して，大学においては放射線診断学から独立した放射線腫瘍学講座開設の必要性が謳われ，各大学および学会による学生および卒後研修医を対象としたセミナーその他の勧誘が積極的に行われているものの，短期間で人材不足の解消を図るのは医師不足に悩む他科と同様に容易ではない．現在，放射線治療を専門とする医師数として，日本放射線腫瘍学会認定医（2008年4月時点で575名）の数が引用されている．ただし，同学会には約1,500名の医師会員が所属しており，これから認定医を取得する放射線治療医や，中には日本医学放射線学会の放射線科専門医を取得しているが認定医は取得していない放射線治療医が少なからず存在する．上記アンケートでは，がん診療連携拠点病院の197施設（58%）は認定医以外により支えられている現状が示されている．一方，我が国では約700の放射線治療施設があり，治療患者数の少ない比較的小規模な施設に常勤の放射線治療医が1名配置されるといった状況も存在し，放射線治療医の効率的配置の観点から問題を孕んでいる．今後は新たな人材育成と同時に，都道府県がん診療連携拠点病院等への集約化・効率化ならびに小規模施設への診療支援体制の構築が必要になると思われる．

次に，上記人材不足とも関連するが，がん診療連携拠点病院で提供すべき各種放射線治療の格差である．放射線治療には大きく分けて体外照射と小線源治療とがあるが，体外照射には特殊なものとして定位照射（SRT）と強度変調放射線治療（IMRT）とがある．いずれも先進的な放射線治療であり，放射線治療機器のみならず高度な技術に対応できる人材も必要となる．上記アンケートによるとがん診療連携拠点病院における実施割合は高くなく，SRTは148

施設（44%），IMRTは44施設（13%）に止まっている．また小線源治療においても前立腺シード治療は63施設（19%）であり，子宮頸がんに対する標準治療手技の一つとしても使用される高線量率ラルスに関しては全国でも180施設程で実施しているのみである．さらに高線量率ラルスは約9割の施設で赤字となっている現状から，実施施設の減少が危惧されている．がん診療連携拠点病院として必要な治療が実施できるよう，人材の確保ならびに診療報酬面による支援など，早急な対策が必要である．

III．放射線治療の質は保たれているか

放射線治療の実施過程は複雑かつ多岐にわたる．1）患者の評価，2）放射線治療の適応の判断，3）放射線治療プロトコールの選択，4）放射線治療のための患者体位の決定および患者固定具の作成，5）コンピュータを用いたバーチャルシミュレーション：治療計画の為の画像撮影，腫瘍および正常組織の輪郭取得，6）照射方法の決定，放射線線量の評価，7）治療計画コンピュータから治療装置へ治療計画情報の転送，8）治療室での患者位置決め，9）照射，10）治療内容の照合など，各段階において不確実性が存在し，エラーが生じる危険性を孕んでいる．例えば，バーチャルシミュレーションでは，腫瘍の進展範囲の判断には施術者間の無視できないばらつきが存在することが言われており[4-5]，また，放射線線量の評価においても施設間較差が存在する危険性が指摘されている[6]．誤って使用すれば死亡にもつながる障害を引き起こす危険もあり，放射線治療の実施にあたっては，その一連の過程に対してQC/QAプログラムを行うことにより治療の質を保つことが必須となる[7]．さらに治療の実施に先立ち放射線照射装置（リニアック）そのもののQC/QAも欠くことができない．一方で近年のinformation Technology（IT）技術の進歩により，放射線治療も従来の二次元的なものから三次元／四次元放射線治療（3D/4D-CRT），SRT，IMRTなどへと急速に高度化が進んでいる．これらの先進的技術を安全に臨床導入するためにも各技術に応じた適切なQC/QAプログラムの実施が求められている[8-9]．

