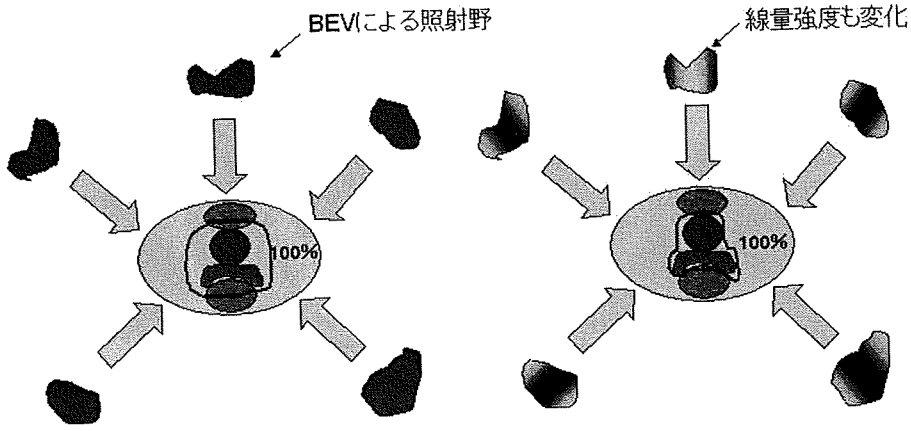


a. 三次元原体照射 (3DCR)　　b. 強度変調放射線治療 (IMRT)

Fig. 1　原体照射では照射野形状を合わせこむことは可能であるが，線量強度は均一なため腫瘍形状に十分に合わせこむことは困難であるが，IMRT では，照射野形状のみでなく，照射方向によって照射したくない領域への線量強度を変化させることが可能であり，これにより腫瘍形状に沿った線量分布の作成が可能となり，腫瘍への線量確保と同時に危険臓器への線量軽減が可能となる．

遮蔽された部位の線量は減少し，遮蔽される時間が短い部位へは多くの線量が照射されるという原理である．

この MLC をどのように移動させることにより適切な線量強度を作成できるのかを計算する際に用いられる計算法が Inverse Plan[1] である．照射したい条件 (腫瘍の最大，最低線量，正常組織の許容線量およびその容積など) をもとにその条件を満たすように最適な照射線量およびそれを作り出す線量強度を計算していくものである．この Inverse Plan がなければ，MLC を用いた IMRT は成り立たない．Inverse Plan においてはコンピュータに十分に照射が必要な範囲と避けるべき範囲を明確に指示することが重要となる．

III. IMRT の利点

IMRT は腫瘍組織への線量を維持しつつ，周囲正常組織への線量軽減が可能である．そのメリットとして

1. 腫瘍組織への安全な線量増加が可能となることから，局所制御率の向上が得られる可能性が高い．前立腺がん，脳腫瘍での治療成績が報告されつつある．

2. 正常組織への線量軽減により治療後の晩期有害事象の軽減が得られる．頭頚部腫瘍で耳下腺への線量軽減により，照射後の唾液分泌機能改善が得られ治療後の QOL 向上が報告されている．また，前立腺がんにおいては治療後の Grade 2 以上の直腸出血の頻度の低下が報告されている．

3. 傍脊椎腫瘍では脊髄に多くの線量が照射されると脊髄神経麻痺の発生が問題となるため根治線量の照射が不可能であった．IMRT により脊髄神経への線量を軽減しながら腫瘍への根治線量照射が可能となった．

4. IMRT では線量集中性が高まるため，一度照射された範囲への再照射が可能といわれている．しかし，これはその部位，腫瘍の性状などにより一概によいとは言い切れないが，脊椎転移で 30 Gy 照射後に腫瘍が再増大し，これによる脊髄圧迫で麻痺を起こした症例などで IMRT による再照射が可能な場合がある．

5. 頚部食道では体厚が急速に変化するため通常の前後対向2門照射では線量分布が不均一となり，十分な線量を腫瘍に照射することが困難な場合があるが，このような症例ではIMRTによる治療がよいことがある．

IV. 適　　応

原則的にはどの部位の腫瘍でも適応とはなるが，呼吸性移動のある臓器に発生した腫瘍はその治療の複雑性から困難な点がある．2008 年 4 月以降，中枢神経系腫瘍，頭頚部腫瘍，前立腺がん[2] の 3 部位のがんに対しては保険適応となった．

V. 臨床成績

1. 脳腫瘍 (特に悪性神経膠芽腫：GM)

GM は生存期間中央値が 10ヶ月程度，3 年生存率 6% と非常に予後不良の脳腫瘍である．これまで陽子線治療，小線源治療，通常の照射法による線量増加など様々な治療法が試みられてきた．しかし，局所制率，生存率共に有意な改善は得られていない．我々は自施設のこれまでの治療による再発様式を検討し，ほとんどの再発が MRI で造影される範囲からおよそ 5–6 mm 以内であり，それより外側の再発はほとんどないことを確認した．そこで，この再発領域への線量増加のみを行い，それ以外の予防照射領域へはさらに少ない線量での照射の可能性を検討し治療を行ってきた．GM に対する照射の難しさは，腫瘍への線量増加と，腫瘍周囲の正常脳組織への線量減少と相反することを同時に行わなければならないこ

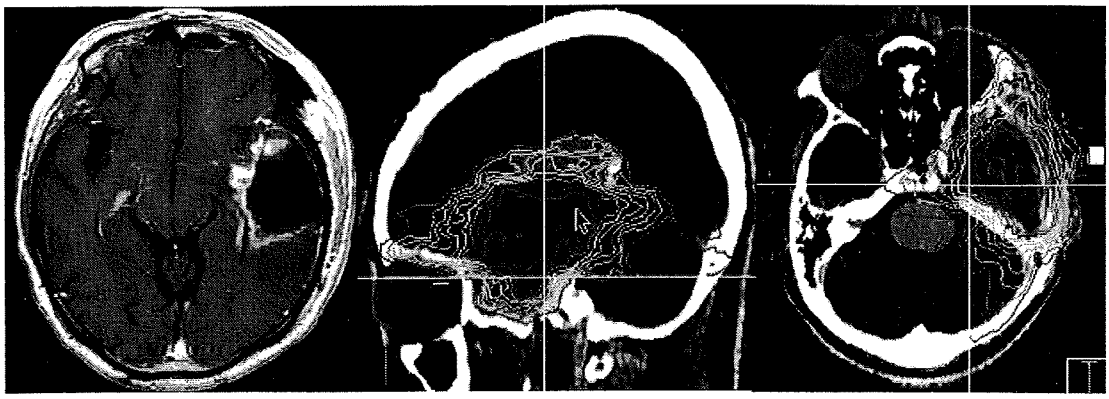


Fig. 2 GM に対する IMRT 線量分布図．左側頭葉の GM に対し腫瘍摘出術を施行後，IMRT 施行．通常照射では脳幹部，左眼球，視神経への高線量照射となってしまうが，IMRT ではこれらの領域への線量を減少させることが可能である．

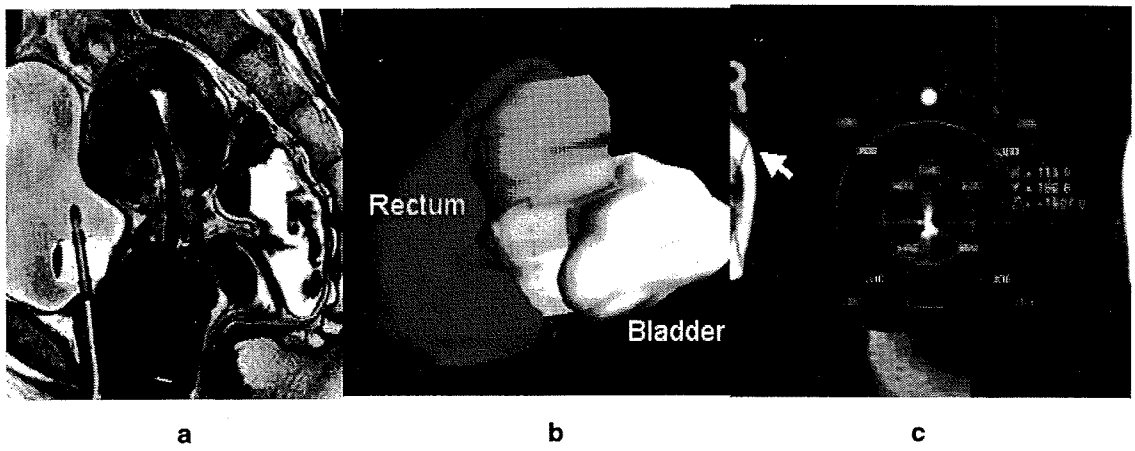


Fig. 3 IGRT による子宮頸癌腔内照射．

a. アプリケータを挿入した状態での MRI 矢状断像であり，アプリケータと子宮内での腫瘍との位置関係が明瞭にわかる．

b. アプリケータから腫瘍辺縁までの距離を計測し，求められた 3 次元線量分布図．

c. CT 画像上での線量分布と A 点線量．この症例では 430c GY である．

とである．IMRT ではこれが可能となる．Fig. 2 に示すような線量分布で治療可能である．これにより生存期間中央値は IMRT のみで 19ヶ月，抗がん剤髄注との併用で 30ヶ月，3 年生存率 20%と改善が見られている[3]．

