厚生労働省科学研究費補助金（医療技術評価総合研究事業）

III. 研究成果の刊行に関する一覧

著書

著者氏名	論文タイトル名	書籍全体の編集者名	書籍名	出版社名	出版地	ページ
宇野　隆, 伊東久夫	子宮頸癌術後照射の適応と方法・治療結果について教えてください。	渋谷　均 笹井啓資	放射線治療(専門医に聞く最新の臨床)	中外医薬社	東京	218-220
宇野　隆, 伊東久夫	子宮頸部断端癌の治療について教えてください。	渋谷　均 笹井啓資	放射線治療(専門医に聞く最新の臨床)	中外医薬社	東京	221-222

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Kawata T, Ito H, et al	G2 chromatid damage and repair kinetics in normal human fibroblast cells exposed to low- or high-LET radiation.	Cytogenet Genome Res	104	211-215	2004
Uno T, Ito H, et al	Postoperative pelvic radiotherapy for cervical cancer patients with positive parametrial invasion.	Gynecol Oncol	96	335-340	2005
Mitsuhashi A, Ito H, et al	Phase 1 study of daily cisplatin and concurrent radiotherapy in patients with cervical carcinoma.	Gynecol Oncol	96	194-197	2005
Ogawa K, Ito H, et al	Long-term results of radiotherapy for intracranial germinoma: a multi-institutional retrospective review of 126 patients.	Int J Radiat Oncol Biol Phys	58	705-713	2004
Takeda A, Ito H, et al.	Evaluation of novel modified tangential irradiation technique for breast cancer patients using dose–volume histograms.	Int J Radiat Oncol Biol Phys	58	1280-1288	2004

Isobe K, Ito H, et al.	Radiation therapy for idiopathic orbital myositis: two case reports and literature review.	Radiat Med	22	429-431	2004
Ikeda M, Ito H, et al.	Warthin tumor of the parotid gland: Diagnostic value of MR imaging with histopathologic correlation.	Am J Neuro-radiol	25	1256-1262	2004
Motoori K, Ito H, et al.	Inter- and intratumoral variability in magnetic resonance imaging of pleomorphic adenoma. An attempt to interpret the variable magnetic resonance findings.	J Comput Assist Tomogr	28:	233-246	2004
Ueda T, Ito H, et al	Selective intraarterial 3-dimensional computed tomography angiography for preoperative evaluation of nephron-sparing surgery.	J Comput Assist Tomogr	28:	496-504	2004
宇野 隆、伊東久夫、他	子宮頸癌 3.ハイリスク症例に対する後療法には adjuvant radiotherapy か adjuvant chemotherapy か － adjuvant radiotherapy + chemotherapy の立場から	産科と婦人科		印刷中	2005

厚生労働省科学研究費補助金（医療技術評価総合研究事業）

IV. 研究成果の刊行物

放射線治療

専門医にきく最新の臨床

●澁谷　均　笹井啓資　小久保雅樹●
編集

中外医学社

5. 術後照射の適応と方法・治療結果について教えてください.

■回答■　宇野　隆・磯部公一・伊東久夫

子宮頸癌に対する術後放射線治療は，主として，術後の病理組織学的検索をもとに，予後不良とされる因子をもつ症例を選んで，経験的に施行されてきた．そのため，術後照射の有用性を支持する根拠のほとんどは，遡及的研究結果によるものであり，よく計画された前向き臨床試験の結果に基づくレベルの高いエビデンスは少ない．したがって，術後照射を行うことによって最終的に患者の予後が改善するかどうかは，いまだ明らかではない．

A. 術後照射の適応

欧米では，IIB期は手術対象外の進行例と考えられており，術後照射は「再発危険因子をもつIIAまでの早期例に対する術後補助療法」と位置づけられている．つまり，術後照射の有用性についての多くの議論は，IB～IIAまでの早期例を対象として進められてきた．一方，日本では，IIB期までは切除対象とされる場合がほとんどであり，「病期は問わず手術後に行われる放射線照射」という考え方である．

