おいては、放射線治療機器の精度管理、照射計画の検証、照射計画補助作業を専ら担当する者(QA担当者)、医師、照射業務を担当しない放射線技師の増加が特に必要であった。

- IMRT未実施施設においては導入のために知識・技術が必要と回答した施設が11施設と最多であり、次に装置の更新(5施設)であった。
- 全ての拠点病院において治療装置の出力線量を第三者により確認を実施することの必須化に対して県拠点・地域拠点の用件とすることに対してそれぞれ86%, 82%の賛成があった。
- 県拠点病院のスタッフの用件を専任から専従にすることに対して医師、技師、QA担当者それぞれ83%, 85%, 74%の賛成があった。またQA担当者の部署の設置、外部委員を含むQA委員会の設置それぞれに72%, 71%の賛成があった。

D. 考察

訪問による研修会実施による技術支援により、研修会を実施した施設でIMRTの臨床導入が可能となった。各施設の努力によるものであるが、支援したことが、臨床導入の一助になったと考える。今後、IMRTを導入していない都道府県がん拠点病院を中心に研修会を実施することで、IMRTの均てん化に貢献できるものと考える。今後、研修会を通じて発見した問題点や課題を解決するための遠隔支援体制の検討が必要である。

IMRT第三者線量評価プログラムにおいては、治療計画用、測定用ファントム２つを組み合わせたシステムを構築した。評価基準を設定した上で臨床試験参加施設に対して第三者評価を実施し、許容値内の結果を得た。しかし、現在のシステムは通常の放射線治療装置のみを対象としているため、Tomotherapy, Cyberknife, Truebeamなどの平坦化フィルタを有しない高精度放射線治療治療装置や、来年度予定されている標準測定法01の改訂への対応が必要である。

がん診療連携拠点病院指定要件（放射線治療部門）の改訂に向けての提言（案）に対するアンケートは、県拠点病院の意見を収集し、結果を提言に反映した。

E. 結論

先端的がん治療であるIMRTの均てん化のためには、各施設への訪問による技術支援プログラムと第三者線量評価プログラムを並行して実施することにより効果的な支援が可能であった。今後は、IMRTを実施していない施設への技術支援プログラム（研修会）の実施と、平坦化フィルタを有しない高精度放射線治療治療装置に対する第三者線量評価プログラムの構築が必要である。

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G. 知的財産権の出願・登録状況(予定を含む)

1. 特許取得
なし

2. 実用新案登録
なし

3. その他
なし

別紙４

研究成果の刊行に関する一覧表

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著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

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ORIGINAL ARTICLE

Radiotherapy quality assurance review for a multi-center randomized trial of locally advanced esophageal cancer: the Japan Clinical Oncology Group (JCOG) trial 0303

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Abstract
Background and purpose The purpose of this study was to evaluate the radiotherapy (RT) quality assurance (QA) for JCOG 0303.
Methods and materials JCOG 0303 was a multi-center phase II/III trial that compared two types of chemotherapy administered concomitantly with RT for locally advanced esophageal cancer. RT requirements included a total dose of 60 Gy in 30 fractions and CTV with a 2-cm margin cranio-caudally to the primary tumor. The QA assessment was given as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable following predefined criteria for quality parameters.
Results A total of 142 cases were accrued. After excluding 36 incomplete/not evaluable, 106 (75%) were fully evaluable for RT quality review. Of these 106, there were 4 VU (4%) and overall RT compliance (PP + DA) was 96%. Comparing the incidence of VU based on the numbers enrolled by institution, the highest quarter of enrollment ($\geq$7 cases) had no VU, while all VU (4; 11%) were from institutions enrolling <7 patients.
Conclusions The results of the RTQA assessment for JCOG 0303 were sufficient to provide reliable results. Additional improvements will be needed for institutions with low accrual rates.

Keywords Clinical trial · Esophageal cancer · Quality assurance · Quality control · Radiotherapy

Introduction

The validity of clinical trials among multiple institutions is predicated on the premise that the selection of patients and their treatments will be uniform at all of the participating institutions. This assumption requires a concise definition of the population to be studied, the treatment regimens to be followed, and the methods used for evaluating the results [1]. Quality assurance (QA) programs attempt to document the validity of the assumptions and to quantify the extent of any variations. High-standard QA programmes result in improvement of practice quality, which is known as a flow-on effect. It is important to apply the study results and to introduce the trial outcomes into practice. A QA evaluation therefore requires consideration of clinical validity and flexibility with regard to reasonable standards of care.

With the development of multi-modality studies, particularly for radiation therapy (RT), RT planning and delivery procedures have changed dramatically. As a result, assessments of the appropriateness of therapies delivered in each institution have become more complex. After the introduction of 3-dimensional (3-D) treatment planning in the 1980s, the improved technology for RT procedures has gradually spread to general practice from

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the mid-1990s up to today. During the transition period from conventional 2-dimensional (2-D) to 3-D RT planning, the first proactive QA programs for the Japan Clinical Oncology Group (JCOG) started in 2002.

JCOG 0202, a multi-center phase III trial, compared two types of consolidation chemotherapy after concurrent chemoradiotherapy for limited-disease, small cell lung cancer. As a result, JCOG 0202 demonstrated excellent compliance, as high as 92% [2]. The next trial for esophageal cancer, JCOG 0303, also implemented an on-going RTQA program. This study is an evaluation of the protocol compliance for JCOG 0303. In addition, by being involved in the JCOG RTQA process, we discuss the current conditions and problems of QA for multi-institution trials, as well as the perspectives for future clinical trials.