VI. 前立腺がん

長期の治療成績の報告はまだ少ないが，Zelefsky ら[4]は 772 例に対し IMRT を施行し，90%の症例は 81 Gy まで照射した結果を報告している．晩期有害事象では Grade 2 の直腸出血が 1.5%に，Grade 3 の直腸有害事象が 0.1%に認められたが，Grade 4 は 1 例も認められなかった．治療後 3 年での Grade 2 以上の晩期有害事象は直腸，膀胱で，それぞれ 4%，15%であり，PSA 無再発生存率は favorable, intermediate, unfavorable 群で，それぞれ 92%, 86%, 81%であったとしている．自験例では 95%, 100%, 93%であり，良好な治療成績が得られている．これまでの 3DCRT の治療成績に比し，PSA 無再発生存率向上および有害事象 (特に直腸出血) の頻度が減少している．

VI. 子宮頸癌腔内照射における IGRT の有用性

我々の施設では以前，治療経過中の子宮頚癌腫瘍の大きさの変化を MRI で観察し治療効果予測因子として報告した[5]．1995 年から CT, MRI 共に使用可能なアプリケータを用いて，アプリケータを挿入した状態で CT, MRI を施行し，MRI で High Intensity Area (HIA) を示す腫瘍に対して辺縁線量で 1 回 6 Gy を照射し，計 24 Gy という高線量率腔内照射を行ってきた．初回及び第 3 回腔内照射時に CT, MRI を施行し，腫瘍縮小に応じて治療計画をやり直し，最適な線量分布を得ることが可能となる．これにより局所制御率を低下させることなく膀胱，直腸の有害事象を減少させることが可能であった．

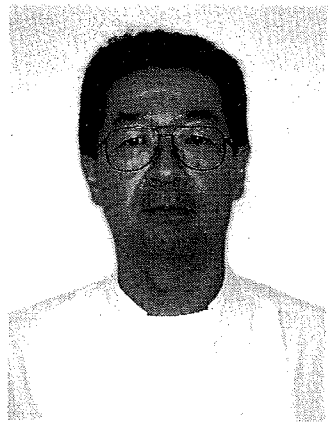
これまで，Grade 2 以上の直腸有害事象は認められてない．MRI を施行するタイミングについては GEC-ESTRO では毎回施行とのことであるが，我々の経験では初回と第 3 回の 2 回施行すれば十分であると考えている．第 2 回，第 4 回の腔内照射はそれぞれ前回の治療計画でおこなっても大きな変化は無いといえる．

ま と め

IGRT によりさらなる腫瘍への線量集中が可能となり，治療成績の向上が期待されるが，マンパワーを含めたハード，ソフトの充実が重要である．

文　献

1) Brahme A. Optimization of stationary and moving beam radiation therapy techniques. *Radiother Oncol* 1988; **12**: 129–140.
2) Kazuo Hatano, Hitoshi Araki, Mitsuhiro Sakai, et al. Current Status of Intensity-modulated radiation therapy for prostate cancer. *Int J Clin Oncol* 2007; **12**: 408–415 (Review).
3) Toshihiko Iuchi, Kazuo Hatano, et al. Hypofractionated high-dose irradiation for the treatment of malignant astrocytomas using simultaneous integrated boost technique by IMRT. *Int J Radiat Oncol Biol Phys* 2006; **64**: 1317–1324.
4) Zelefsky MJ, Fuks Z, Hunt M, et al. High-Dose intensity modulatedradiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. *Int J Radiat Oncol Biol Phys* 2002; **53**: 1111–1116.
5) Kazuo HATANO, et al. Evaluation of the therapeutic effect of radiotherapy on cervical cancer using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 1999; **45**: 639–644.



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主な研究領域と抱負：放射線治療の中でも，IMRT を中心とした高精度放射線治療および子宮頸癌放射線治療における MRI を用いた腔内照射の確立が主たる研究領域である．今後は，PET/CT などを用いて，癌組織内における低酸素細胞領域の同定や腫瘍活性などを検討し，これまでよりもさらに線量集中性を高めた放射線治療を行っていきたい．

子宮頸癌放射線治療

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小玉卓史／小島　徹／小川博明／笹川　竜／河内　徹／
宇野純一郎／清水孝行／岩瀬　勉／篠塚　稔／石垣秀世

はじめに

子宮頸癌における放射線治療の歴史は長く、その重要性は認められている。世界的な標準治療法であるマンチェスター法にのっとった治療が行われてきたことがその要因である。しかし近年、CT、MRIなどの画像診断法が進歩し、放射線治療に応用可能な時代において、従来の仮想のA点に一定線量を照射する手法が見直されるようになった。GEC-ESTRO[1~2]、ABS[3]から画像誘導小線源治療に関してガイドラインが示されるようになり、子宮頸癌放射線治療は新たな時代を迎えようとしている。

ここでは、これまでの放射線治療をもとに新たなIGRTの時代に移行しつつある子宮頸癌放射線治療について述べる。

欧米との違い

子宮頸癌への放射線治療は、外照射と腔内照射（あるいは組織内照射）を組み合わせて行われる。子宮頸癌は高線量を照射すればそれなりの局所制御は得られるが、これを外照射のみで行うと、周囲正常組織である小腸、膀胱、直腸の障害が問題となる。そこで、外照射線量を制限する代わりに、腔内照射あるいは組織内照射で子宮および腫瘍に対して限局したさらなる高線量を照射する。

日本では、外照射を先行させ腫瘍縮小後腔内照射を追加する手法で、総治療期間はほぼ50日以内となっているが、欧米では外照射50Gy終了後に腔内照射を行う施設が多く、そのため総治療期間が延長されるため、治療成績は日本の方が良好である。A点線量も欧米の方が高く、このために有害事象も多い傾向にある。

外照射の変遷

子宮および骨盤リンパ節領域を含めた広い範囲に照射を行う。明らかなリンパ節転移がない場合でも、予防的に骨盤リンパ節領域は照射される。従来は全骨盤照射を前後対向2門で行う施設が多かった。また、4門照射で行うとしても教科書的な、ある決められた範囲を設定し、長方形の画一的な照射野で治療が行われてきた(図1)。しかし、CTやMRIなどが治療計画に応用可能な現在では、こうした画一的治療計画は見直されつつある。たとえば、図2aに示すような症例において従来法で照射野を設定すると、子宮底部が照射野外になる危険性がある。もちろんCT画像をもとに照射野設定がなされればこうした間違いはなくなるが（図2b)、従来は正側2方向のX線フィルム上に照射野を描いて治療を行うことが多かった。こうした時代では、このような問題が隠されていた可能性がある。また、CT治療計画においては余分な小腸などへの被ばくをも軽減することが可能となる。このように近年、外照射ではほとんどの施設において三次元治療計画が行われるようになってきた。

腔内照射の変遷

これまでは、マンチェスター法にのっとって、A点という仮想の点に対して一定線量を処方する治療が行われてきた（図3)。これは、CTやMRIのない時代に、どの施設においても比較的安全で画一的な治療を行うことができるという利点があ