術後の再発危険因子は，切除後の病理組織学的所見と再発様式とを対比することによって遡及的研究で抽出されてきた．腫瘍径，骨盤リンパ節転移，リンパ節転移の個数，筋層浸潤の程度，脈管侵襲，病理組織型，分化度など様々な因子があげられてきた．これらのうち，最も重要な予後因子は，骨盤内リンパ節転移の有無であるとされている．IB期における，骨盤内リンパ節転移陰性群の5年生存率は85～90%と良好であるのに対して，転移陽性群では50～60%程度と明らかに予後不良である．なお，切除断端陽性を再発危険因子に含めているかどうかは研究ごとにまちまちであり，注意が必要である．

IB～IIA期子宮頸癌に対する術後放射線照射の適応は，上述のような再発危険因子を症例ごとに検討したうえで決定する必要がある．近年，これらの因子を組み合わせて検討することで，放射線照射を必要としない症例，術後照射によって骨盤内制御率が上昇し，ひいては予後の向上につながる可能性のある症例，および全身化学療法を併用すべき症例に分類する努力がなされている．Gynecologic Oncology Group (GOG) の基準によれば，骨盤リンパ節転移が陰性で，腫瘍径が4cm未満，リンパ管侵襲がなく，筋層浸潤が1/3未満のものは，骨盤内再発の可能性がきわめて低いとされ，術後照射の適応外とされる．骨盤リンパ節転移陰性の症例のうち，リンパ管侵襲があるものでは，間質浸潤が外側1/3におよぶ，中間1/3で腫瘍径が2cm以上，内側1/3までで腫瘍径が5cm以上，のいずれかの場合，あるいは，リンパ管侵襲がないものでは，腫瘍が径4cm以上かつ間質浸潤1/3以上の場合は，根治術後の経過観察のみでは，骨盤内制御率が不充分とされ，これらを中等度再発危険因子群としている（表1）．GOGでは広汎子宮全摘術および骨盤リンパ節郭清が行われたIB期子宮頸癌の中等度再発危険因子群に対して，術後骨盤照射の有用性を検討するランダム化比較試験を行った（GOG 92）．照射群では再発率が47%減と有意に低下し，2年無再発率は

JCLS 498-06510

表1　Gynecologic Oncology Groupによる中等度再発危険因子群

脈管侵襲	筋層浸潤	腫瘍径
あり	外側1/3	すべて
あり	中間1/3	2cm以上
あり	内側1/3	5cm以上
なし	中間1/3以上	4cm以上

照射群88%に対して非照射群79%（p = 0.008）であった[1]．この研究により，中等度再発危険因子群では骨盤照射によって再発率が有意に低下することが示された．しかし，この試験には，経過観察が不充分で生存率の解析がまだ行われていない，術後例にもかかわらず客観性を欠く術前の双合診で決定された腫瘍径を用いた，放射線治療のコンプライアンスが低い，減少したものの骨盤再発が照射群で13%とまだ高かった，消化管障害，下肢の浮腫など重要な晩期有害事象について検討されていないなどの様々な問題点があった．したがって，今のところ，中等度再発危険因子群に対して術後骨盤照射が有用であるかどうかについてのエビデンスは充分ではない．

一方，骨盤リンパ節転移陽性例では，遠隔転移出現の可能性が高く，術後照射を行っても，他の因子によって術後照射が施行されたリンパ節転移陰性群と比較して，生存率は有意に低い．米国では，骨盤リンパ節転移陽性例を85%含むIA2～IIA期の再発危険因子群を対象とした大規模なランダム化比較試験（SWOG 8797）が行われた．全身化学療法としてCDDPと5-FUの同時併用による化学放射線療法群で4年生存率が81%であり，術後照射単独群の71%を有意に上回った[2]．術後の治療方針の違いが生存率に有意な差をもたらすことを示した最初の大規模な前向き研究となった．しかし，この試験では，有用性の証明されていない骨盤照射が両群に施行されていた．化学放射線療法群は補助化学療法単独群とも比較される必要があった．さらに，この研究での照射法は1回1.7Gy週5回（週間線量8.5Gy）で，通常よりも治療期間の長くかかるものであった．また，骨盤リンパ節転移以外の因子でエントリーされた症例や，癌遺残症例も含めていた．したがって，この試験の結果だけからは，対象とした症例すべてに術後化学放射線療法が標準治療となるとはいい切れない．

B．治療法

術後放射線治療は，傍大動脈リンパ節領域を含めて照射する場合以外は，基本的に全骨盤照射が行われる．手術標本で腟断端の切除が不充分と判断された場合には，断端への腔内照射を併用する場合がある．

