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.

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**Conflict of interest statement**
None declared.

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**Review Article**

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

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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).

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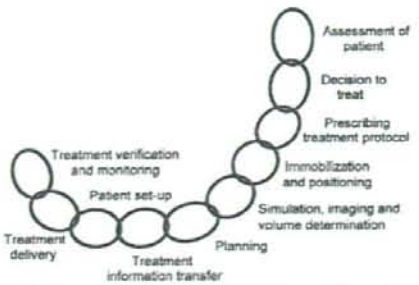


Figure 1. Sequential process of planning and delivering radiotherapy to patients.

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

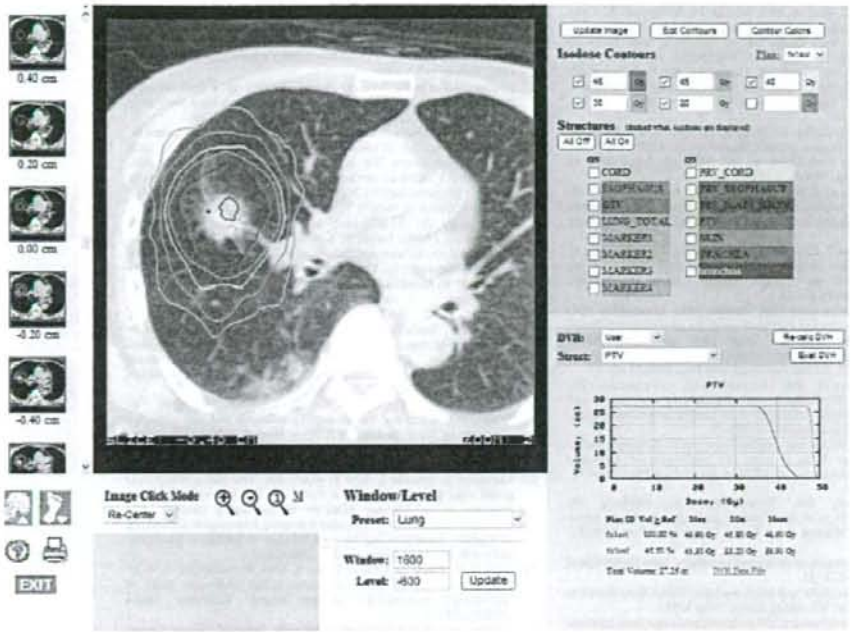


Figure 3. Advanced Technology Quality Assurance Consortium remote review tool.

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.

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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

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

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**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

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**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%），

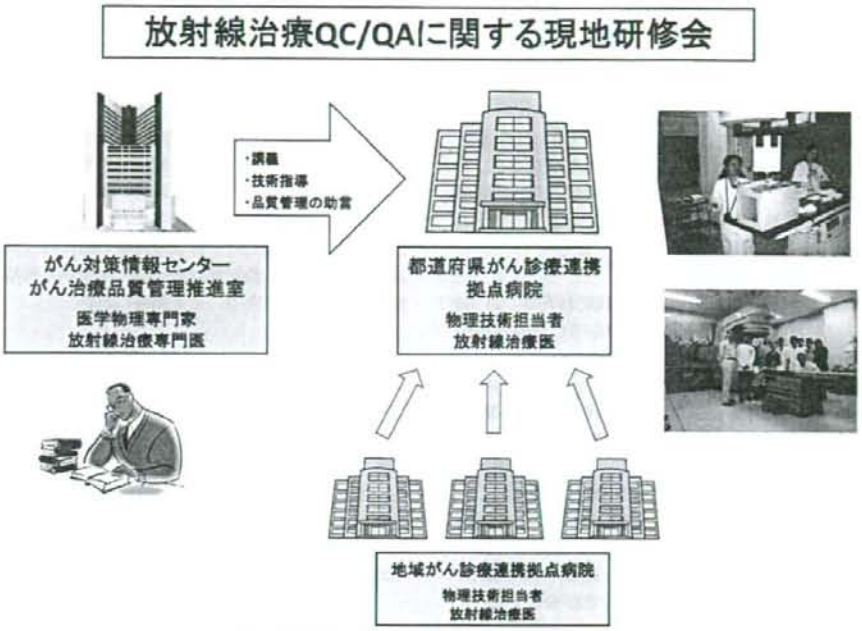


図1 放射線治療 QC/QA に関する現地研修会のスキーマ

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．

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# Computerized method for estimation of the location of a lung tumor on EPID cine images without implanted markers in stereotactic body radiotherapy