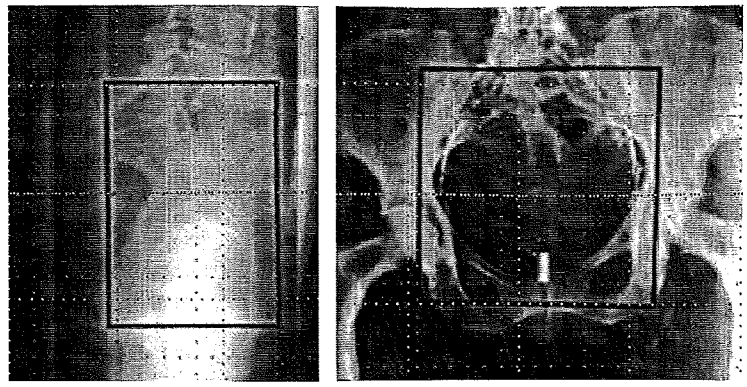

図1　典型的な骨盤4門照射
正側2方向からのX線シミュレータによる照射野である（FletcherのTextより）。

図2a | 図2b

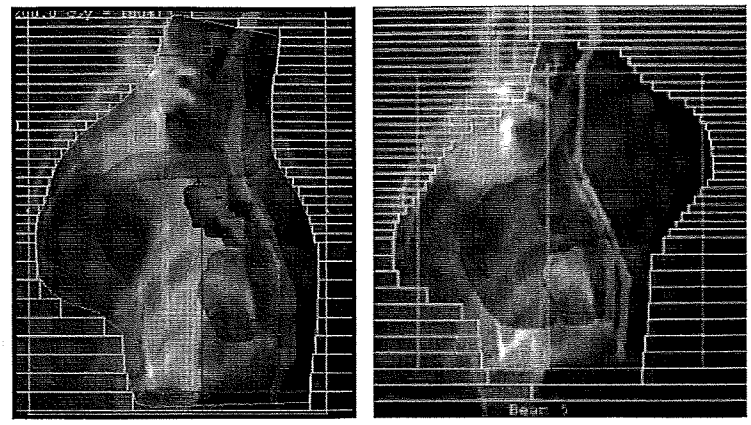

図2　3次元治療計画における側方からの照射野
子宮の大きさが通常であれば前方からのブロックはaでよいが、子宮が大きく腫大している場合には、照射野をその形状に合わせて拡大する必要がある。 IMAGE PREVIEW 参照

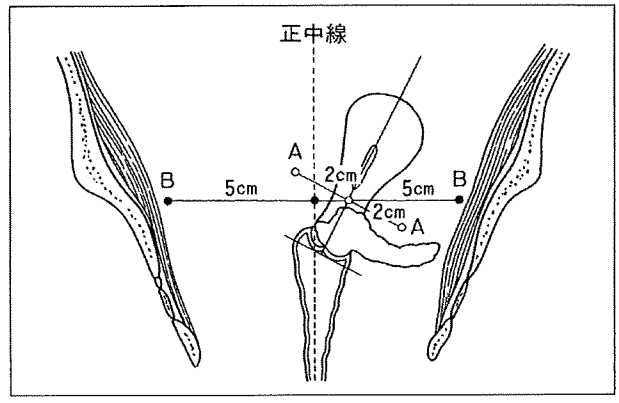

図3　子宮頸癌放射線治療における線量評価点
A点：原発巣の治癒と膀胱・直腸有害事象の指標
B点：骨盤壁浸潤の治癒と腸管有害事象の指標

った。しかし近年、MRIで腫瘍容積および進展範囲が描出可能となると、実際に従来法によるA点線量で治療をしようとした場合、MR画像上、腫瘍線量不足であったり、逆に腫瘍線量過多ではないかと思われる症例があることがわかってきた。また、毎回の腔内照射において治療回数の進行とともに腫瘍は縮小していくこと、あるいは症例ごとにまちまちであり、けっして同じ腫瘍容積ではないこともわかってきた。これについては、これまではほとんど考慮されてこなかった。このMRIで認められる腫瘍容積をGTVとし、これに安全域をもたせ、CTV（HR CTV、IR CTV）を設定し、その領域に対して線量を処方するように変化してきている。

GEC-ESTROからのガイドラインが示されている（**図4**）。これまで、いわゆるA点線量として処方線量を規定し、腔内照射を行ってきたが、MRIを用いた治療計画により、A点線量と実際のGTV_Bを囲む線量との比較が可能となった。しばらくはこの方法で局所制御可能な線量の評価がな

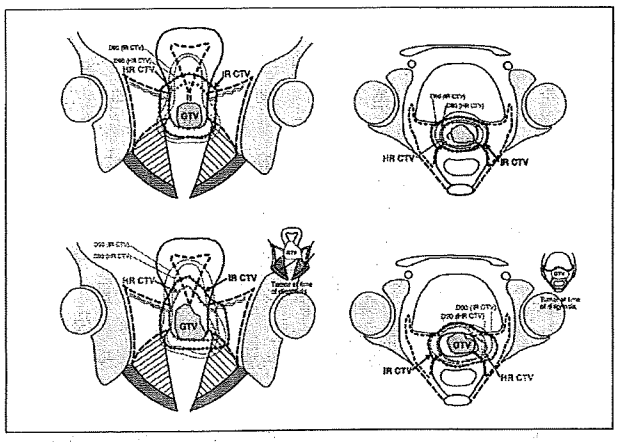

図4a | 図4b
図4c | 図4d

図4　GEC-ESTROによるガイドライン
a、b：早期癌におけるHR CTV、IR CTV。
c、d：進行癌におけるHR CTV、IR CTV。
この領域に一定線量を照射する。従来のA点線量では規定していない。
HR CTV：High risk clinical target volume
IR CTV：Intermediate risk clinical target volume

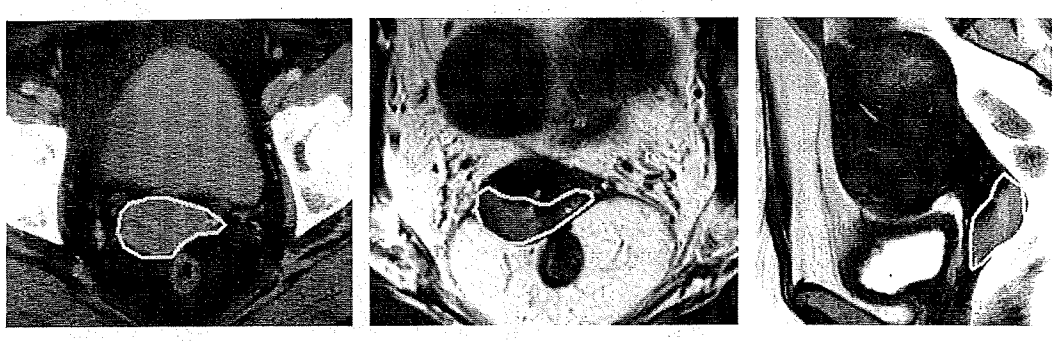

図5a | 図5b | 図5c

図5　腫瘍進展範囲の描出能（黄色線はそれぞれの画像でのGTV_Bを示す）
a：造影CTでは子宮頸部内の腫瘍範囲は判別できない。
b：MR T2WI、axial imageでは子宮頸部の前方寄りに、正常と思われるlow intensity area (LIA)と腫瘍を示す。High intensity area (HIA)が明瞭に描出されている。
c：MR T2WI、saggital imageでは子宮頸部腫瘍（HIA)と正常子宮頸部（LIA)が明瞭に描出されており、子宮体部浸潤がないことが示唆される。

IMAGE PREVIEW 参照

されていくであろう。

われわれの施設においては、1995年からMRIを用いた腔内照射の線量計算を行ってきた。この際A点線量で規定することなく、いわゆるGTV_Bをある一定線量で囲む方法で行ってきた。1回6Gyで可能な限りGTV_Bを囲むような治療計画を行い、計24Gy照射を行うものである。CTにおいては腫瘍と正常子宮頸部との鑑別が困難であるため、子宮頸部すべてをGTV_Bとする以外にないが、MRIでは正常子宮頸部内に腫瘍の範囲が明らかとなるため、より正確なGTV_Bの設定が可能である(**図5**)。この10年間における治療成績でみると、局所制御率を低下させることなく有害事象発生頻度を減少させることが可能であった。

参考文献

1) Haie-Meder C et al: Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Onocol 74(3): 235-245, 2005
2) Potter R et al: Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 78(1): 67-77, 2006
3) Nag S et al: Proposedguidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. Int J Radiat Oncol Biol Phys 60(4): 1160-1172, 2004

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REVIEW ARTICLE

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Current status and perspectives of brachytherapy for cervical cancer

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Abstract Standard definitive radiotherapy for cervical cancer consists of whole pelvic external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). In Japan, high-dose-rate ICBT (HDR-ICBT) has been utilized in clinical practice for more than 40 years. Several randomized clinical trials demonstrated that HDR-ICBT achieved comparative outcomes, both for pelvic control and incidences of late complications, to low-dose-rate (LDR) ICBT. In addition, HDR-ICBT has some potential advantages over LDR-ICBT, leading to further improvement in treatment results. Prior to the current computer planning systems, some excellent treatment planning concepts were established. At present, systems modified from these concepts, or novel approaches, such as image-guided brachytherapy (IGBT) are under investigation. One serious problem to be solved in HDR-ICBT for cervical cancer is that of the discrepancy in standard treatment schedules for combination HDR-ICBT and EBRT between the United States and Japan. Prospective studies are ongoing to assess the efficacy and toxicity of the Japanese schedule.