Materials and methods

Study design and RT requirements

JCOG 0303 was a multi-center phase II/III trial that compared two types of chemotherapy which were administered concomitantly with radiotherapy for locally advanced (T4 and/or unresectable metastatic lymph nodes) thoracic esophageal cancer (Fig. 1). The primary endpoint of this study was overall survival and the secondary endpoints included the proportion of complete responses and the toxicity profile of each treatment. JCOG 0303 was carried out according to the principles set out in the Declaration of Helsinki 1964 and all subsequent revisions, informed consent was obtained, and the relevant institutional review board had approved the study.

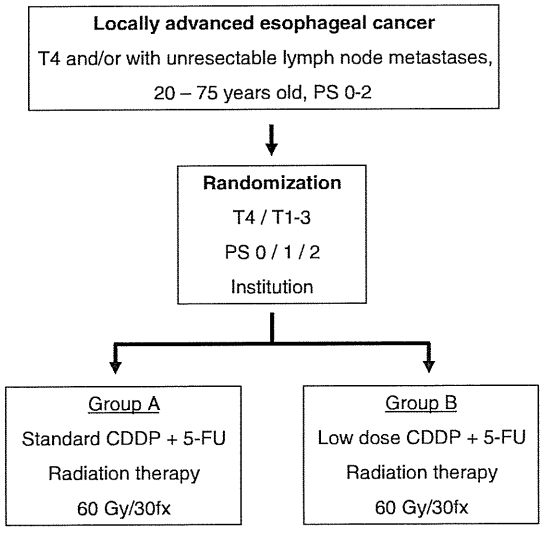

Fig. 1 Outline for JCOG 0303. *PS* performance status, *CDDP* cisplatin, *5-FU* 5-fluorouracil

Patients were randomized to receive either low-dose cisplatin/5-fluorouracil (5-FU) (6 weeks of cisplatin 4 mg/m^2 plus 5-FU 200 mg/m^2 on days 1–5) or standard-dose cisplatin/5-FU (cisplatin 70 mg/m^2 on days 1 and 29 plus 5-FU 700 mg/m^2 for days 1–4, and 29–32). Both regimens included concurrent RT.

Regarding the current practice for advanced esophageal cancer, RT requirements included a total dose of 60 Gy in 30 fractions and an overall treatment period of 40–63 days [3–5]. For treatment planning, both conventional 2-D X-ray simulation and 3-D computed tomography (CT) simulation were allowed. Gross tumor volume (GTV) was defined as the volume of a primary tumor demonstrated by a CT scan and/or an endoscope, as well as metastatic lymph nodes that measured $\geq$1 cm in the long axis. For this trial, a clinical target volume (CTV) for the primary tumor was created to add a 2-cm margin cranio-caudally by considering subclinical extension. A CTV margin for metastatic lymph nodes was not added and CTV did not include elective regional lymph nodes. A planning target volume (PTV) was defined by adding margins at the discretion of radiation oncologists (typically 0.5–1 cm for lateral margins and 1–2 cm for cranio-caudal margins, depending on respiratory motion and patient fixation). A dose of 60 Gy was prescribed at the center of the PTV. Tissue heterogeneity correction was not used for monitor unit calculation, because if heterogeneity correction was required and different calculation algorithms were allowed, the inter-institutional variation of the delivered dose would have been significant, and the convolution–superposition algorithm was not available in some participating institutions at the beginning of this trial.

Dose constraints were defined with regard to maximum point doses to the spinal cord and the digestive organs. The dose to the spinal cord was kept at $\leq$44 Gy. The doses to the gastric antrum, small intestine, and colon were kept at <50, <40, and <45 Gy, respectively.

If a tumor was located in the middle or lower thoracic esophagus, treatment using 3–4 ports was recommended to reduce the possible risk of heart toxicity. For the treatment of tumors in the upper thoracic esophagus and supraclavicular lymph node metastases, the number of ports used was at the discretion of each institution.

Quality assurance review

For the initial QA review, copies of pre-treatment diagnostic X-rays and CTs, simulation and verification films, worksheets for monitor unit calculations for the prescribed doses, and RT charts were sent to the QA review center within 7 days after beginning RT. Information on the total RT course was required to be sent within 30 days after completing RT. These documents were to be submitted for

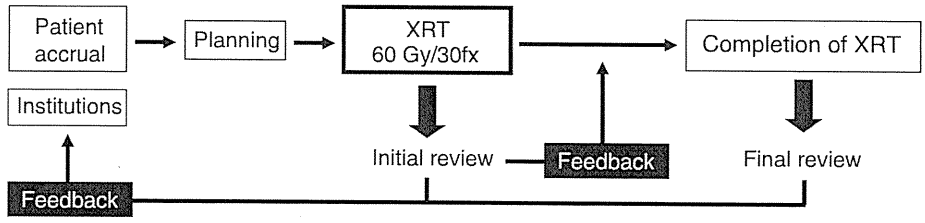

Fig. 2 Flow chart for QA review After the QA review, feedback was given to the institutions. Treatment planning was modified when possible