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**Abstract**

The purpose of this study was to develop a computerized method for estimation of the location of a lung tumor in cine images on an electronic portal imaging device (EPID) without implanted markers during stereotactic body radiotherapy (SBRT). Each tumor region was segmented in the first EPID cine image, i.e., reference portal image, based on a multiple-gray level thresholding technique and a region growing technique, and then the image including the tumor region was cropped as a 'tumor template' image. The tumor location was determined as the position in which the tumor template image took the maximum cross-correlation value within each consecutive portal image, which was acquired in cine mode on the EPID in treatment. EPID images with 512 × 384 pixels (pixel size: 0.56 mm) were acquired at a sampling rate of 0.5 frame $s^{-1}$ by using energies of 4, 6 or 10 MV on linear accelerators. We applied our proposed method to EPID cine images (226 frames) of 12 clinical cases (ages: 51–83, mean: 72) with a non-small cell lung cancer. As a result, the average location error between tumor points obtained by our method and the manual method was 1.47 ± 0.60 mm. This preliminary study suggests that our method based on the tumor template matching technique might be feasible for tracking the location of a lung tumor without implanted markers in SBRT.

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## 1. Introduction

In stereotactic body radiotherapy (SBRT), high dose per fraction is delivered to small tumors and early metastases in lesser fractions. However, it could be possible that enough high doses would not be delivered to a target in a body such as a lung due to respiratory motion (Suh *et al* 2004, Vedam *et al* 2005). Therefore, International Commission on Radiation Units and Measurements (ICRU 1999) Report 62 recommends that the internal margin (IM) should be added outside the clinical target volume (CTV) while taking into account uncertainties in size, shape, locations of the CTV, etc. The sufficient IM to tolerate respiratory motion can be determined, for example, by a slow scan computed tomography (CT) or four-dimensional (4D) CT in each radiotherapy treatment planning (Ford *et al* 2003, Rietzel *et al* 2006, Slotman *et al* 2006, Keall *et al* 2006, Shekhar *et al* 2007, Seco *et al* 2008). However, it is very important to monitor the location of a tumor in cine images by using an electronic portal imaging device (EPID) during SBRT because it has been unclear whether the IM is appropriate for displacements of a tumor due to respiratory motion.

Several methods for monitoring the location of a lung tumor have been developed with or without implanted markers (Keall *et al* 2006, 2004, Shirato *et al* 2000a, 2000b, Shimizu *et al* 2001, Meyer *et al* 2006, Berbeco *et al* 2007). Shirato *et al.* developed a system which was capable of tracking the three-dimensional (3D) position of a metallic marker in the body in real time by means of four sets of diagnostic x-ray imaging equipment (Shirato *et al* 2000a, 2000b, Shimizu *et al* 2001). The system significantly improved the accuracy of irradiation of targets in motion at the expense of an acceptable amount of diagnostic x-ray exposure. Keall *et al* (2004) developed an EPID-based marker-tracking system that can be used for real-time tumor targeting, or 4D radiotherapy. Their study showed that the EPID-based system was feasible for 4D radiotherapy. Meyer *et al* (2006) investigated different algorithms with regard to their suitability to detect and track a moving object in TV camera-based portal images of a phantom without implanted markers. As a result, the best geometric tracking was obtained with the mean of the sum of squared differences. Berbeco *et al* (2007) developed an image-guided method for treatment verification and adaptation during SBRT by using implanted radio-opaque markers. Their clinical experience with the tool indicated that the cine EPID verification modality is a useful tool for tumor localization while the treatment beam is on. Our motivation for this study is a clinical need of software for (1) investigating whether the IM is appropriate for a moving tumor due to respiration, and (2) tracking the moving tumor in real time without implanted markers, because a majority of researchers have used markers implanted adjacent to a tumor, which are invasive approaches for patients. Therefore, our goal of this study was to develop a computerized method for estimation of the location of a lung tumor in EPID cine images during treatment without implanted markers in SBRT.

## 2. Materials and methods

Figure 1 shows an overall algorithm for estimation of the location of the lung tumor on EPID cine images, which was based on a template matching technique with cross-correlation coefficient (hereafter referred as cross-correlation value). Details of the proposed method are described in this section.