Key words Uterine cervical cancer · Radiotherapy · Intracavitary brachytherapy · High-dose-rate · Chemoradiotherapy

Introduction

Radiotherapy plays an important role in the treatment of uterine cervical cancer, and definitive radiotherapy is considered to be one of the curative treatment methods for all disease stages in Western Europe and North America. By contrast, Japanese clinicians prefer to utilize surgery when treating patients with uterine cervical cancer, and will resort to radiotherapy only as a second-line treatment for elderly or comorbid patients who are unable to undergo surgery. However, the status of radiotherapy in uterine cervical cancer has gradually changed also in Japan recently. A randomized study demonstrated that definitive radiotherapy achieved a survival rate equivalent to that with surgery but had less late toxicity for patients with early-stage resectable cervical cancer.[1] In addition, several large multi-institutional randomized studies have demonstrated a significant survival advantage of concurrent chemoradiotherapy (CCRT) over definitive radiotherapy alone for locoregionally advanced uterine cervical cancer.[2–4] These reports have led to the increased use of definitive radiotherapy in Japanese clinical practice. Definitive radiotherapy and CCRT are both listed as treatment options in the *Japanese treatment guidelines for cervical cancer* published in late 2007.[5]

Standard definitive radiotherapy consists of external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT). Intracavitary brachytherapy can deliver an adequate dose for tumor sterilization, while limiting the dose to surrounding critical normal organs. It achieves this by a unique dose distribution which is characterized by a very steep dose gradient around the sources.

In this article, we review the current status, issues, and future perspectives of ICBT for uterine cervical cancer, with special attention to high-dose-rate intracavitary brachytherapy (HDR-ICBT).

ICBT for cervical cancer: current status and issues

Dose rate

In Japan, the clinical application of HDR-ICBT started in the 1960s with the use of definitive radiotherapy for cervical cancer.[6] Through trial and error in clinical practice, a standard treatment schedule for HDR-ICBT was established,[6] and has been in use throughout Japan. Although a concern exists regarding the narrow therapeutic range of HDR-ICBT compared with low-dose-rate (LDR)-ICBT, several randomized controlled trials (RCTs) have revealed that there were no significant differences between HDR-ICBT

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and LDR-ICBT in either local control or late toxicity.[7,8] HDR-ICBT is performed through a remote afterloading system. Table 1 lists the advantages of using HDR over LDR in ICBT for cervical cancer.[9] Patterns of Care Studies (PCSs) have repeatedly shown that the use of HDR-ICBT is less popular in the United States than in Japan.[10–12]

CCRT became a standard treatment for patients with locoregionally advanced uterine cervical cancer after the publication of several RCTs in the United States in 1999.[2–4,13] In these trials, only LDR-ICBT was utilized and not HDR-ICBT.[2–4] Although data from retrospective and small phase I and phase II studies are available (Table 2), there has been no scientific consensus on the efficacy and toxicity of CCRT using HDR-ICBT.[14–19] Recent CCRT studies involving large clinical study groups in the United States and Europe, including the Gynecologic Oncology Group (GOG), Radiation Therapy Oncology Group (RTOG), and European Organization for Research and Treatment of Cancer (EORTC), now allow the use of HDR-ICBT as well as LDR-ICBT; however, clinical results from these major study groups are currently limited.[20,21] At present, a multi-institutional prospective study on CCRT using HDR-ICBT is ongoing in Japan [Japanese Gynecologic Oncology Group (JGOG)1066]. This study will primarily assess the feasibility of delivering CCRT with the global standard chemotherapeutic regimen of the weekly administration of cisplatin at 40 mg/m^2 × five courses, and will also determine the efficacy and toxicity when using HDR-ICBT in CCRT (Table 3).

Table 1. Advantages of HDR over LDR for uterine cervical cancer

1. Elimination of radiation exposure to medical staff
2. Shorter treatment time
   (1) Less patient discomfort
   (2) Lower risk of applicator movement during treatment
   (3) Allows for greater displacement of the rectum and bladder
   (4) Ability to treat a large number of patients
3. Use of smaller sources
   (1) Easy insertion of applicators into the cervix and uterus
   (2) Ability to optimize dose distribution

HDR, high-dose-rate; LDR, low-dose-rate

Dose calculation and treatment planning

Because ICBT has an extremely high dose gradient around the sources, it is difficult to describe doses and compare treatments. Prior to the use of computer technology, several systems were used to express the ICBT dose that allowed for comparisons. In addition, treatment planning concepts that can be adapted more accurately for individualized treatment have been rapidly developing recently.

Classical methods

Several classical treatment planning concepts are used to achieve standardized treatment in patients,[22] including the Manchester method, Fletcher method, Stockholm method, and Paris method. Of these, the Manchester system[23] has

Table 2. Concurrent chemoradiotherapy with cisplatin and HDR-ICBT

Author	Year	No. of patients	Chemotherapy regimen	BED at point A (EBRT + ICBT)	Pelvic control	Survival	Late complicaton (≥Grade 3)
Souhami[14]	1993	50	Cisplatin 30 mg/m^2, weekly, 5 courses	115 Gy_{10}	74% (3 Years)	65% (3 Years)	26%
Strauss[15]	2002	13	Cisplatin 40 mg/m^2, weekly, 6 courses	83 Gy_{10}	–	–	–
Chung[16]	2005	63	Cisplatin 50–80 mg/m^2, triweekly, 2 courses	86 Gy_{10}	86% (3 Years)	81% (3 Years)	6%
Toita[17]	2005	40	Cisplatin 20 mg/m^2 × 5 days, triweekly, 2–3 courses	77 Gy_{10}	91% (3 Years)	79% (3 Years)	2%
Chen[30]	2006	70	Cisplatin 40 mg/m^2, weekly, 5–6 courses	92 Gy_{10}	87% (4 Years)	74% (4 Years)	14%
Potter[18]	2006	48	Cisplatin 40 mg/m^2, weekly, 5 courses	101 Gy_{10}	85% (3 Years)	61% (3 Years)	4%
Novetsky[19]	2007	77	Cisplatin 20 mg/m^2 × 5 days, triweekly, 2–3 courses	87 Gy_{10}	88% (5 Years)	75% (5 Years)	6%

HDR-ICBT, high-dose-rate intracavitary brachytherapy; BED, biologically effective dose; EBRT, external beam radiation therapy

Table 3. Summary of JGOG1066

Eligibility: FIGO stage III/IVA cervical cancer (squamous call carcinoma, adenosquamous carcinoma, adenocarcinoma)
PS 0–1, 20–70 years
- Primary endpoint: 2-year progression-free survival
- Secondary endpoints: treatment completion and compliance, 2-year local regional control, 2-year distant control, 2-year disease-free survival, 2-year overall survival, late complications
- Planned sample size: 70
- Accrual duration: 2 years (April 2008-)
- Treatment: Concurrent chemoradiotherapy with HDR-ICBT
  - Radiotherapy
    Whole pelvic radiotherapy 50–50.4 Gy/25–28 fs
    (Central shielding after 30–41.4 Gy)
    HDR-ICBT 6 Gy × 3–4 fs.
    = total BED at point A: 74–78 Gy_{10}
  - Chemotherapy
    Cisplatin 40 mg/m^2, weekly, 5 courses