Table 1 Criteria for QA scores

	PP	DA	VU
GTV			
Distance to field borders	Lateral: 1–2.5 cm	Neither PP nor VU	Lateral: <1 cm or >2.5 cm
	Cranio-caudal: 3.5–6 cm		Cranio-caudal: <2 cm or >6 cm
Overall treatment time	40–63 days	NA	<40 or >63 days
Organs at risk			
Spinal cord	≤44 Gy	Neither PP nor VU	>50 Gy
Gastrointestinal	Within constraints (gastric antrum: 50 Gy, small intestine: 40 Gy, Colon: 45 Gy)	NA	Above constraints
Total dose at reference point	57–63 Gy	Neither PP nor VU	<54 Gy or >66 Gy
Heterogeneity correction	No	Yes (≤10% total dose difference)	Yes (>10% total dose difference)

GTV gross tumor volume, *PP* per protocol, *DA* deviation acceptable, *VU* violation unacceptable, *NA* not applicable

all accrued patients. They were collected during patient accrual and after the completion of accrual to provide for a final compliance assessment. The criteria for QA assessment were defined before the start of this trial, but they were not described in the protocol. Immediately after the initial records were available, the radiation oncology principal investigator (S.I.) sent each institution a letter reporting whether they had complied with the treatment protocol and an inquiry regarding QA documentation, when necessary (Fig. 2). Progress remarks and problems were reported at periodic meetings for investigators.

To assess RT protocol compliance, the following parameters were reviewed: dose and field border placement (adequacy of margins for GTV), doses to organs at risk, overall treatment time, and dose calculations without heterogeneity corrections. The QA assessment was given as per protocol (PP), deviation acceptable (DA), violation unacceptable (VU), and incomplete/not evaluable. "Protocol compliance" included both PP and DA.

Individual cases were reviewed both by an independent radiation oncologist (N.S.) and the radiation oncology principal investigator (S.I.) using the same criteria. For GTV coverage, VU was defined as the distance from the field edge of the blocks or multi-leaf collimators to the periphery of GTV <1 cm or >2.5 cm laterally and <2 cm or >6 cm cranio-caudally. For the dose at the reference point, a dose <54 or >66 Gy was judged as VU. If the margins for GTV were insufficient in order to avoid an overdose to the organs at risk, this was regarded as DA. However, if GTV was shielded for any reason, it was regarded as VU. If heterogeneity correction was considered for dose calculation and the dose difference exceeded 10%, it was judged as VU. Other criteria for the QA assessment are listed in Table 1.

Details of each assessment were analyzed. The incidence of VU was compared based on the numbers enrolled by institution among 106 fully evaluable cases.

Results

A total of 142 cases were accrued from April 2004 to September 2009. After excluding 36 cases, 106 (75%) were fully evaluable (Table 2). Partially evaluable cases were included for the evaluation of each item.

Among 132 patients who were evaluable for the treatment planning methods, conventional 2-D X-ray simulations were performed for 9 (7%) patients and 123 (93%) had 3-D CT simulations. Of 31 participating institutions, 22 institutions had introduced 3-D CT simulations, 3 used only 2-D X-ray simulations, and 6 used both. Two opposing ports were used for 61 (46%) patients. Three

ports, 4 ports, and 5 or more ports were used for 27 (21%), 40 (30%), and 4 (3%) patients, respectively.

Overall RT compliance (PP + DA) was 96% (102 of 106 fully evaluable). Details for the QA scores are listed in Table 3. There were 4 VU cases: 3 in GTV coverage with insufficient margins for GTV (although 1 VU case resulted from avoiding an excessive dose to the spinal cord); 1 in organs at risk due to an excessive dose to the gastric antrum. No VU case was found for the overall treatment period, dose to the spinal cord, or total dose and dose calculations.

A miscellaneous variation, other than the pre-defined criteria for the QA assessment, was found for 4 cases; although CTV was not intended to include regional lymph nodes in the protocol, elective nodal irradiation was performed for these 4 cases (3 cases to the supraclavicular region and 1 case to the paraesophageal region).

Institutions with the highest quarter of enrollment recruited more than 7 patients (mean = 11, range = 7–18), which accounted for 68 patients. In those centers that enrolled fewer than 7 patients (mean = 2, range = 1–5) and that recruited a total of 38 patients, 4 cases (11%) were judged as VU, while all of the cases from centers that enrolled 7 patients or more were compliant (Table 4).

Table 2 Numbers of evaluable cases and QA scores

	Number	%
Total	142	
Data insufficient/partially evaluable	25	
Off-protocol	8	
Ineligible	3	
Fully evaluable	106	100
PP	80	75
DA	22	21
VU	4	4
Compliance (PP + DA)	102	96

QA quality assurance, *PP* per protocol, *DA* deviation acceptable, *VU* violation unacceptable

Discussion

An overall compliance of 96% was sufficient to provide reliable results for the current study. There was a substantial number of feedbacks in QA assessment reports after initial case reviews between the radiation oncology principal investigator and investigators at participating institutions, and these were effective in better understanding of the protocol specification and in preventing unacceptable violations. In this trial, the number of unacceptable violations was too few to see the feedback effects, but such were observed in JCOG 0202 [2] in which protocol violations and deviations were seen more frequently in the earlier period of the trial. In the previous esophageal trial JCOG 9708, RT quality was not optimal [6]. JCOG 9708 was conducted to evaluate the efficacy and toxicity of chemoradiotherapy with 5-FU plus cisplatin for patients with Stage I esophageal squamous cell carcinoma. According to a retrospective RTQA review after the closure of this trial, the overall protocol compliance was 70%. After this review, the QA assessment reports were sent to participating institutions, most of which overlapped with those in JCOG 0303. As the influence of clinical trial experience over the years was recognized in RTOG studies [7], the good RTQA compliance in JCOG 0303 also appeared to be attributable to JCOG 9708 experience. Furthermore, as the importance of the pre-trial QA program has been well recognized [8–13], JCOG will also implement a dry-run as a pre-trial credentialing program.