### *2.1. Determination of an irradiation field image by an automated thresholding technique*

The irradiation field region was cropped from an original EPID cine image by analyzing the histogram of the original EPID image (Arimura *et al* 2007). Figure 2 shows the illustration

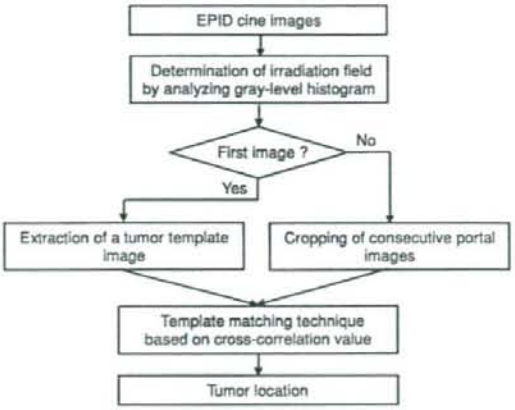


**Figure 1.** Overall algorithm for estimation of the location of the lung tumor on EPID cine images.

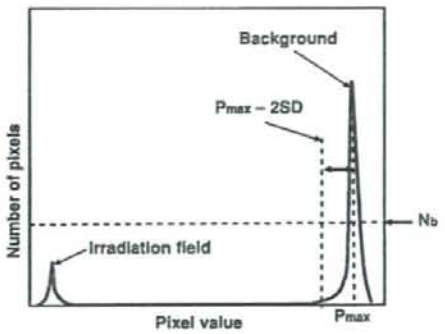


**Figure 2.** Illustration of a typical histogram in the EPID image, which has small and large peaks corresponding to an irradiation field region and a background (non-irradiation field), respectively.

of a typical histogram in the EPID image, which has small and large peaks corresponding to an irradiation field region and a background (non-irradiation field), respectively. The large peak of the background usually has more than a certain number of pixels, Nb, in the EPID image as shown in figure 2. For extracting the irradiation field region, the maximum pixel value corresponding to the large peak and the standard deviation (SD) were calculated only for a part of the histogram with more than the threshold number of pixels, Nb, which was constant for all cases. Finally, the irradiation field region was determined by binarizing the original EPID image using the maximum pixel value minus twice the SD as shown in figure 2. Figures 3(a) and (b) show an original EPID image and segmented irradiation field region, respectively. Note that the threshold number of pixels, Nb, was empirically determined so that the irradiation fields can be well segmented for all cases, as shown in figure 3(b), where Nb

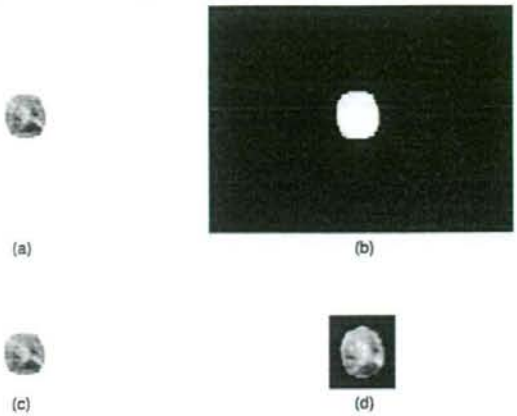


**Figure 3.** Illustration of (a) an original EPID image, (b) segmented irradiation field region, (c) a rectangular area fitted with the irradiation field region, indicated by dotted lines and (d) cropped image assigned pixel values outside the irradiation field region zero and smoothed by a Gaussian filter, which correspond to the reference portal image or consecutive portal image.

was set as 800. A rectangular area fitted with the irradiation field indicated by a dotted line, as shown in figure 3(c), was cropped as the irradiation field image. The pixel values outside the irradiation field were assigned zero, and the area corresponding to 'set-up margin' defined as 5 mm was eroded by a morphological filter with a $3 \times 3$ square kernel. Finally, the irradiation field image was smoothed by a Gaussian filter and one of the irradiation field images is shown in figure 3(d).

### 2.2. *Extraction of a tumor region and a tumor template image from a reference portal image*

A tumor region was extracted from the first irradiation field image, i.e., reference portal image, by using a multiple-gray level thresholding technique (Arimura *et al* 2004), which is described in the next paragraph, and a region growing technique, and then the cropped image including the tumor region was used as a 'tumor template' image. A Gaussian function was used for the stable production of a tumor template, because it could be easy to segment the tumor region by weighting each pixel value in the reference portal image, where noise and pixel value fluctuations are possible, with the Gaussian function. Since we assume that the tumor would be located at around the centroid of the irradiation field region in the reference portal image, the center of the Gaussian function was put at the centroid of the irradiation field region. The Gaussian-weighted image $I_G(x, y)$ was obtained by the following equation:

$$I_G(x, y) = F(x, y)\left\{-\frac{(x - x_0)^2 + (y - y_0)^2}{2\sigma^2}\right\}, \tag{1}$$

where $x$ and $y$ are the coordinates in the images, $x_0$ and $y_0$ were the coordinates of the centroid of the irradiation field region in the reference portal image and $\sigma$ is the standard deviation of the Gaussian function. The standard deviation was empirically determined so that all tumor