わが国においては，リニアック等の治療装置の線量管理を行なう物理技術的QC/QAおよび放射線治療の内容に関する臨床的QC/QAを全国規模で体系的に実施するシステムがようやく動き出した状況である．物理技術的QC/QAについてはIAEAや欧米のQAセンターの手法に準じ[10]，2007年11月から全国の放射線治療施設を対象として「治療用照射装置（X線）の出力線量測定（郵送測定）」事業が開始されたところである．一方，臨床的QC/QAに関しては2002年から日本臨床腫瘍研究グループ（JCOG）の臨床試験では射線治療QC/QAプログラムが導入され，短期間のうちにプロトコール規定の遵守率が飛躍的に向上するなど，一般診療の質の向上への波及効果も期待されている[11]．2006年には国立がんセンターがん対策情報センターにがん治療品質管理推進室が設置され，がん診療連携拠点病院および臨床試験参加施設等を対象として物理技術的QC/QAおよび臨床的QC/QAを支援する体制が整備されつつある[12]．

IV．まとめ

近年の技術革新による先進的放射線治療の導入に伴い，これまで以上に放射線治療の発展が期待される一方で，それを支える基盤整備が求められている．ここで述べたのは数あるアプローチの一部に過ぎないが，今後これらの対策が実を結び，先進的放射線治療技術の臨床導入が安全かつ効果的に行われ，放射線治療の均てん化とともにがんの治療成績向上に寄与することを期待したい．

文献：

1）JASTROデータベース委員会．全国放射線治療施設の2005年定期構造調査報告（第1報）．日放腫会誌 2007;19:181-192.

2）Delaney G, Jacob S, Featherstone C, Barton M. The role of radiotherapy in cancer treatment: Estimating optimal utilization from a review of evidence-based clinical guidelines. Cancer 2005;104:1129–37.

3）Inter-Society Council for Radiation Oncology. Radiation oncology in integrated cancer management. Philadelphia, PA: ISCRO; 1991.

4）Chao KS, Bhide S, Chen H, Asper J, Bush S, Franklin G, et al. Reduce in variation and improve efficiency of target volume delineation by a computer-assisted system using a deformable image registration approach. Int J Radiat Oncol Biol Phys 2007;68: 1512-1521.

5）Steenbakkers RJ, Duppen JC, Fitton I, Deurloo KE, Zijp L, Uitterhoeve AL, et al. Observer variation in target volume delineation of lung cancer related to radiation oncologist-computer interaction: a 'Big Brother' evaluation. Radiother Oncol 2005;77: 182-190.

6）Izewska J, Georg D, Bera P, Thwaites D, Arib M, Saravi M, et al. A methodology for TLD postal dosimetry audit of high-energy radiotherapy photon beams in non-reference conditions. Radiother Oncol 2007;84:67-74.

7）加藤洋一．ISO9000による品質保証の基本的な考え方．臨床評価2000;28:33-50.

8）Shortt K, Davidsson L, Hendry J, Dondi M, Andreo P. International perspectives on quality assurance and new techniques in radiation medicine: outcomes of an IAEA conference. Int J Radiat Oncol Biol Phys 2008;71:S80–84.

9）Williamson JF, Dunscombe PB, Sharpe MB, Thomadsen BR, Purdy JA, Deye JA. Quality

assurance needs for modern image-based radiotherapy: recommendations from 2007 interorganizational symposium on "quality assurance of radiation therapy: challenges of advanced technology". Int J Radiat Oncol Biol Phys 2008;71:S2–12.

10) Mizuno H, Kanai T, Kusano Y, Ko S, Ono M, Fukumura A, et al. Feasibility study of glass dosimeter postal dosimetry audit of high-energy radiotherapy photon beams. Radiother Oncol 2008;86:258-263.

11) Sanuki-Fujimoto N, Ishikura S, Kubota K, Nishiwaki H, Tamura T. Radiotherapy Quality Assurance Review in the Multi-center Randomized Trial for Limited-disease Small Cell Lung Cancer: The Japan Clinical Oncology Group (JCOG) Trial 0202. Int J Radiat Oncol Biol Phys 2008;72:S449.