Impact of RT quality on treatment outcome

The Trans-Tasman Radiation Oncology Group (TROG) conducted a large international phase III trial to evaluate any additional benefit of tirapazamine (TPZ), an hypoxic cytotoxin agent, to standard cisplatin-based chemoradiotherapy for locally advanced head and neck cancer [14]. Although this trial failed to demonstrate any benefits for TPZ, they reported the outcomes of a planned secondary analysis that was used to assess the impact of RT quality planning and delivery on outcomes, which might have

Table 3 Breakdown of QA scores

	Evaluable cases	PP	%	DA	%	VU	%
GTV	122	99	81	20	16	3	3
Overall treatment time	108	108	100	NA		0	0
Organs at risk							
Spinal cord	117	117	100	0	0	0	0
Gastrointestinal	125	124	99	NA		1	1
Total dose	108	106	98	2	2	0	0
Heterogeneity correction	126	120	95	6	5	0	0

QA quality assurance, *GTV* gross tumor volume, *NA* not applicable

Table 4 Numbers of VU cases based on the numbers enrolled among 106 fully evaluable cases

	Number of cases evaluable/NE	VU	%	*p* value
High-volume institutions ($n = 8$)[a]	68/20	0	0	0.015
Low-volume institutions ($n = 23$)[b]	38/16	4	11	

NE not evaluable

[a] High-volume institutions, with the highest quarter of enrollment, accrued 7 cases or more

[b] Low-volume institutions accrued less than 7 cases

provided some explanation for the negative overall trial results [15]. As a result, they found a 20% absolute difference in 2-year overall survivals between those who had protocol-compliant plans and those with plans that had a predicted major adverse impact on tumor control (70 vs. 50%, respectively). This was twice the hypothesized survival benefit of TPZ used in the trial design.

They also showed that centers that treated only a few patients were the major source of RT quality problems. While many reports have shown that failure to adhere to the treatment protocol degraded the outcomes of clinical trials [7, 16–22], for the first time they quantified the penalty associated with poor RT and demonstrated a more substantial impact of RT quality on outcomes than any additional effects for new agents. In our study, the numbers enrolled by each institution also adversely affected the number of VU cases. The overall outcomes may also have been influenced by poor quality RT, even though the absolute number of VU cases was small. As pointed out by the TROG trial, it is desirable to limit a trial's participation to those sites that can contribute a significant number of patients.

Relationships between deviation, eligibility criteria, and protocol

Although the first step in minimizing the variations in clinical trials is the use of a detailed trial protocol, it is sometimes impossible to define a uniform acceptable technique for the treatment of advanced esophageal cancers; however, a certain margin is usually included to cover individual variations in order to identify those variations that are due to clinically valid judgments.

The significance of elective nodal irradiation for locally advanced esophageal cancer, especially for those with T4 and/or unresectable metastatic lymph nodes, has not yet been clarified [3, 23, 24]. In the current JCOG 0303 trial, the protocol specified that such subclinical areas were not to be included as CTV. However, there were 4 cases that received elective nodal irradiations, all of which did not appear to have predicted impacts on tumor control or toxicity. They were still acceptable when assessed by the criterion of reasonable standards of care and, therefore, were judged as DA cases.

We found that most of the DA cases were due to insufficient margins for GTV caused by avoiding overdoses to organs at risk. Such conditions are often experienced due to the anatomy of esophageal cancer. The esophagus is located in contact with vertebrae that embrace the spinal cord. Esophageal cancer often grows to be a bulky mass lying across the anterior walls of the vertebrae, or it frequently metastasizes to the lymph nodes along the right recurrent nerve. Therefore, an off-cord boost is often difficult to create for delivering an adequate dose to the PTV while avoiding an overdose to the spinal cord. In fact, in the current trial, there was one VU case for GTV that was due to avoiding an excessive dose to the spinal cord. This may be more a matter of the eligibility criteria for this trial than of protocol compliance. As a result, during a QA assessment, it can sometimes be difficult to distinguish a VU case from a DA case. Effects of these variations on outcomes are to be assessed with the final results.

Suboptimal proportion of evaluable cases

In the current study, there was a substantial number of cases that were excluded ($n = 36$; 25% of all cases), while the overall compliance was excellent when the subjects were limited to fully evaluable cases. Among the 36 excluded cases, the data were insufficient or only partially evaluable for 25 cases, 8 cases went off protocol, and 3 cases were ineligible. Improvements of evaluability are another challenge for RTQA, not only for trial outcomes, but also for trial cost effectiveness. Although the support of cooperative group trials is costly due to the involvement of various professionals, improvement of evaluability would make up for the cost by decreasing the exclusion loss from the analysis [1].