HDR-ICBT, high-dose-rate intracavitary brachytherapy; BED, biologically effective dose

been the most broadly used, with some modifications from the original.[24] The system provides a dose calculation concept using reference points. The dose delivery is prescribed at one reference point, "point A". A set of strict rules is imposed regarding the intrauterine/vaginal activity ratio and size of the vaginal ovoids. A large amount of clinical experience has been accumulated using this system. Although a dose calculation using a single point as reference would seem to be outdated, the concept is still considered practical and is widely used worldwide. In the Group European de Curietherapies and European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) recommendation, reporting the prescribed dose at point A is stated as a minimum requirement (level 1).[22] However, some degree of variation can occur in the definition of point A among institutions.[25] In the classical Manchester system, the origin is at the level of the cranial surface of the ovoid (vaginal vault).[23] Tod and Meredith[24] made a sight modification and chose the lower end of the intrauterine radium tubes as the origin of point A. Currently, in clinical practice, a flange on the tandem tube (external os) is primarily used as the origin. The current Japanese treatment system, which is presented in the *General rules for clinical and pathological study of uterine cervical cancer in Japan*, clearly states this method as the standard.[26] Because the method is easily applied using two projection radiographs, most centers can utilize this method. However, as Potish and Gerbi[25] pointed out, this modified method could lead to some degree of variation regarding the prescribed versus the intended dose of ICBT. The GEC-ESTRO recommends the modified Manchester method, with point A originating from the the tandem flange.[22] The American Brachytherapy Society (ABS) recommends another reference point, "point H", which is similar to the original Manchester system.[9] For an appropriate comparison between institutions, it is necessary to standardize the point A definition. In the Japanese Radiation Oncology Group (JAROG)0401/Japanese Radiation Oncology Study Group (JROSG)04-2 study, a multi-institutional phase II study to determine efficacy and the late toxicity profile for patients with early-stage cervical cancer treated by EBRT and HDR-ICBT using the Japanese standard treatment schedule, point A was defined as originating from the flange of the tandem; however, when the cranial surface of the ovoid deeply filled the vaginal vault, i.e., the flange of the tandem was located at the caudal level to the ovoid surface, point A was defined based on the level of the vaginal vault (Fig. 1). We believe that this is an appropriate arrangement that allows universal comparisons among institutions.

International Commission on Radiation Units and Measurements (ICRU) 38

In 1985, the ICRU published a recommendation on the method of reporting ICBT for cervical cancer.[26] This recommendation was made to facilitate communication between institutions by presenting a common language and terminology in order to provide a reliable comparison of methods and clinical results. The ICRU 38 recommendation addressed the following items: description of the technique used; total reference air kerma (TRAK); description

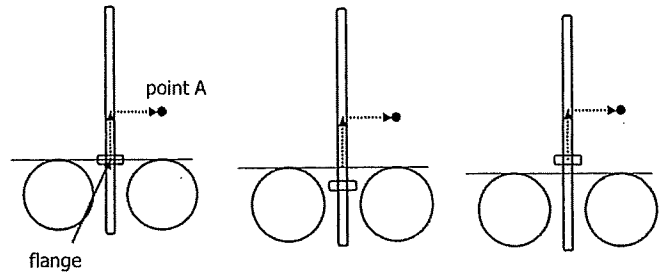

Fig. 1. Various "point A" definitions according to the conditions of applicator placement

of the reference volume; absorbed dose at reference points; and time dose patterns. The most important concept in this recommendation is the definition of the reference volume (e.g., 60 Gy) and its three dimensions. For the purpose of reporting and comparison, a dose description at one reference point is inadequate because of the significantly steep dose gradient around the sources of ICBT. The reference volume concept is considered reasonable and potentially leads to updated concepts such as image-guided ICBT.

Another important recommendation is the absorbed dose determination at several reference points. For organs at risk, such as the rectum and bladder, specific reference points have been defined. In addition to these critical organs, ICRU 38 also provides two sets of reference points related to bony structures and the lymphatic trapezoid.

ICRU 38 has provided several important concepts for ICBT in cervical cancer. However, the methods recommended have not proven popular in current clinical practice.[27] The TRAK and 60-Gy reference volume have rarely been described and reported in clinical practice. Although several reports have indicated that the cumulative dose at the rectal reference point correlated well to the incidence of proctitis,[28–30] the clinical application of this concept is limited.[27,31]

Image-guided brachytherapy (IGBT)

Recently, image-guided brachytherapy (IGBT), which incorporates three-dimensional (3D) sectional imaging such as computed tomography (CT) and magnetic resonance imaging (MRI) into ICBT planning, has been enthusiastically investigated.[32] Cross-sectional imaging studies can provide more information on the shape of tumors and adjacent critical organs. MRI can accurately visualize the gross tumor extent and volume in the cervix. Detailed delineation of the gross tumor volume, clinical target volume, and planning target volume, as well as detailed delineation of the critical organs is performed in the process. After this process, the dwell patterns of the sources can be calculated according to the individual topography of the tumor and critical organs.[32]

The formulation and description of terminology for IGBT has been independently discussed by groups in Europe (GEC-ESTRO) and the United States (Image Guided Brachytherapy Working Group). These two groups have independently published guidelines on IGBT.[33–35] Recently, some Japanese investigators have begun a trial of

IGBT which, mainly using CT,[36] and with preliminary data, has suggested that the risk of late complication can be better predicted with this method than with previous methods such as ICRU 38 reference points.[37] However, there are some concerns regarding the application of IGBT in clinical practice, including the cost-benefit-ratio if the need for frequent CT or MRI examinations occurs, as well as interobserver variability in the delineation of the target volume and risk organs.

Future perspectives

Optimum treatment schedule (dose)

There is one serious problem with regard to HDR-ICBT for cervical cancer, and that is the discrepancy in the standard treatment schedule for combination HDR-ICBT and EBRT between the United States and Japan. Table 4 shows a comparison of the standard treatment schedules and doses of definitive radiotherapy for HDR-ICBT and EBRT between Japan and the United States.[5,9,31] The Japanese standard schedule has lower total radiation doses compared with those in the United States. Several PCSs have revealed this observation in clinical practice.[10,11,31] The Japanese schedule was determined based on extensive clinical experience from the National Institute of Radiological Sciences in Chiba, Japan.[6] In other words, this standard schedule is empirical and has not yet been determined through prospective trials. However, there has been much clinical data to indicate favorable local control with acceptable incidences of late complications.[7,8,38] On the other hand, the United States schedule was determined by radiobiological calculations based on data from the clinical experience of LDR-ICBT.[9,39] As with the Japanese schedule, the reliability of the United States schedule has never been tested through prospective clinical studies. In addition, clinical data are extremely limited.[40] Lanciano et al.[41] demonstrated a dose-response relationship for pelvic control in patients with stage III cervical cancer through PCS data. They showed that the highest pelvic control was achieved in patients who received a total dose to point A of more than 85 Gy with the use of LDR-ICBT.[41] Perez et al.[42] retrospectively analyzed data with LDR-ICBT from a single institution and demonstrated that stage IIB/III patients who received 60–90 Gy of radiotherapy had a significantly lower pelvic failure rate than those with less than 60 Gy. However, no significant dose response was demonstrated within the range of 60–90 Gy for all stages.[42] Taking these observations into account, we assume that there is no firm conclusive data regarding the optimum radiotherapy dose even in patients treated with LDR-ICBT. HDR-ICBT requires an extremely short treatment time (i.e., 10 to 30 min), and sufficient adaptation of the brachytherapy sources to the tumor would be expected compared with patients treated with LDR-ICBT, which requires a longer treatment time (i.e., 2 to 3 days). This could be one of the reasons that lower doses are adequate for treatment with HDR-ICBT.

To determine the optimum schedule, a well-designed prospective study would be necessary. We conducted a multi-institutional prospective study to assess whether the Japanese standard schedule could achieve favorable pelvic disease control with acceptable toxicity for patients with early-stage cervical cancer (JAROG0401/JROSG04-2). Table 5 shows a summary of this study. Patient accrual went smoothly, with 13 institutions participating, and the study was closed in August 2007. In this study, we also performed quality assurance (QA) on the radiotherapy including HDR-ICBT, so as not to jeopardize the internal validity of the study.[43] Final outcome data are expected in late 2009. At present, another multi-institutional phase II study (JGOG1066) is being performed to evaluate the clinical validity of the Japanese radiotherapy schedule for locoregionally advanced (stage III, IVa) uterine cervical cancer (Table 3). As mentioned above, this study also intends to clarify the feasibility of CCRT using HDR-ICBT. We believe that these studies will clarify the optimum clinical properties for the Japanese schedule.

Can high-quality EBRT be an alternative to ICBT?