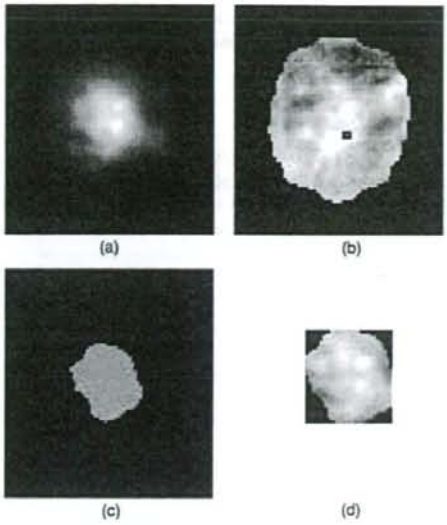


**Figure 4.** Illustration of (a) a reference portal image multiplied by a 2D Gaussian function, (b) an original reference portal image with a candidate point indicated by an open circle, which was determined by the multiple gray-level thresholding technique, (c) a tumor region segmented by the region growing technique and (d) a tumor template image produced by the proposed method.

regions can be well segmented. In this study, the standard deviation was set as 6.5 mm. Figure 4(a) shows an example of the reference portal image multiplied by the Gaussian filter.

The candidate location of a tumor was identified, as shown in figure 4(b), in the reference portal image by means of the multiple-gray level thresholding technique (Arimura *et al* 2004), which is one of methods for detecting local maximum points in an image in terms of a pixel value by using multiple binary images produced by the corresponding threshold levels. Each threshold level was determined according to a certain specific percentage of the area under the pixel-value histogram in the image. The beginning, ending and increment percentages used for the multiple-gray level thresholding technique were empirically determined so that the local maximum points of all tumor regions can be detected for all cases. The beginning and ending percentages determine the highest and lowest levels, respectively, in terms of the local maximum point, and the increment value determines the resolution of finding local maximum points. The local maximum point was considered as the candidate location of a tumor in this step. In this study, the specific percentages of 1% and 28% were selected as the beginning and ending percentage threshold levels, respectively, with an increment of 1%.

For extracting a tumor region, the region growing started at the candidate location of a tumor determined by the multiple gray-level thresholing technique. A tumor region in the reference portal image was automatically segmented by monitoring two image features, i.e. normalized effective diameter and contrast of the grown region, while a threshold value was changed from the maximum pixel value in the tumor region to 10% of the maximum value, with an increment of 1%. The normalized effective diameter was defined as an effective

diameter, which is a diameter of a circle with the same area as that of the tumor, divided by a longer side length of the reference portal image. The contrast was defined by the following equation:

$$\text{Contrast} = \frac{H_p - L_p}{H_p}, \tag{2}$$

where $H_p$ is the mean pixel value in nine neighbors including a pixel with the maximum pixel value within the tumor region, and $L_p$ is the mean pixel value in the outer region (i.e. narrow band region) of a tumor region. The outer region was considered as a portion of the background of the target, which was empirically determined by dilation of the tumor region so that enough area can be obtained as the background, but the dilated region cannot go over the IF region. In this study, 2.2 mm narrow band-width was set as the outer region. The tumor region was determined if the normalized effective diameter exceeded 0.4 or the contrast exceeded 0.8. This condition was empirically determined so that all tumor regions can be well segmented. Figure 4(c) shows a tumor region obtained by the region growing technique and the morphological dilation operation. The tumor template image, as shown in figure 4(d), was obtained by cropping a rectangular area from the reference portal image fitted with the tumor region and by assigning pixel values outside the tumor region zero.