Frequency of 3-D CT simulation and credentialing

In early clinical trials, data acquisition was non-uniform and inconsistent, and radiation dose calculations varied significantly. Improvements in the QA procedures have increased treatment uniformity of the study, which has helped to validate the study conclusions. Recently, protocols have been developed with increasing complexity. Especially for RT, current studies have introduced CT-based treatment planning, enabling precise target definitions and dose deliveries. The use of advanced treatment modalities in clinical trials requiring volumetric digital

data submission is one of the great challenges in RTQA [25].

Previously, the Radiation Therapy Oncology Group (RTOG) 9415, a randomized phase III trial that compared high-dose radiotherapy with standard doses for esophageal cancer, recommended the use of CT simulation, although it was not mandatory. Dose prescription was conventionally specified at an isocenter. As from the next esophageal trial, E0113, a randomized phase II study of two paclitaxel-based chemoradiotherapy regimens, all participating institutions had to utilize 3-D CT planning. Furthermore, RTOG 0436, a phase III trial evaluating the addition of cetuximab to paclitaxel, cisplatin, and radiation for patients with esophageal cancer, required a facility questionnaire for each institution, as well as a dry-run QA test, in order to prove that the institution was eligible to enter patients into the study.

In the current JCOG 0303 trial, a majority of the participating institutions had introduced 3-D CT simulations; however, in patients with 2-D X-ray simulation, precise 3-D volumetric dose evaluation was not available. Today, CT-based 3-D planning is standard and it will be mandatory in coming JCOG trials. In 2004, the JCOG RT group implemented a pre-trial credentialing program for a phase II trial of stereotactic body RT for early stage non-small cell lung cancer (JCOG 0403). The next trial for intensity-modulated RT for nasopharyngeal cancer will require a dry-run test for all participating centers. As we move to multimodal image-based definitions of target volumes for protocols, timely interactions between study investigators and QA centers through protocol development will become more and more important in future trials.

In conclusion, the results of the RTQA assessment for JCOG 0303 were sufficient to provide scientifically reliable results. Further improvements will be needed for institutions with low accrual rates. A dry-run and credentialing program are being implemented in JCOG trials to further improve RT quality.

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Conflict of interest No author has any conflict of interest.

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Q28 前立腺がん

回答：九州大学病院別府先進医療センター 放射線科 中村和正（なかむらかつまさ）

point

- 前立腺がんの放射線治療は大きな進歩をとげ，3次元原体照射，強度変調放射線治療，小線源療法など，前立腺に線量を集中し，その周囲への被曝を低減する種々の技術が開発された．
- 早期前立腺がんに対する放射線治療の治療成績は手術とほぼ同等である．
- 放射線治療の主な有害事象は直腸障害であるが，男性機能，尿路系機能などを含めた生活の質を高く保つことができる．
- 放射線治療は，前立腺全摘除術後のアジュバント療法または救済療法として行われることがある．
- 骨転移の痛み，脊髄圧迫，下部尿路閉塞などの症状緩和にも放射線治療が用いられる．

Q 前立腺がんに対する放射線治療の役割は何ですか？

A 前立腺がんの放射線治療は，治す目的で行う根治的放射線治療，手術後に行う術後照射，がんの進行に伴う症状を緩和するために行う緩和的放射線治療に分かれます．根治的放射線治療は，後述するように近年急速に進歩し，治療成績は手術とほぼ同等のレベルに向上し，根治的な治療を検討する場合の重要な選択肢の一つとなっています．また，前立腺全摘除術が行われた後に，再発を予防するためや再発した場合の治療として，術後に放射線治療が行われることがあります．骨転移による痛みやホルモン療法抵抗性で腫大した前立腺による排尿障害などの症状を緩和するためにも，放射線治療が用いられます．

Q 前立腺がんの根治的な治療を考えるにあたり，注意すべき点は何ですか？

A 前立腺がんの特徴は，他の悪性腫瘍と比較して予後が良好であることです．早期の前立腺がんであれば，適切な治療を行うことにより前立腺がんで命を落とす可能性はかなり低いと考えられます．また，前立腺がんは，前立腺特異抗原（prostate specific

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antigen：PSA）というきわめて鋭敏な腫瘍マーカーをもつことも特徴です．PSAは早期診断や治療効果の優れた指標として用いられ，再発の早期発見にも威力を発揮します．しかし，たとえPSA再発が起こっても，それがすぐに前立腺がん死と結びつくわけではないことが多いため，前立腺がんの治療方針を決定する場合，治療後の患者の生活の質（quality of life：QOL）をいかに高く保つかが重要になります．年齢，合併症などで患者の期待生存期間が短い場合や，進行のリスクが非常に小さいと判断される場合には，無治療も一つの選択肢となる場合があります．

前立腺がんは，通常の悪性腫瘍のように病期分類としてTNM分類が用いられ，遠隔転移やリンパ節転移があれば，それだけ予後が不良となります．さらに，治療前PSA値，Gleason scoreなども重要な予後予測因子となります[1]．つまり，前立腺がんの放射線治療は，単にTNM分類のみならず，これらのリスク因子を考慮に入れた治療戦略を立てる必要があります．リスク分類にはいろいろなものがありますが，米国のNCCN Clinical Practice Guidelines in Oncology[2]では，T1～2aかつGleason score 2～6かつPSA＜10 ng/mLを低リスク群，T3a以上またはGleason score 8～10またはPSA＞20 ng/mLを高リスク群，それ以外を中リスク群と分類し，治療方針の決定を行っています．