12) http://ganjoho.ncc.go.jp/hospital/practice_support/consultation03.html

J Cancer Res Clin Oncol
DOI 10.1007/s00432-009-0553-0

ORIGINAL PAPER

Palliative radiation therapy for hemorrhage of unresectable gastric cancer: a single institute experience

Kenji Hashimoto · Hiroshi Mayahara · Atsuo Takashima · Takako Eguchi Nakajima · Ken Kato · Tetsuya Hamaguchi · Yoshinori Ito · Yasuhide Yamada · Yoshikazu Kagami · Jun Itami · Yasuhiro Shimada

Received: 5 December 2008 / Accepted: 19 January 2009

Abstract
Purpose To clarify the toxicity of palliative radiotherapy (RT) and its efficacy against bleeding of unresectable gastric cancer.
Methods Clinical data of 19 patients received palliative RT for bleeding from unresectable gastric cancer were reviewed. The median total dose and dose per fraction were 40 Gy (range 2–50 Gy) and 2.5 Gy (range 1.8–3 Gy).
Results The treatment success rate was 68.4%. By using a tumor alpha/beta ratio of 10, biological effective dose of 50 Gy_{10} or more was significantly correlated with treatment success ($P = 0.040$). The median event-free survival was 1.5 months after RT and the median overall survival from starting RT was 3.4 months. Grade 3 nausea and anorexia were recorded in 1 and 3 patients, respectively.
Conclusion Palliative RT was effective for hemostasis in patients with gastric cancer bleeding with minor adverse events.

Keywords Gastric cancer · Radiotherapy · Bleeding · Hemostasis

K. Hashimoto · A. Takashima · T. E. Nakajima · K. Kato · T. Hamaguchi · Y. Yamada · Y. Shimada
Gastrointestinal Oncology Division,
National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan

H. Mayahara (✉) · Y. Ito · Y. Kagami · J. Itami
Radiation Oncology Division,
National Cancer Center Hospital,
5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: hmayahar@ncc.go.jp

Published online: 10 February 2009

Introduction

Gastric cancer is the fourth most common malignancy and is the second leading cause of death, accounting for 700,000 confirmed deaths annually with about 930,000 new cases in the world (Kamangar et al. 2006). In Japan, about 100,000 patients suffer from gastric cancer, and roughly half of them died in 2002. These patients were unfortunately not localized at the first diagnosis. Unresectable gastric cancer has poor prognosis, with the 5-year overall survival (OS) rate of 10%. Fluorouracil-based chemotherapy for patients with unresectable gastric cancer has shown some benefits in improving survival compared with the best supportive care (Glimelius et al. 1994; Murad et al. 1993; Pyrhönen et al. 1995). However, no international standard regimens have been established to date (Ohtsu et al. 2006).

Gastric cancer induces various local symptoms such as bleeding, obstruction, anorexia and pain. Chronic bleeding from gastric cancer can lead to anemia, anorexia, dehydration or hypoalbuminemia. Anemia, in particular, occasionally interrupts the continuity of chemotherapy, and thus control of bleeding is important to improve the quality of life (Pereira and Phan 2004).

Several modalities can be considered as the treatment of choice against bleeding from gastric cancer; nevertheless, which treatment is more effective remains a matter of debate. For example, palliative gastrectomy may be appropriate only for well-selected patients with severe hemorrhage refractory to conservative treatment. Endoscopic hemostasis achieved using thermal probes or by epinephrine injection is temporarily effective in limited cases (Savides et al. 1996). Endoscopic intervention including argon plasma coagulation (APC) has achieved hemostasis in 67% of patients with gastroduodenal tumor bleeding (Loftus et al. 1994).

However, APC sometimes causes severe complications such as perforation in 5–15% of patients, and recurrence of bleeding was frequently found (Loftus et al. 1994). Some investigators have applied gastrointestinal arterial embolization to stop bleeding from gastric cancer, and they have proven its safety and efficacy in limited cases (Encarnacion et al. 1992; Srivastava et al. 2000).