Recently, 3D conformal EBRT has been rapidly increasing in use in clinical practice for various cancers. Some enthu-

Table 4. Standard treatment schedules (EBRT + HDR-ICBT) for cervical cancer

	Point A dose Gy)		Point A BED (Gy_{10}) (EBRT + HDR-ICBT)
	EBRT	HDR-ICBT	
Early stage (FIGO I/II and < 4 cm)			
Japan	0–20	23/4–29/5	46–60
ABS	20	45/6–48/8	99–103
	45	30/5–31.8/6	101–102
Advanced disease (FIGO III/IVA, I/II > 4 cm)			
Japan	20–50	15/3–23/4	60–83
ABS	45	32.5/5–34.8/6	107–108
	50.4	28/4–31.8/6	107–108
GOG	45	30/5	101

EBRT, external beam radiation therapy; HDR-ICBT, high-dose-rate intracavitary brachytherapy; BED, biologically effective dose; ABS, American Brachytherapy Society; GOG, Gynecologic Oncology Group

Table 5. Summary of JAROG0401/JROSG04-2

Eligibility: FIGO stage IB, II cervical cancer (squamous cell carcinoma)
<4 cm and no pelvic lymphadenopathy (assessed by MRI)
PS 0–2, 20–85 years
- Primary endpoint: 2-year pelvic progression-free
- Secondary endpoints: treatment completion, acute and late toxicity, 2-year cause-specific survival, 2-year disease free survival, 2-year overall survival, site of failure
- Planned sample size: 60
- Accrual duration: 3 years (September 2004-September 2007)
- Treatment
  - Radiotherapy
    Whole pelvic radiotherapy 50 Gy/25 fs
    (Central shielding after 20 Gy)
    HDR-ICBT 6 Gy × 4 fs
    = total BED at point A: 62 Gy_{10}

HDR-ICBT, high dose rate intracavitary brachytherapy; BED, biologically effective dose

siastic investigators have reported encouraging preliminary clinical outcomes for cervical cancer patients treated with 3D conformal EBRT.[44] However, some problems remain that should be resolved prior to applying this strategy as an alternative for ICBT in clinical practice. Further investigation is necessary regarding target volume delineation, minimum dose required to control tumors, and patterns of internal organ motion (inter/intra-fractions).

Domestic problems to be solved in Japan

The Japanese Patterns of Care Study Group (JPCS) has reported some problems in the clinical practice of ICBT in Japan.[31] Table 6 shows treatment parameters that could be quality indicators for ICBT. Regrettably, the quality of some procedures was noted as unsatisfactory. For example, almost all patients received ICBT without definitive sedation. Lack of sedation could allow patients to feel major discomfort and lead to improper application, resulting in an unfavorable treatment outcome. Most Japanese textbooks include limited descriptions of these technical issues in ICBT for cervical cancer. Official organizations such as the Japanese Group of Brachytherapy/Japanese Society for Therapeutic Radiology and Oncology (JGB/JASTRO) should provide an educational program, not only on the technical aspects but also on some basic rules concerning ICBT as mentioned above.

Another critical problem is that many Japanese institutions cannot replace older HDR-ICBT systems. The low profit margins for HDR-ICBT could be one reason for this problem. In Japan, the treatment fee for HDR-ICBT is unsuitably low in view of its large contribution. In such a situation, modern HDR-ICBT techniques such as IGBT may not spread into Japanese clinical practice. Needless to say, increasing staff is a big priority for most institutions, but the challenge of increasing treatment fees for ICBT is also a big issue to be resolved in order to facilitate proper ICBT penetration throughout Japan.

Conflict of interest

No author has any conflict of interest.

Table 6. ICBT parameters: data from JPCS (1999–2001)[31]

Parameters	%
Dose rate	
HDR	89
LDR	11
Source	
Co-60	46
Ir-192	42
Cs-137	9
Others	3
Applicator	
Rigid	63
Nonrigid	25
Unknown	12
ICRU 38: bladder[a]	
Yes	18
ICRU 38: rectum[a]	
Yes	25
Continuous sedation	
Yes	3
Each fraction planned	
Yes	74

ICBT, intracavitary brachytherapy; JPCS, Japanese Patterns of Care Study; HDR, high-dose-rate; LDR, low-dose-rate
[a]Adherence to ICRU 38 recommendation

References

1. Landoni F, Maneo A, Colombo A, et al. (1997) Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet 350:535–540
2. Morris M, Eifel PJ, Lu J, et al. (1999) Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 340:1137–1143
3. Rose PG, Bundy BN, Watkins EB, et al. (1999) Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 340:1144–1153
4. Whitney CW, Sause W, Bundy BN, et al. (1999) Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. J Clin Oncol 17:1339–1348
5. Japan Society of Gynecologic Oncology (ed) (2007) Treatment guidelines for uterine cervical cancer; 2007 edition. Kanehara Shuppan, Tokyo
6. Inoue T (2003) The trial of the development of high-dose-rate brachytherapy for cervical cancer in Japan. Jpn J Clin Oncol 33:327–330