メモ

●Gleason score

前立腺がんの病理組織学的分類として用いられます．がんの悪性度を5段階に評価し，前立腺がんの組織像の多様性を考慮して，量的に最も優位なパターンと次に優性なパターンの数の合計をグリーソンスコア（＝Gleason score, Gleason sum）として表現します．グリーソンスコアでは，6以下が低リスク，7は中リスク，8～10は高リスクとされ，治療法選択の重要な情報の一つです．

Q 前立腺がんの根治的放射線治療には，どのようなものがありますか？

A 前立腺がんの放射線治療は，大きく外部照射と小線源療法に分かれます．外部照射は体外からX線などの放射線を照射する方法で，3次元放射線治療（3 dimentional conformal radiation therapy：3DCRT），強度変調放射線治療（intensity-modulated radiation therapy：IMRT）などの照射方法があります．また，これらの治療を行う直前に治療計画との位置のずれを補正して照射する，画像誘導放射線治療（image-guided radiation therapy：IGRT）が近年普及しています．さらに，陽子イオンや炭素イオンを使った粒子線治療も近年普及しつつあります（3DCRT，IMRT，IGRTについての詳細は総論の項を参照ください）．前立腺がんは，このような高精度放射線治療の利点を最も生かすことができる疾患の一つです．なぜなら，前立腺がんの放射線治療では直腸出血の頻度をいかに低減させるかが重要なポイントとなり，これらの高精度放射線治療は直腸の被曝線量を効率的

に低減できるからです.

小線源療法では，小さい金属容器に密封された放射性同位元素（これを小線源といいます）から放出されるγ線などを治療に用います．前立腺がんに対する小線源療法は，経直腸的超音波のガイドを用いることにより，線源またはアプリケータ針を正確に挿入できるようになり，成績が飛躍的に向上しました．小線源療法は，直接前立腺またはその周囲に線源を挿入するため，組織内照射ともよばれます.

前立腺がんに対する小線源療法には低線量率，高線量率の2種類の方法があります．低線量率による小線源療法は，ヨード125という放射線を放出する物質を直径0.5 mm，長さ約5 mmの筒型容器に封入した小さい線源を，会陰部より前立腺組織に永久的に挿入します．数日程度の短期入院での治療が可能です.

小線源療法には，高線量率組織内照射という方法もあり，前立腺にアプリケータ針とよばれる細いチューブを数日間挿入したままにし，そのチューブ内に小さいイリジウム192などの線源を繰返し一時的に挿入して治療する方法です．線量率が高いため，まずチューブのみを挿入し，遠隔から操作して線源をチューブ内に挿入するため，術者の被曝がありません．この方法は，remote after-loading system（RALS）ともよばれます.

小線源療法は麻酔が必要なため，外部照射より侵襲的ですが，外部照射よりさらに多くの線量を前立腺に照射でき，短期の入院のみで治療が終了するなどの利点があります.

Q 根治目的での放射線治療は，どのように実施されますか？ またその治療成績はどのくらいですか？

A 外部照射では，通常，一回1.8～2 GyのX線にて70～78 Gy程度の総線量が選択されます．3DCRTでは70～72 Gyが，IMRTでは74～78 Gyが投与されることが多いようです．外部照射は，外来での治療で十分ですが，治療期間として7～8週間程度必要となります.

前立腺がんの根治的外部照射では，リスク分類に従って，治療方針が変わります．たとえば，NCCNガイドラインでは，低リスク群では外部照射単独が推奨されています[2]．一方で，リスクが高くなるにしたがって前立腺外への浸潤やリンパ節転移の可能性が高くなり，ホルモン療法と併用することによって再発率を低下させることができます．中リスク群には，4～6ヵ月の短期間のホルモン療法との併用，高リスク群では2～3年以上の長期のホルモン療法との併用が推奨されています[2].

低線量率での小線源療法は，低リスク群に関しては小線源療法単独にて，中リスク群には外部照射との併用にて治療が行われることが一般的です[3]．高リスクでは再発する可能性も高いため，あまり推奨されていません．高線量率での小線源療法は，外部照射と併用したブースト照射として使用されることが多く，本邦では比較的高リスクの症例に行われます.

局所療法，すなわち手術や放射線治療での10年PSA非再発率は，低リスク群で約80%，中等度リスク群で約50%，高リスク群で約30%とされています[4]．しかし，中～高リスク群では高線量投与により治療成績が向上する可能性があり，また，内分泌療法を併

用することによっても成績の向上が見込めます．これはあくまでPSAの非再発率であり，全生存率は通常の悪性腫瘍と比べて，一般的に非常に良好です．

Q 放射線治療に伴う副作用（有害事象）について教えてください

A 急性の有害事象として，下痢・軟便，頻尿，排尿痛などがありますが，可逆的です．晩期有害事象として最も問題となるものは直腸出血です．手術を要するような出血などをきたす頻度は1％以下ですが，輸血を含めた内科的な処置の必要な出血の起こる頻度は，数パーセントから20％程度にみられます[5]．これは直腸の線量に依存しますので，強度変調放射線治療などの高精度放射線治療を行うことにより，有害事象の頻度を低減することができます．尿路系の有害事象として，血尿，尿道狭窄などがあります．性機能障害が起こる可能性もありますが，手術に比べ頻度は低いとされています．