Radiation therapy (RT) has been shown to palliate bleeding from every type of malignant tumors, such as cervical, lung and bladder cancers (Ferris et al. 2001; Onsrud et al. 2001; Hoskin 1998). Recently, two retrospective analyses have been reported regarding the benefit of palliative RT for symptomatic advanced gastric cancer (Kim et al. 2007; Tey et al. 2007). In these reports, palliative RT successfully controlled tumor bleeding in 53–70% of patients without causing severe toxicity. As a clinical practice, we have applied RT for the palliation of bleeding from gastric cancer at our institution. We report here the results of our retrospective analysis of palliative RT for patients with bleeding from gastric cancer, particularly focusing on the dose–fractionation relationship and treatment outcome.

Methods

We retrospectively reviewed the clinical data from the database of our institution of patients with advanced gastric cancer receiving palliative RT between January 1994 and October 2007. Of these patients, those who received RT for a primary lesion for the purpose of palliating tumor bleeding were identified. This study was performed in accordance with Declaration of Helsinki in 1964.

The following clinical characteristics of the patients were reviewed: age, Eastern Cooperative Oncology Group performance status (PS), endoscopic findings, primary site, tumor histology, oral intake status, serum hemoglobin (Hb) level, chemotherapy regimens, dose fractionation of RT, adverse events and treatment outcome. The amount of transfused red blood cells (RBCs) within 1 month before RT was also recorded. Successful treatment was defined as a patient being alive with no need for blood transfusion after more than 1 month following RT. Even if endoscopy proved bleeding improvement, patients who did not meet the successful treatment criterion were considered as treatment failure.

All patients included in this study received external beam RT. They were treated with 6–25 MV X-ray beams from a linear accelerator or microtron. All patients were conformally treated based on CT planning. The typical irradiation technique applied was opposed anterior–posterior two fields. Oblique opposed two fields were sometimes used to avoid irradiation of the right kidney or spinal cord. The biological effective dose (BED) was calculated using a tumor alpha/beta ratio of 10 using the linear-quadratic formalism. Adverse events were retrospectively recorded according to the Common Terminology Criteria for Adverse Events version 3.0.

We defined event-free survival (EFS) as the interval from the last day of RT to the first day of an event including blood transfusion or any cause of death. OS was defined as the interval from the first day of RT to the day of death. Survival curve was estimated by the Kaplan–Meier method (Kaplan and Meier 1958). Univariate analysis was performed using the Fisher's exact test to determine the factors correlating with treatment success. Statistical analysis was performed using StatView version 5.0 (SAS Inc., USA).

Results

Patients' characteristics

Nineteen patients with advanced gastric cancer receiving RT for the palliation of bleeding from primary gastric cancer ($n = 18$) or with postoperative local recurrence

Table 1 Patients' characteristics at the time of starting radiation

$n = 19$	Number
Male/female	13/6
Median age (range)	61 (33–78)
Performance status	
1	5
2	10
3	3
4	1
Histopathology	
Adenocarcinoma	18
Interstitial	11
Diffuse	6
Unknown	1
Squamous cell carcinoma	1
Location	
Upper	7
Middle	5
Lower	6
Stump	1
Macroscopic type classification	
Type1	2
Type2	4
Type3	11
Type4	2
Median quantity of transfusion one month prior to radiation (range) (ml)	2,400 (0–4,600)

Table 2 Dose, fractionations of radiation therapy, regimens of chemotherapy and clinical outcomes in each case