7. Teshima T, Inoue T, Ikeda H, et al. (1993) High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. Cancer 72: 2409–2414
8. Hareyama M, Sakata K, Oouchi A, et al. (2002) High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. Cancer 94:117–124
9. Nag S, Erickson B, Thomadsen B, et al. (2000) The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 48:201–211
10. Eifel PJ, Moughan J, Owen J, et al. (1999) Patterns of radiotherapy practice for patients with squamous carcinoma of the uterine cervix: Patterns of Care Study. Int J Radiat Oncol Biol Phys 43:351–358
11. Eifel PJ, Moughan J, Erickson B, et al. (2004) Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a Patterns of Care Study. Int J Radiat Oncol Biol Phys 60: 1144–1153
12. Nag S, Orton C, Young D, et al. (1999) The American Brachytherapy Society survey of brachytherapy practice for carcinoma of the cervix in the United States. Gynecol Oncol 73:111–118
13. www.nccn.org/professionals/physician_gls/PDF/cervical.pdf. Accessed 20 Nov 2008
14. Souhami L, Seymour R, Roman TN, et al. (1993) Weekly cisplatin plus external beam radiotherapy and high dose rate brachytherapy in patients with locally advanced carcinoma of the cervix. Int J Radiat Oncol Biol Phys 27:871–878
15. Strauss HG, Kuhnt T, Laban C, et al. (2002) Chemoradiation in cervical cancer with cisplatin and high-dose rate brachytherapy combined with external beam radiotherapy. Results of a phase-II study. Strahlenther Onkol 178:378–385
16. Chung YL, Jian JJ, Cheng SH, et al. (2005) Extended-field radiotherapy and high-dose-rate brachytherapy with concurrent and adjuvant cisplatin-based chemotherapy for locally advanced cervical cancer: a phase I/II study. Gynecol Oncol 97:126–135
17. Toita T, Moromizato H, Ogawa K, et al. (2005) Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. Gynecol Oncol 96:665–670
18. Pötter R, Dimopoulos J, Bachtiary B, et al. (2006) 3D conformal HDR-brachy- and external beam therapy plus simultaneous cisplatin for high-risk cervical cancer: clinical experience with 3 year follow-up. Radiother Oncol 79:80–86
19. Novetsky AP, Einstein MH, Goldberg GL, et al. (2007) Efficacy and toxicity of concomitant cisplatin with external beam pelvic radiotherapy and two high-dose-rate brachytherapy insertions for the treatment of locally advanced cervical cancer. Gynecol Oncol 105:635–640
20. Lanciano R, Calkins A, Bundy BN, et al. (2005) Randomized comparison of weekly cisplatin or protracted venous infusion of fluorouracil in combination with pelvic radiation in advanced cervix cancer: a Gynecologic Oncology Group study. J Clin Oncol 23:8289–8295
21. Gaffney DK, Winter K, Dicker AP, et al. (2007) Efficacy and patterns of failure for locally advanced cancer of the cervix treated with Celebrex (celecoxib) and chemoradiotherapy in RTOG 0128. Int J Radiat Oncol Biol Phys 69:111–117
22. Gerbaulet A, Potter R, Haie-Meder C. Cervical carcinoma. In: Gerbaulet A, Potter R, Mazeron J-J, Meertens H, Limbergen EV (eds) (2002) The GEC ESTRO handbook of brachytherapy. ESTRO, Brussels, pp 301–363
23. Tod M, Meredith W (1938) A dosage system for use in the treatment of cancer of the uterine cervix. Br J Radiol 11:809–824
24. Tod M, Meredith WJ (1953) Treatment of cancer of the cervix uteri, a revised Manchester method. Br J Radiol 26:252–257
25. Potish RA, Gerbi BJ (1986) Role of point A in the era of computerized dosimetry. Radiology 158:827–831
26. Japan Society of Obstetrics and Gynecology, The Japanese Society of Pathology, Japan Radiological Society (eds) (1997) Part II Treatment. The general rules for clinical and pathological management of uterine cervical cancer, 1st English Edition. Kanehara Shuppan, Tokyo, pp 14–17.
27. ICRU, International Commission on Radiation Units and Measurement (1985) Dose and volume specification for reporting intracavitary therapy in gynecology. ICRU report 38. ICRU, Bethesda, MD
28. Pötter R, Van Limbergen E, Gerstner N, et al. (2001) Survey of the use of the ICRU 38 in recording and reporting cervical cancer brachytherapy. Radiother Oncol 58:11–18
29. Clark BG, Souhami L, Roman TN, et al. (1997) The prediction of late rectal complications in patients treated with high dose-rate brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 38:989–993
30. Ogino I, Kitamura T, Okamoto N, et al. (1995) Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. Int J Radiat Oncol Biol Phys 31:725–734
31. Chen SW, Liang JA, Hung YC, et al. (2006) Concurrent weekly cisplatin plus external beam radiotherapy and high-dose rate brachytherapy for advanced cervical cancer: a control cohort comparison with radiation alone on treatment outcome and complications. Int J Radiat Oncol Biol Phys 66:1370–1377
32. Toita T, Kodaira T, Shinoda A, et al. (2008) Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): Patterns of Care Study in Japan. Int J Radiat Oncol Biol Phys 70:788–794
33. Potter R, Kirisits C, Fidarova EF, et al. (2008) Present status and future of high-precision image guided adaptive brachytherapy for cervix carcinoma. Acta Oncol 47:1325–1336
34. Nag S, Cardenes H, Chang S, et al. (2004) Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. Int J Radiat Oncol Biol Phys 60:1160–1172
35. Haie-Meder C, Pötter R, Van Limbergen E, et al. (2005) Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. Radiother Oncol 74:235–245
36. Pötter R, Haie-Meder C, Van Limbergen E, et al. (2006) Recommendations from Gynaecological (GYN) GEC ESTRO Working Group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy – 3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. Radiother Oncol 78:67–77
37. Sakurai H, Shioya M, Okamoto M, et al. (2008) High-dose-rate 3D image-based brachytherapy for uterine cervical cancer – evaluation of Japanese cervical cancer protocol based on Gynaecological GEC-ESTRO recommendations. Brachytherapy 7:124
38. Pelloski CE, Palmer M, Chronowski GM, et al. (2005) Comparison between CT-based volumetric calculations and ICRU reference-point estimates of radiation doses delivered to bladder and rectum during intracavitary radiotherapy for cervical cancer. Int J Radiat Oncol Biol Phys 62:131–137
39. Nakano T, Kato S, Ohno T, et al. (2005) Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. Cancer 103:92–101
40. Nag S, Gupta N (2000) A simple method of obtaining equivalent doses for use in HDR brachytherapy. Int J Radiat Oncol Biol Phys 46:507–513
41. Petereit DG, Sarkaria JN, Potter DM, et al. (1999) High-dose-rate versus low-dose-rate brachytherapy in the treatment of cervical cancer: analysis of tumor recurrence – the University of Wisconsin experience. Int J Radiat Oncol Biol Phys 45:1267–1274
42. Lanciano RM, Martz K, Coia LR, et al. (1991) Tumor and treatment factors improving outcome in stage III-B cervix cancer. Int J Radiat Oncol Biol Phys 20:95–100
43. Perez CA, Fox S, Lockett MA, et al. (1991) Impact of dose in outcome of irradiation alone in carcinoma of the uterine cervix: analysis of two different methods. Int J Radiat Oncol Biol Phys 21:885–898
44. Toita T, Oguchi M, Ohno T, et al. (2008) Quality assurance for a prospective multi-institutional trial of definitive radiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer: the individual case review. Radiother Oncol 88 (Suppl 2): S245–246
45. Matsuura K, Tanimoto H, Fujita K, et al. (2007) Early clinical outcomes of 3D-conformal radiotherapy using accelerated hyperfractionation without intracavitary brachytherapy for cervical cancer. Gynecol Oncol 104:11–14

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Clinical Trial Notes

Phase II Trial of Concurrent Chemoradiotherapy with S-1 Plus Cisplatin in Patients with Unresectable Locally Advanced Squamous Cell Carcinoma of the Head and Neck: Japan Clinical Oncology Group Study (JCOG0706)

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A Phase II study was started in Japan to evaluate the efficacy and safety of concurrent chemoradiotherapy with S-1 plus cisplatin in patients with unresectable locally advanced squamous cell carcinoma of the head and neck. This study began in July 2008, and a total of 45 patients will be accrued from 13 institutions within 2 years. The primary endpoint is the clinical complete remission rate. The secondary endpoints are local progression-free survival, overall survival, progression-free survival, time to treatment failure, proportion of patients who achieve nutritional support-free survival and adverse events.

Key words: head and neck neoplasms – chemoradiotherapy – clinical trials – Phase II

INTRODUCTION

More than 60% of squamous cell carcinomas of the head and neck (SCCHN) are revealed to be Stage III or IV at diagnosis, because they are not symptomatic and it is difficult to detect them in their early stages (1). The prognosis of unresectable locally advanced SCCHN is still poor.

The standard therapy for locally advanced SCCHN is chemoradiotherapy (CRT) with cisplatin alone or 5-fluorouracil (5-FU) plus cisplatin (2–5). S-1 is a new oral fluoropyrimidine, consisting of tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate, which as monotherapy led to a response rate of 34.1% in patients with progressive or recurrent SCCHN (6). S-1 monotherapy also demonstrated a response rate of 30.4% in patients with pre-treated SCCHN, which was much better than the response rate of 15% seen with 5-FU continuous infusion (6). Thus, higher efficacy may be expected if 5-FU is replaced with S-1 in CRT as well as in chemotherapy alone. A Phase I study of concurrent CRT with S-1 plus CDDP in patients with unresectable locally advanced SCCHN showed quite a high complete response rate (86%) (7). Therefore, we have undertaken a Phase II study to evaluate the efficacy and safety of concurrent CRT with S-1 plus CDDP for patients with unresectable locally advanced SCCHN. The Protocol Review Committee of the Japan Clinical Oncology Group (JCOG) approved the protocol in June 2008 and the study was activated in July 2008. This trial was registered at the UMIN Clinical Trials Registry as UMIN000001272 (http://www.umin.ac.jp/ctr/index.htm).

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Purpose

The aim of this study is to evaluate the efficacy and safety of concurrent CRT with S-1 plus cisplatin in patients with unresectable locally advanced SCCHN.

Study Setting

The study is a multi-institutional Phase II study.

Resources

The study is supported by Grants-in-Aid for Cancer Research (18-19, 20S-3, 20S-6) from the Ministry of Health, Labour and Welfare of Japan.

Endpoints

The primary endpoint is the clinical complete remission rate, which is the proportion of complete response (CR) and good partial response (good PR) in all eligible patients. Good PR is defined as a remaining secondary change with tumor shrinkage such that the remaining tissue is not regarded as residual tumor but rather as scar material. Our evaluative guidelines suggested identifying good PR lesions as ~10 mm or less in size and not enhanced on contrasted computed tomography scan. The secondary endpoints are local progression-free survival, progression-free survival, overall survival, time to treatment failure, proportion of patients achieving nutritional support-free survival and adverse events.

Local progression-free survival is the time from enrollment to local disease progression or death from any cause. Progression-free survival is defined as the time from enrollment to any disease progression or death from any cause. Overall survival is defined as days from enrollment to death from any cause. Time to treatment failure is defined as the time from enrollment to any disease progression, off-protocol treatment or death from any cause. Proportion of nutritional support-free survival denotes the percentage of surviving patients not requiring any nutritional support at the time of treatment start and then 2, 6, 12 and 24 months after registration.