全骨盤照射の照射野は，根治照射の場合と同様である．腟および傍子宮結合織の切除断端と，すでに郭清された骨盤内リンパ節領域が照射野に含まれる．上縁は第5腰椎上縁，下縁は閉鎖孔下縁，左右の外側は小骨盤腔から1.5～2cm外側とした照射野となる．症例によって，下縁は腟断端の高さに対応させて，その下方マージンをもたせる．治療装置は，直線加速器（リニアック）を使用し，通常10MV以上の高エネルギーX線で治療する．線量投与法は，1回1.8～2.0Gy，週5回法にて総線量45～50Gy程度が基本であるが，1回2.3～2.5Gy，週4回法で治療する施設もある．また，小腸線量を低減するために，前後対向二門ではなく，腹臥位で四門照射を用いる施設もある．四門照

射の場合は，特に，側方からの照射野における，前方（外腸骨リンパ節領域）および後方（仙骨子宮靱帯にそった腫瘍の後方進展が存在した場合）のマージン設定に注意が必要である．

根治術後の骨盤内リンパ節転移陽性例，特に総腸骨リンパ節など高位のリンパ節転移陽性群に対して，予防的な傍大動脈リンパ節照射が推奨されてきた．しかし，この領域に再発する可能性の高い症例では，予後に影響する因子は，むしろ他臓器への転移の出現と考えられていて，骨盤照射と全身化学療法を同時併用する方向にある．したがって，現在，傍大動脈リンパ節領域への放射線治療は，臨床的あるいは病理組織学的に転移が陽性である症例に限局されつつある．

C．治療成績

術後照射の治療成績は，対象とする病期，予後因子により幅がみられ，5年生存率はIB～IIA期で70～85%，IIB期で60～70%である．

●文　献

1) Sedlis A, Bundy BN, Rotman MZ, et al. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol Oncol 1999; 73: 177-83.
2) Peters III WA, Liu PY, Barrett II RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18: 1606-13.

498-06510

6. 子宮頸部断端癌の治療について教えてください.

■回答■　宇野　隆・磯部公一・伊東久夫

子宮筋腫などの良性疾患に対する腟上部切断術の施行後，残存した子宮頸部に子宮頸癌が発症した場合を子宮頸部断端癌という．一般の子宮頸癌とは，病理組織学的な違いあるいは放射線感受性などの違いは全くなく，病期の決定法も同じである．治療方針は，子宮頸癌に準ずる．しかし，先行する手術による腸間癒着，子宮傍組織の線維化などがあるため，手術は困難である場合が多い．また同様に，消化管の癒着により，放射線治療による有害事象発症の可能性が通常より高くなるとされている．特に，腔内照射においては，子宮腔内線源（タンデム）が充分に挿入できないという大きな制約がある点に，充分な注意が必要である．

A. 放射線治療法

子宮頸部断端癌に対する放射線治療の基本は，外部照射と腔内照射の併用とされる．しかし，これらをどのように組み合わせるのがよいかについては，一般の子宮頸癌の場合とは違って明瞭な治療指針がない．症例によっては，腔内照射よりも組織内照射で治療を行う方が，適切な場合があると思われる．したがって，標準的治療法は存在せず，腫瘍の大きさ，進展範囲，周辺正常組織の被曝線量などを評価しながら，患者ごとに個別化した治療を行うべきである．

1) 外部照射

外部照射は，一般に全骨盤照射を行う．照射方法，X線エネルギー，標的体積などは子宮頸癌の場合と全く同様である．1回1.8～2.0Gy，週5回の通常分割法で，総線量50Gy程度とする．高線量率治療が主体である日本では，外部照射の適切な時期に中央遮蔽をおくのが一般的である．ただし，腔内照射における線量分布は，一般の子宮頸癌の場合のような良好なものが期待できない場合がほとんどである．したがって，中央病変に対する線量は，外部照射からの比率を高くすることが多い．