Patient no.	Age	Sex	Performance status	Total dose (Gy)	Fractions	BED (Gy)	Completion of RT	Prior chemotherapy	Concurrent chemotherapy	Post RT chemotherapy	Lowest Hb level prior to RT (g/dl)	Prior transfusion one month before RT (ml)	Hb level one month after RT (g/dl)	Oral intake before RT	Oral intake after treatment	Treatment outcome	OS (days)	EFS (days)	Status
1	70	M	2	5,000	25	60	Complete	1. CDDP/CPT 2. S1	None	None	4.7	1,700	9.5	Possible	Possible	Succeeded	248	56	Death
2	68	F	2	4,000	16	50	Complete	None	None	S1	7.1	1,000	10	Possible	Possible	Succeeded	1,157	1,136	Alive
3	60	M	4	4,000	16	50	Complete	5FU	None	1. PTX 2. CPT/MMC	6	3,400	10.1	Impossible	Possible	Succeeded	340	318	Death
4	68	M	2	4,000	16	50	Complete	1. 5FU 2. CDDP/CPT 3. PTX	None	None	4.3	1,200	8.3	Possible	Possible	Succeeded	275	254	Death
5	33	M	1	4,000	16	50	Complete	5FU	FP	1. S1 2. CDDP/CPT	6.6	500	8.6	Possible	Possible	Succeeded	194	173	Unknown
6	62	M	3	4,000	16	50	Complete	5FU	None	None	6.8	0	10.1	Impossible	Possible	Succeeded	191	66	Death
7	46	M	1	4,000	16	50	Complete	CDDP/CPT	None	S1	5	2,400	8.4	Possible	Possible	Succeeded	125	38	Death
8	69	M	2	4,000	16	50	Complete	CDDP/S1	None	PTX	5.1	1,700	9.2	Possible	Possible	Succeeded	101	56	Death
9	78	F	1	4,000	16	50	Complete	S1	None	None	5.3	700	7.6	Possible	Possible	Succeeded	88	66	Death
10	53	M	2	4,000	16	50	Complete	S1	S1	None	6.1	1,000	10.2	Possible	Possible	Succeeded	66	41	Death
11	62	M	3	4,000	16	50	Complete	CDDP/CPT	PTX	None	3.5	3,100	NE	Possible	Possible	Failed	29	7	Death
12	53	M	2	4,000	20	48	Discontinue[a]	1. FP 2. CDDP/CPT 3. DTX 4. MMC/CPT	None	None	4.9	1,900	10.2	Impossible	Possible	Succeeded	75	45	Death
13	61	F	3	3,500	14	44	Suspend[b]	1. S1 2. CDDP/CPT	None	None	7	1,000	NE	Possible	Possible	Failed	29	3	Death
14	57	M	1	2,700	9	35	Discontinue[a]	CDDP/CPT	None	PTX	5.4	4,600	8	Impossible	Possible	Succeeded	265	32	Death
15	51	M	2	2,000	10	24	Complete	None	MF	PTX	8.4	3,400	12.3	Impossible	Impossible	Succeeded	77	64	Death
16	51	F	2	2,000	10	24	Discontinue[a]	None	None	None	5.9	1,200	NE	Impossible	Impossible	Failed	30	3	Death
17	71	M	2	1,800	9	22	Suspend[b]	1. 5FU 2. CDDP/CPT	None	None	4.8	1,900	6.4	Possible	Possible	Failed	39	1	Death
18	71	F	2	720	4	8.5	Suspend[c]	S1	None	None	6.5	1,000	NE	Impossible	Impossible	Failed	30	21	Alive
19	33	F	3	200	1	2.4	Suspend[c]	CDDP/CPT	None	None	4.6	2,500	NE	Impossible	Impossible	Failed	3	2	Death

CDDP cisplatin, *CPT* irinotecan, *FP* 5FU/cisplatin, *DTX* docetaxel

MMC mitomycin C, *PTX* paclitaxel, *MF* methotrexate/5FU

RT radiation therapy, *BED* biological effective dose (α/β ratio of 10), *OS* overall survival, *EFS* event free survival, *NE* not examined

[a] Stopped because bleeding improved

[b] No clinical symptom improved

[c] General condition deteriorated

($n = 1$) were identified. The median age of the patients was 61 years (range 33–71) and the median PS was 2 (range 1–4). Table 1 shows the characteristics of the patients. All patients were classified as stage IV at the time of RT and ineligible for surgery because of tumor invasion to other organs. To confirm the bleeding site, all patients underwent endoscopy before RT.

Radiotherapy and patient condition

The dose fractionation of RT, prior chemotherapy, previous blood transfusion and treatment outcomes are shown in Table 2. All but one patient received blood transfusion to improve serum Hb level within 1 month prior to RT. The lowest serum Hb level before RT ranged from 3.5 to 8.4 g/dl (median 5.4 g/dl; Table 2). RBCs corresponding to a median of 1,700 ml of total blood (range 700–4,600 ml) were transfused prior to RT.