### *2.3. Estimation of a tumor location based on a template matching technique*

The tumor location was estimated as the position in which the target template image took the maximum cross-correlation value within the consecutive portal image. The coordinate system in the reference portal image was used for the template matching technique. For performing the template matching between the tumor template image $T(x, y)$ and the consecutive portal image $C(x, y)$, the cross-correlation coefficient $R$ was calculated, within the irradiation field as shown in figure 3(b), based on the following equation (Arimura *et al* 2002):

$$R = \frac{1}{N} \sum_{x=0}^{X-1} \sum_{y=0}^{Y-1} \frac{(T(x, y) - \bar{T})(C(x, y) - \bar{C})}{tc}, \tag{3}$$

where $x$ and $y$ are the coordinates in the image, $T(x, y)$ is the pixel value at $(x, y)$ in the tumor template image, $C(x, y)$ is the pixel value at $(x, y)$ in the consecutive portal image, $\bar{T}$ and $t$ are the mean and the standard deviation of the pixel values within the tumor template image $T(x, y)$, respectively, $\bar{C}$ and $c$ are the mean and the standard deviation of the pixel values within the consecutive portal image $C(x, y)$, respectively, and $X$ and $Y$ are the numbers of pixels in $x$ and $y$ widths of the template image, respectively, $N$ is the number of pixels within the irradiation field. The correlation value ranges from $-1.0$ to 1.0. The template matching was performed for finding a rough tumor location with the maximum cross-correlation value between the tumor template image and the consecutive portal image, by shifting the position of the tumor template image within the irradiation field of the consecutive portal image. Finally, the tumor location was determined by the centroid of the tumor region in the tumor template image, which was put on the consecutive portal image at the pixel with the maximum cross-correlation value.

### *2.4. Test cases*

Twelve cases (age: 51–83 years old, mean: 72) with a non-small cell lung cancer who received a lung stereotactic radiotherapy were selected for this study under the protocol approved by an institutional review board in Kyushu University Hospital. Portal images of these cases

**Table 1.** Case characteristics for 12 cases used for this study.

| Case number | Age (years) | Gender | Tumor location | Effective diameter (mm) | Number of frames |
|---|---|---|---|---|---|
| 1 | 77 | M | RL | 24 | 16 |
| 2 | 68 | M | RL | 15 | 17 |
| 3 | 51 | F | RU | 20 | 21 |
| 4 | 81 | F | LM | 35 | 7 |
| 5 | 69 | F | LM | 22 | 36 |
| 6 | 56 | M | RL | 15 | 20 |
| 7 | 80 | F | RM | 20 | 17 |
| 8 | 75 | F | RM | 30 | 15 |
| 9 | 83 | F | LU | 27 | 18 |
| 10 | 71 | M | LM | 20 | 18 |
| 11 | 73 | M | RU | 40 | 19 |
| 12 | 85 | M | LM | 20 | 22 |
| Mean | 72 | – | – | 24 | 19 |
| SD | 10 | – | – | 8 | 7 |

were acquired in cine mode (sampling rate: 0.5 frame $s^{-1}$) by using an EPID (AS-500, Varian Medical System, Palo Alto, USA) with energies of 4, 6 or 10 MV on linear accelerators (Clinac 21EX, Varian Medical System, Palo Alto, USA). The number of all frames (reference portal images and consecutive portal images) in 12 cases was 226, and the number of all consecutive portal images was 214. Each EPID image consisted of 512 × 384 pixels with a pixel size of 0.56 mm and a gray level scale of 16 bits. The source tumor distance (STD) and the source detector distance (SDD) were 100 cm and 140 cm, respectively. The case characteristics of test cases are shown in table 1. A total dose of 48 Gy was delivered for all patients in four fractions in 1 week. Lung tumors in various locations, i.e. the upper lobe ($n = 3$), middle lobe ($n = 6$) or lower lobe ($n = 3$), were chosen for this study because the displacements of tumor motion depend on the location in a lung due to respiratory motion. The effective diameter $d$ was measured from the clinical target volume (CTV) by using the following equation:

$$d = 2\sqrt[3]{\frac{3V_{\mathrm{CTV}}}{4\pi}} \tag{4}$$

where $V_{\mathrm{CTV}}$ is the CTV determined by a radiation oncologist on a treatment planning system (Eclipse, Valian Medical System, Palo Alto, USA).

### 2.5. *Performance evaluation of our proposed method*

For performance evaluation of the proposed method, we calculated the following two values: (1) the location error, i.e., the Euclidean distance from the 'tumor' point to the candidate point and (2) the overlap measure between the target candidate regions obtained by the manual method and our automated segmentation method. The tumor 'truth' point was defined as the centroid of a tumor region determined manually by a radiation oncologist and a medical physicist, and the tumor region was determined manually by them by using image processing software (Image J, National Institute of Health).

The overlap measure was obtained by the following equation, which denotes the degree of coincidence between the target candidate region $C$ (as shown by a white line in figure 6)