2) 腔内照射

a) 線量評価法

腔内照射については，推奨される照射法はもちろん，その評価点についても一定の見解はない．充分な子宮腔内線源長がとれない以上，いわゆるマンチェスター法のA点近傍では線量勾配がより急峻となる．したがって，A点を線量評価点とすることは適切ではない．そもそもマンチェスター法に準じた線源配置がほぼ不可能であることから，線量評価点としてA点を用いることには明らかな矛盾がある．したがって，子宮頸癌の治療に準ずるとしながらも，子宮頸部断端癌に対する小線源治療の方法は，全く異なる治療であると認識するべきである．子宮頸部断端癌に対する腔内照射における線量は，画像上描出される腫瘍容積内の最低線量など，実際に腫瘍に投与されている線量を考慮して評価すべきである．

b) 至適線量と分割法

今のところ，子宮頸部断端癌に対する治療の指標となるような至適線量と分割法は示されておらず，個々の症例ごとの個別化が必要である．腔内照射で投与可能な線量は，子宮腔内線源長に依存する．子宮腔内に線源が全く入らないような場合は，腟内線源（オボイド）のみの照射となり，腫瘍に対するconformityがきわめて悪くなる一方で，直腸・膀胱線量が非常に高くなる．また，A点線量で算出された子宮頸癌の標準治療法をそのまま用いることはできない．組織内照射による子宮頸癌治療例の報告を参考にすると，外部照射（全骨盤照射）30～40Gyと併用する場合は，高線量率換算で腫瘍線量20～30Gyを4～5分割で投与し，単純加算で計60Gy程度が総投与線量の目安となる[1]．

c) 組織内照射

子宮頸部断端癌に対する小線源治療では，腔内照射よりも組織内照射の方が線量分布が優れている．腔内照射と比較すると簡便性が劣るものの，可能であれば，治療の適応について組織内照射に精通した放射線腫瘍医にコンサルトするべきである．

B．その他の治療法

現在，子宮頸癌IB2期以上のほとんどにcisplatinを中心とした化学療法が推奨されている．子宮頸部断端癌のみに限ったエビデンスがあるわけではないが，子宮頸癌治療同様に，外部照射に同時併用で化学療法を行う根拠は充分にあると考えられる．むしろ，外部照射の比率が高く，腔内照射の前に腫瘍の充分な縮小が必要となることから，同時併用化学放射線療法は積極的に検討されるべきであろう．

小線源治療を行うことが不可能な子宮頸癌症例に対して，3次元原体照射などの最新の技術を用いた外部照射，あるいはその化学療法との併用が行われる場合がある．このような治療が子宮頸部断端癌における腔内照射の代替治療となりうるかについては，今後の検討が必要である．

C．治療成績

治療成績は一般の子宮頸癌と同等とされる．5年生存率はI期が90%，II期が70～80%，III期が50～60%程度とされる[2]．

●文　献

1) Haie-Meder C, Gerbaulet A, Potter R. Interstitial Brachytherapy in Gynaecological Cancer. In: Gerbaulet A, Potter R, Mazeron JJ, et al, editors. The GEC ESTRO Handbook of Brachytherapy. Brussels: ESTRO; 2002. p.417-33.

2) Stehman FB, Perez CA, Kurman RJ, et al. Uterine Cervix. In: Hoskins WJ, Perez CA, Young RC, editors. Principles and Practice of Gynecologic Oncology. Philadelphia: Lippincott Williams & Wilkins; 2000. p.841-918.

JCLS 498-06510

Cytogenet Genome Res 104:211–215 (2004)
DOI: 10.1159/000077491

Cytogenetic and Genome Research

G2 chromatid damage and repair kinetics in normal human fibroblast cells exposed to low- or high-LET radiation

T. Kawata,[a] H. Ito,[a] T. Uno,[a] M. Saito,[a] S. Yamamoto,[a] Y. Furusawa,[b] M. Durante,[c] K. George,[d] H. Wu,[d] and F.A. Cucinotta[d]

[a] Department of Radiology, Graduate School of Medicine, Chiba;
[b] Heavy-Ion Research Group, National Institute of Radiological Sciences, Chiba (Japan);
[c] Department of Physics, University Federico II, Naples (Italy);
[d] NASA Lyndon B. Johnson Space Center, Houston, TX (USA)

Abstract. Radiation-induced chromosome damage can be measured in interphase using the Premature Chromosome Condensation (PCC) technique. With the introduction of a new PCC technique using the potent phosphatase inhibitor calyculin-A, chromosomes can be condensed within five minutes, and it is now possible to examine the early damage induced by radiation. Using this method, it has been shown that high-LET radiation induces a higher frequency of chromatid breaks and a much higher frequency of isochromatid breaks than low-LET radiation. The kinetics of chromatid break rejoining consists of two exponential components representing a rapid and a slow time constant, which appears to be similar for low- and high-LET radiations. However, after high-LET radiation exposures, the rejoining process for isochromatid breaks influences the repair kinetics of chromatid-type breaks, and this plays an important role in the assessment of chromatid break rejoining in the G2 phase of the cell cycle.