The prescribed dose–fractionation regimen ranged from 20 Gy in 10 fractions to 50 Gy in 25 fractions. The median BED was 50 Gy_{10}, which corresponds to a dose of 40 Gy in 16 fractions. Thirteen of 19 (68%) patients completed the total prescribed dose. Three discontinued the prescribed irradiation course because they were clinically judged as treatment success, while another three did not complete the planned irradiation course because of deterioration of general condition.

Treatment outcomes

Treatment success was observed in 13 of 19 patients (68%). The typical endoscopic findings of patients successfully treated are shown in Fig. 1. Complete hemostasis was confirmed in six of seven patients who underwent endoscopy after RT. The median BED was 50 Gy_{10}. Of those who completed the total prescribed dose, successful hemostasis was observed in 11 (92%) of 12 patients. In contrast, of those who were unable to complete the planned irradiation course, successful hemostasis was seen in only two of seven (29%) patients. Treatment success group received significantly higher dose than failure group (median total dose 40 Gy vs. 19 Gy, $P = 0.026$; Fig. 2). The causes of treatment failure ($n = 6$) were deterioration of general condition ($n = 2$), poor treatment effect ($n = 2$) and re-bleeding ($n = 2$). A BED of 50 Gy_{10} or more was significantly correlated with treatment success compared with a BED of <50 Gy_{10} ($P = 0.040$). Other factors considered to affect treatment success such as good PS (1 or 2) and Hb level before RT were not correlated with outcome ($P = 0.26$ and $P > 0.99$, respectively).

After completion of RT, two of three patients without prior chemotherapy could switch to chemotherapy, whereas seven of ten patients with one previous chemotherapy regimen could shift to second-line chemotherapy. Only one of six patients with two prior chemotherapy regimens could continue chemotherapy. Of eight patients in whom oral

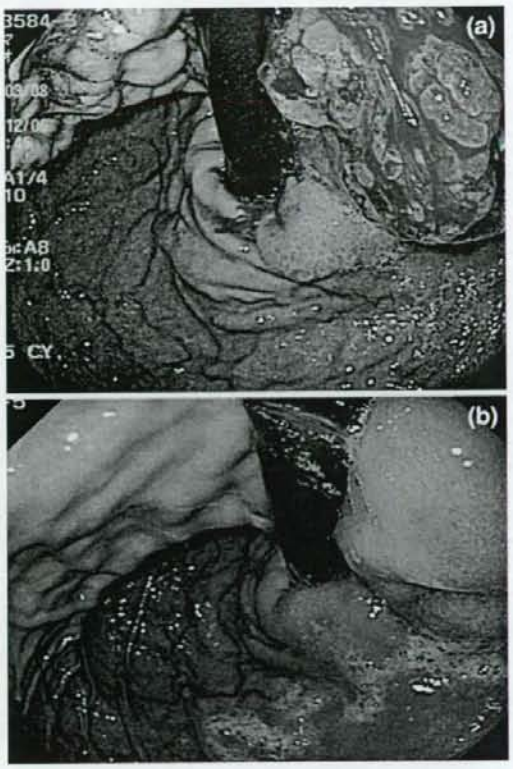

Fig. 1 Typical endoscopic findings. **a** Hemorrhagic gastric cancer of stomach body before radiation therapy. **b** Complete hemostasis following radiation therapy (40 Gy) of the same site

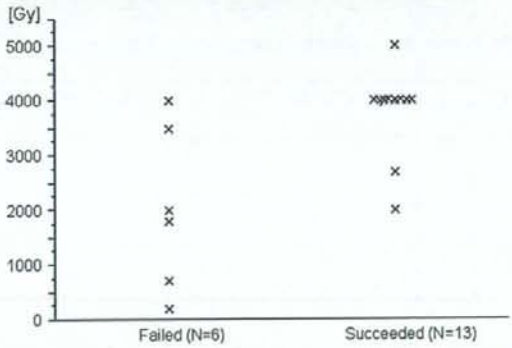

Fig. 2 Dose–effect relationship