Q 前立腺がんの手術後に放射線治療を行うことがあるのですか？

A 前立腺全摘除術を行い，断端陽性などで再発のリスクが高いと判断した場合，アジュバント療法として外部照射を行うことがあります．一方，たとえ再発のリスクが高くても，PSAの上昇を確認してから救済放射線治療を行う場合もあり，一定のコンセンサスは得られていません[6]．近年，pT3，断端陽性など，再発のリスクの高い症例に，アジュバント放射線治療を加える群と加えない群の比較試験の結果がいくつか報告され，外部照射を加えたほうが，PSA再発率が低いことが証明されました[6]．ただし，全生存率に影響するかどうかについては，はっきりしていません．

術後にPSAが上昇し，明らかな遠隔転移がない場合には，救済療法として外部照射を考慮する必要があります．治療開始の目安となるPSA値は0.4～1.0 ng/mL程度とされ，早い時期での治療開始がよいとされています．膀胱尿道吻合部を十分含めた前立腺床を照射野とし，64 Gy以上の線量が推奨されています[7]．有害事象として，尿道狭窄などの合併症が1～3％に認められます．

Q 前立腺がんの緩和的な放射線治療について教えてください

A 緩和的な放射線治療としては，骨転移の痛みの緩和，脊髄圧迫の解除，下部尿路閉塞などの症状緩和などを目的として行われます[8]．

骨転移の痛みに対する治療効果は，一般的な疼痛改善率は約70～85％で，完全除痛率は30～50％程度といわれています．30 Gy/10分割，20 Gy/5分割などの線量分割が一般的に用いられ，1～2週間の短期間で治療を終了しますが，さらに短期照射として，8 Gy程

度の１回照射が行われることがあります．この利点としては，１回来院するだけで治療が完了することや，費用も安価であることなどがあり，外来通院が困難な患者さんなどで行われます．前立腺がんの骨転移は多発する場合も多いのですが，すべての骨転移部位への照射は容易ではなく，近年はストロンチウム89という放射性同位元素を注射して，骨転移部位に集積させ，痛みを改善する治療も導入されています．

骨転移に伴う脊髄圧迫は，患者のQOLを大きく低下させるため，その予防・治療は，進行前立腺がんのマネジメントにとってきわめて重要です．手術が第一選択ですが，手術は侵襲性も大きく，状態の安定した患者が主に適応となりますので，実際には放射線治療が行われることも多くみられます．

ホルモン療法に抵抗・再燃となった場合で，前立腺の腫大に伴う下部尿路閉塞などの症状緩和に対しても放射線治療は有効で，通常の前立腺がん根治照射と異なり，比較的少ない線量で，短い期間で治療を終了します．

前立腺がんに対する緩和的医療として治療を行う場合には，患者のQOLを考えながら，なるべく短い期間で，患者の身体的負担がなるべく少なくなるように治療する必要があります．

[文　献]

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ORIGINAL ARTICLE

Radiotherapy quality assurance of the Japanese Gynecologic Oncology Group study (JGOG1066): a cooperative phase II study of concurrent chemoradiotherapy for uterine cervical cancer

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Abstract
Background To assess radiotherapy protocol compliance in a multi-institutional phase II study of concurrent chemoradiotherapy for patients with locally advanced cancer of the uterine cervix (JGOG1066).
Methods For study protocol development, various radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with cervical cancer treatment expertise. Quality assurance (QA) was also discussed and included in the protocol. A credentialing process was used to select institutions for participation in the study. Individual case reviews referring to 18 QA items were undertaken for each patient. Radiotherapy data were submitted to the Japanese Gynecologic Oncology Group (JGOG) data center and reviewed by the members of the radiotherapy committee. The QA evaluation was classed as per protocol, deviation, and violation.
Results Individual case reviews were performed on 69 of 72 patients entered in the study. In 24 patients (35%), there

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were no deviations for any QA items. There were also no deviations seen for 5 of the 18 items in 69 patients evaluated. Deviations of 64 QA items were seen in 45 cases, and violations were seen in 4 cases (4 items). The most common deviation concerned appropriate application for the external beam radiotherapy (EBRT) boost to involved nodes or parametrium (32 cases). The 4 violations were identified in the QA items regarding high-dose rate intracavitary brachytherapy.

Conclusions Radiotherapy protocol compliance was favorable except for the EBRT boost indications. The results of this study validate the quality of radiotherapy in JGOG1066, and indicate that the final analysis will provide meaningful results.

Keywords Carcinoma of the uterine cervix · Radiation therapy · Chemoradiotherapy · Intracavitary brachytherapy · High dose rate

Introduction

Concurrent chemoradiotherapy (CCRT) is a standard treatment for patients with locoregionally advanced uterine cervical cancer [1]. However, some Japanese physicians remain cautious about employing CCRT as a standard treatment, for 2 reasons. The first concerns the feasibility of using the standard chemotherapy of weekly 40 mg/m^2 cisplatin concurrently with radiotherapy. There have been several reports that Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 cisplatin may not be feasible for Japanese patients [2, 3]. The second is that there are limited data on CCRT using high-dose-rate intracavitary brachytherapy (HDR-ICBT) [4, 5]. In addition, total radiation doses to the primary tumor seem to be extremely low compared with doses for definitive radiotherapy or CCRT in the United States [4–7]. A large amount of data concerning excellent outcomes and toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data were limited [8]. Therefore, the 2007 Japanese treatment guidelines for uterine cervical cancer recommended a B grade for CCRT [9]. We undertook a prospective study (JGOG1066) to evaluate toxicities and outcomes in patients treated with CCRT using the standard dose/schedule of cisplatin and the standard Japanese radiotherapy dose schedules for HDR-ICBT.