A number of experiments have been performed to quantify the biological effects of high-LET radiation exposure and results prove that this type of radiation is more lethal to cells than equivalent doses of sparsely ionizing radiation such as γ- or X-rays (Suzuki et al., 1989; Raju et al., 1991; Napolitano et al., 1992). High-LET radiation exposures produce more chromosome breakage and more complex chromosome rearrangements, which usually leads to cell death. However, some types of damage may confer a proliferative advantage on cells leading to oncogenic cell transformation and carcinogenesis. Indeed, the frequencies of transformation and mutations induced by high-LET radiation have been shown to be greater than those induced by similar doses of low-LET radiation (Thacker et al., 1979; Yang et al., 1985; Suzuki et al., 1989; Tsuboi et al., 1992), suggesting that carcinogenesis is the most important biological effect caused by exposure to high-LET radiation.

Chromosome aberration analysis is one of the most reliable and sensitive methods of measuring radiation-induced damage. Although cytogenetic damage is typically evaluated in the mitotic phase of the cell cycle, this raises problems because many cells experience severe cell cycle delays and interphase cell death (Suzuki et al., 1990; Ritter et al., 1992, 1996; Edwards et al., 1994, 1996; George et al., 2001), especially after high-LET radiation exposure. Assessing damage in interphase chromosomes can reduce some of these problems and produce a more accurate determination of cytogenetic effects following high-LET exposure. The premature chromosome condensation (PCC) technique, first described by Johnson and Rao (Johnson and Rao, 1970), condenses interphase chromosomes by fusion to mitotic inducer cells, and this method contributed greatly to the study of early effects of radiation damage and chromosome break rejoining. However, this fusion PCC method is technically difficult to perform and laborious; the PCC index is low, and

This work was partly supported by NASA Space Radiation Health Program.

Received 16 September 2003; accepted 24 November 2003.

Request reprints from: Dr. Tetsuya Kawata, Department of Radiology (L1)
Graduate School of Medicine, Chiba University
1-8-1 Inohana Chuo-ku Chiba-shi, Chiba 260-8670 (Japan)
telephone: +81-43-226-2100; fax: +81-43-226-2101
e-mail:tkawata@med.m.chiba-u.ac.jp.

0301–0171/04/1044–0211$21.00/0

Accessible online at:
www.karger.com/cgr

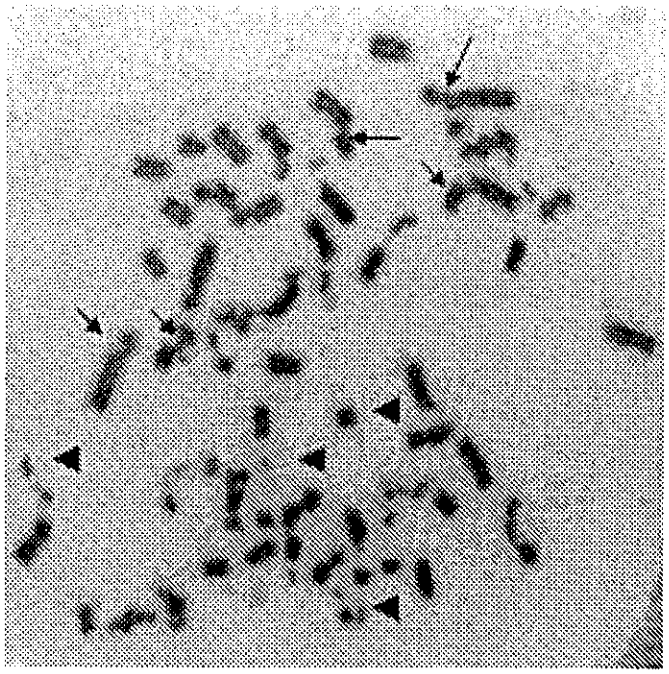

Fig. 1. An example of G2 PCC immediately after exposure to 2 Gy of 80 keV/μm carbon particles. Arrows show chromatid-type breaks and arrow heads show isochromatid breaks.

chromosomes are not well condensed. The fusion PCC technique also requires a considerable manipulation time and is therefore not amendable to studying chromosomal breaks induced immediately after irradiation.