Eligibility Criteria

Inclusion Criteria

For inclusion in the study, the patient must fulfill all of the following criteria: (i) histologically proven squamous cell carcinoma; (ii) primary lesion located at oropharynx, hypopharynx or larynx; (iii) unresectable locally advanced head and neck cancer which fulfills at least one of the following conditions: (a) primary lesion or cervical lymph node metastasis to carotid artery, cranial base or cervical vertebrae; (b) cervical lymph node metastasis of N2c or N3 (UICC/TNM, 6th edition); and (c) T4 primary lesion located at oropharynx; (iv) no fistula due to primary lesion or cervical lymph node metastasis; (v) no distant metastasis; (vi) age between 20 and 75 years old; (vii) ECOG performance status of 0 or 1; (viii) no prior radical surgery for head and neck cancer; (ix) no prior treatment for any other malignancies with chemotherapy, radiation therapy or endocrine therapy; (x) sufficient organ function; (xi) normal electrocardiogram; and (xii) 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 except carcinoma *in situ* or intramucosal tumor; (iii) women during pregnancy or breastfeeding; (iv) active gastrointestinal bleeding; (v) pleural effusion, pericardial effusion or massive ascites; (vi) history of severe heart disease, heart failure, myocardial infarction within 6 months or angina pectoris attack within 6 months; (vii) cerebrovascular disease within 6 months; (viii) diabetes mellitus treated with insulin or poorly controlled; (ix) poorly controlled hypertension; (x) chronic pancreatitis; (xi) positive HBs antigen; (xii) impossibility to refrain from smoking and drinking during treatment; and (xiii) requiring systemic steroids medication.

Treatment Methods

The protocol treatment consists of concurrent CRT, adjuvant chemotherapy and salvage surgery if necessary (Fig. 1).

First, patients receive concurrent CRT with S-1 plus cisplatin. S-1 (60 mg/m^2/day) is orally administered for two weeks and cisplatin is infused on days 8 through 11, repeated every five weeks for two courses.

Radiation therapy is administered with high-energy photons of 4–10 MV X-rays to a total dose of 70 Gy in a fraction of 2 Gy five times weekly. The gross tumor volume (GTV) includes the volumes of both the primary tumor and metastatic cervical lymph nodes with a short axis of 1 cm or larger. The clinical target volume 1 (CTV1) includes GTV and bilateral regional cervical lymph node area with a 1–2 cm margin, and CTV2 includes GTV with a 0.5–2 cm margin. The planning target volumes (PTVs) for CTV1 and CTV2 (PTV1 and PTV2) are defined as 0.5–1 cm margins around CTV to compensate for set-up variations and internal organ motion. A total of 40 Gy is delivered toward PTV1, and then an additional 30 Gy is boosted to PTV2.

For patients with an objective response (CR, good PR or PR) at the first evaluation after CRT, adjuvant chemotherapy with S-1 plus cisplatin is administered for two more courses. In adjuvant chemotherapy, S-1 (60 mg/m^2/day) is orally administered for 2 weeks and cisplatin (20 mg/m^2/day) is infused on days 8 through 11, repeated every 4 weeks. At the second evaluation after adjuvant chemotherapy, patients diagnosed with CR or good PR are regarded as having completed the protocol treatment. Patients not diagnosed with CR or

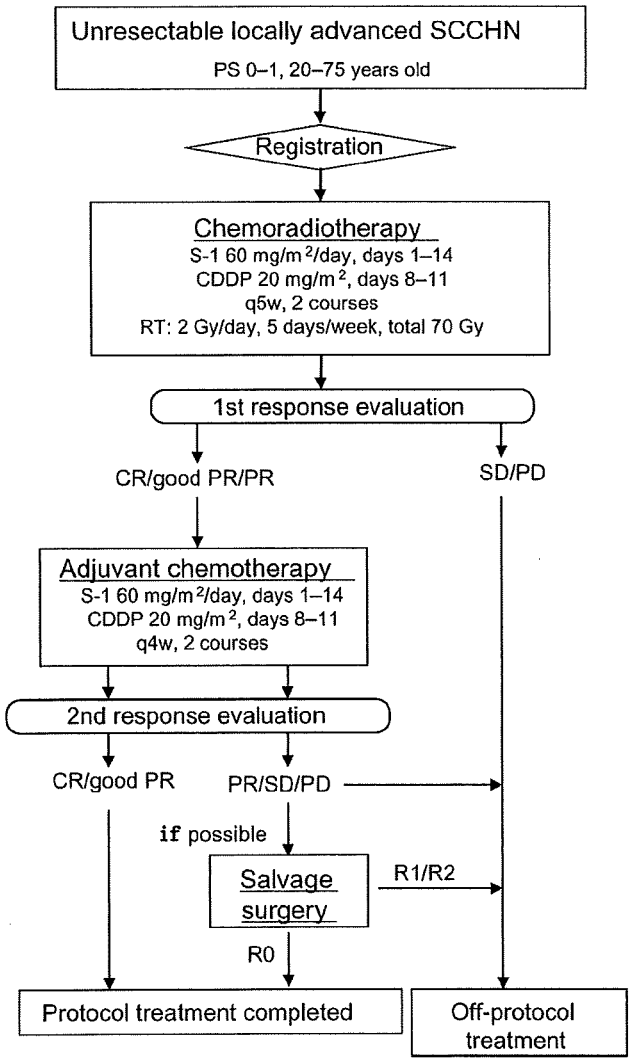

Figure 1. Schema of the study. SCCHN, squamous cell carcinoma of head and neck; PS, performance status; CDDP, cisplatin; RT, radiation; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

good PR are discontinued from treatment, and salvage surgery is planned if it is judged to be clinically feasible.

Follow-up

All enrolled patients are followed up for at least 3 years. Efficacy and safety are to be evaluated at least every 3 months during the first year, at least every 4 months during the second year and then every 6 months during the third year. Data on the use and methodology of nutritional support are reported at 2, 6, 12 and 24 months after registration.

Study Design and Statistical Analysis

This trial is designed to evaluate the efficacy and safety of CRT with S-1 plus cisplatin and to determine the viability of proceeding to a Phase III trial. In this Phase II trial, the planned sample size is 45 patients, which was calculated by SWOG's (Southwest Oncology Group) two-stage attained design (8) based on an expected clinical complete remission rate of 60% and a threshold of 45%, with a one-sided α error of 0.1 and a β error of 0.1. If at least 10 clinical complete remissions occur after the first 25 patients enroll, another 20 patients will be accrued.

If the clinical complete remission rate is as high as expected, the subsequent Phase III trial will be designed to confirm the superiority of CRT with S-1 plus cisplatin to CRT with cisplatin alone.

Interim Analysis and Monitoring

In this Phase II trial, an interim analysis is planned once, which corresponds to the first-stage analysis in the two-stage design. The Data and Safety Monitoring Committee (DSMC) of the JCOG will independently review the interim analysis reports and recommend that the trial either be continued or terminated early. Central 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)

Hokkaido University Hospital, Miyagi Cancer Center, Yamagata Prefectural Central Hospital, Jichi Medical University Hospital, National Cancer Center Hospital East, Tokyo Women's Medical University Hospital, National Hospital Organization Tokyo Medical Center, Kanagawa Cancer Center, Shizuoka Cancer Center, Aichi Cancer Center, Kobe University Hospital, Hyogo Cancer Center and Shikoku Cancer Center.

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Conflict of interest statement

None declared.

References

1. Forastiere AA, Ang KK, Brizel D, Brockstein BE, Burtness BA, Cmelak AJ, et al. Head and neck cancers. *National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology*. v.2.2008.
2. Adelstein DJ, Li Y, Adams GL, Wagner H, Jr, Kish JA, Ensley JF, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;21:92–8.
3. Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent

chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 1998;338:1798–804.
4. Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: a systematic review of the published literature with subgroup analysis. *Head Neck* 2001;23:579–89.
5. Merlano M, Corvo R, Margarino G, Benasso M, Rosso R, Sertoli MR, et al. Combined chemotherapy and radiation therapy in advanced inoperable squamous cell carcinoma of the head and neck. The final report of a randomized trial. *Cancer* 1991;67:915–21.
6. Inuyama Y, Kida A, Tsukuda M, Kohno N, Satake B. Late phase II study of S-1 in patients with advanced head and neck cancer. *Gan To Kagaku Ryoho* 2001;28:1381–90.
7. Tahara M, Minami H, Mukai H, Kawada K, Kawashima M, Ogino T, et al. Phase I trial of concurrent chemoradiotherapy with S-1 and CDDP in patients with unresectable locally advanced squamous cell carcinoma of the head and neck (SCCHN). *American Society of Clinical Oncology (ASCO) Anuual Meeting*; 2005. p. 518s.
8. Green SJ, Dahlberg S. Planned versus attained design in phase II clinical trials. *Stat Med* 1992;11:853–62.