For scientifically valid CCRT clinical trial results, it is essential to develop an adequate protocol and assure compliance with the radiotherapy protocol. In developing the JGOG1066 protocol, several Japanese radiation oncology experts on cervical cancer undertook extensive deliberations on radiotherapy methods. In addition, effective quality assurance (QA) for radiotherapy was also discussed. In this paper, we describe the process for QA and present results of independent case reviews (ICRs) from the CCRT study.

Patients and methods

Summary of the JGOG1066

The Japanese Gynecologic Oncology Group (JGOG) conducted a phase II trial (JGOG1066) to evaluate the feasibility, toxicity and efficacy of CCRT using the standard global schedule for cisplatin (40 mg/m^2 weekly, 5 courses) and standard Japanese dose schedules for HDR-ICBT. Table 1 summarizes the trial, listing the criteria for patient eligibility, the endpoints, and treatments.

Protocol development

Radiotherapy parameters were examined and consensus was reached by Japanese radiation oncologists with expertise in the treatment of cervical cancer. A nationwide questionnaire on radiotherapy methods including treatment schedules, delivery of an external beam radiotherapy (EBRT) boost to lymph nodes and the parametria, and bladder/rectum dose calculations (ICRU38) was first distributed to radiation oncologists. Treatment schedule queries included total and fractional doses of whole-pelvis EBRT (with/without midline block) and also total and fractional doses of HDR-ICBT. In developing protocols for radiotherapy methods, data from the questionnaire and from previous published reports were extensively discussed, and a consensus was reached.

To determine location of point A, a rule was established based on the topographical relationships between tandem and ovoid. Basically, a coordinate at the external os (usually equivalent to the position of the tandem flange) was selected as the geographic origin of point A. In cases where the external os was located caudally to the cranial ovoid

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Table 1 Summary of JGOG1066

Eligible patients

1. FIGO stage III/IVA uterine cervical cancer
2. Squamous cell carcinoma, adenosquamous cell carcinoma, adenocarcinoma
3. ECOG performance status 0–1
4. Age 20–70 years
5. No para-aortic lymphadenopathy (≥10 mm assessed by CT)
6. No prior treatment
7. Adequate organ (bone marrow, hepatic, renal, heart) functions
8. Written informed consent

Endpoints

Primary: 2-year progression-free survival rate

Secondary: treatment completion rate, toxicity rates (acute and late), complete response rate, 2-year survival rate, 2-year pelvic progression-free rate, 2-year distant metastases-free rate

Planned sample size and accrual duration:

70 within 2 years

Treatment

Concurrent chemoradiotherapy (CCRT)

Chemotherapy

Cisplatin 40 mg/m^2, weekly, 5 courses

Radiotherapy

External beam radiotherapy (EBRT) and high-dose-rate intracavitary brachytherapy (HDR-ICBT)

Radiotherapy schedules

WP	WP + MB	HDR-ICBT[a]	BED (WP + HDR-ICBT)[a]
30 Gy/15f	20 Gy/10f	24 Gy/4f	74.5Gy$_{10}$
30.6 Gy/17f	19.8 Gy/11f	24 Gy/4f	74.4Gy$_{10}$
40 Gy/20f	10 Gy/5f	18 Gy/3f	76.8Gy$_{10}$
41.4 Gy/23f	9 Gy/5f	18 Gy/3f	77.8Gy$_{10}$

WP whole pelvic radiotherapy, *MB* midline block, *BED* biologically effective dose, *f* fraction

[a] Prescribed at point A

surface (i.e. patients with roomy vaginal vaults), a coordinate at the vaginal vault was selected as the origin of the vertical level with the point A. The concept behind the latter definition is essentially the same as that of point H proposed by the American Brachytherapy Society (ABS) [6]. Four radiotherapy schedules were provided for the protocol (Table 1). Because these schedules have almost biologically equivalent doses, the treating radiation oncologist was allowed to apply one of the schedules at their discretion. The protocol stated that enlarged pelvic node(s) (greater than 10 mm in the shortest diameter) visualized by pretreatment computed tomography (CT)/magnetic resonance imaging (MRI), and palpable nodular parametrium(s) fixed to the wall(s) should received an EBRT boost, with a total dose of 6–10 Gy/3–5 fractions.

To maintain radiotherapy quality, methods for QA were also examined. A credentialing process for participating institutions and independent case reviews (ICRs) of all treated patients were adopted for the QA. A description of the QA process was included in the protocol.

Credentialing

For institutional participation in this study, credentialing was required. The participating institutions had to meet the following 3 criteria:

1. Institution was certified by the Japanese Society for Therapeutic Radiology and Oncology (JASTRO) with JASTRO-certified radiation oncologist(s).
2. All HDR-ICBT procedures (i.e., applicator insertions, calculations, and evaluations) were carried out by JASTRO-certified radiation oncologist(s) or their colleagues.
3. At least 10 cervical cancer cases per year were treated by definitive radiotherapy using HDR-ICBT.

Meeting the first requirement indicated that the institution had a specified accuracy of external beam radiation dose delivery, since JASTRO-certified institutions must regularly undertake output measurements and calibrations of their linear accelerators. The second and third