With the recent introduction of a technique using the protein phosphatase inhibitor calyculin-A to induce condensation in interphase cells (Gotoh et al., 1995; Durante et al., 1998a), PCC collection is now technically much simpler and a higher index of well-condensed chromosomes can be obtained. Calyculin-A can induce PCC in many types of cells and in different phases of the cell cycle, especially in G2-phase cells and condensation is induced within five minutes of application. Using this technique, Durante and colleagues (Durante et al., 1999) found similar frequencies of aberrations in G2 chromosomes condensed using calyculin-A and in chromosomes condensed in G1 using the fusion PCC technique. However, lower frequencies were observed in chromosomes collected at metaphase, apparently due to the effect of cell cycle delay or cell cycle block. In this report, high-LET radiation-induced chromosome aberrations in G2-phase normal human fibroblast cells are discussed.

Initial chromatid breaks

Gotoh et al., (1999) studied radiation-induced G2 chromatid breaks using calyculin-A-induced PCC from human fibroblast cells (AG01522) after γ-ray exposure during exponential growth phase, and initial chromatid breaks were found to increase linearly with dose. Using a similar method, Kawata et al. (2000, 2001a, 2001b) studied high-LET radiation-induced G2 chromosome aberrations in AG01522 cells. An example of chromatid damage observed immediately after exposure to 2 Gy of 80 keV/μm carbon ions is shown in Fig. 1, where more than 20 isochromatid breaks (G2 fragments) and a number of chromatid breaks are observed.

The dose-response curves for chromatid-type breaks, isochromatid breaks, and total break yield (chromatid-type plus isochromatid-type) after exposure to radiation of different LET values are summarized in Fig. 2. The LET values for the radiation used here range from 0.6 to 440 keV/μm. A linear increase in chromatid breaks and total break yield was discovered, which was independent of the radiation type. On the other hand, isochromatid breaks increased linearly after exposure to high-LET radiation, and a linear quadratic increase was observed after γ-ray and 13 keV/μm carbon exposure. Interestingly, as the LET value increased, the initial percentage of chromatid-type breaks decreased and the percentage of isochromatid breaks increased, until finally isochromatid breaks predominated over chromatid-type breaks after the 440 keV/μm iron irradiation. More than 50% of the initial breaks are isochromatid-type after 440 keV/μm iron particle exposure, while more than 90% are chromatid-type breaks after γ-ray exposure.

The differences in break patterns for low- and high-LET radiations may be attributed to the structure of G2 chromosomes and densely ionizing clusters produced by high-LET radiation. In the G2 phase of the cell cycle, sister chromatids are tightly attached to one another (Murray and Hunt, 1993) and the two chromatid breaks that lead to an isochromatid break would be in close proximity. The probability of a single track of low-LET radiation producing two breaks on sister chromatids is low because ionizations are generally spaced farther apart than the distance between sister chromatids, and therefore chromatid-type breaks would predominate after low-LET exposure. However, the probability of an isochromatid break occurring from a single track of high-LET radiation is proportional to the LET of the charged particles because the distance between the ionization clusters decreases with increasing LET. An increased yield of isochromatid breaks after α-particles or neutron exposure has also been reported (Durante et al., 1994; Griffin et al., 1994; Vral et al., 2000) using mitotic collection and the G2-assay. A high percentage of isochromatid breaks can, therefore, be a signature of high-LET radiation exposure of G2 phase cells.

When the distribution of isochromatid breaks is assessed within the cell, an overdispersion is observed for high-LET exposure when compared with similar doses of low-LET radiation. Kawata et al. (2002) calculated the relative variance (s^2/y) from the measured value of the mean value (y) and the variance (s^2), which was around 1.3 for 1.2 Gy of γ-rays, 2.0 for 1.5 Gy of 185 keV/μm iron, and around 3.1 for 1.5 Gy of 440 keV/μm iron particles, respectively. Because energy deposition is focused along the high-LET particle tracks, some cells will be very heavily damaged, while cells hit by δ-rays alone will suffer modest damage, and other cells with no hits will be normal (Cucinotta et al., 1998). This is in contrast to low-LET radiation exposure, such as γ-rays, where a more even distribution of damage will induce a uniform distribution of isochromatid breaks.

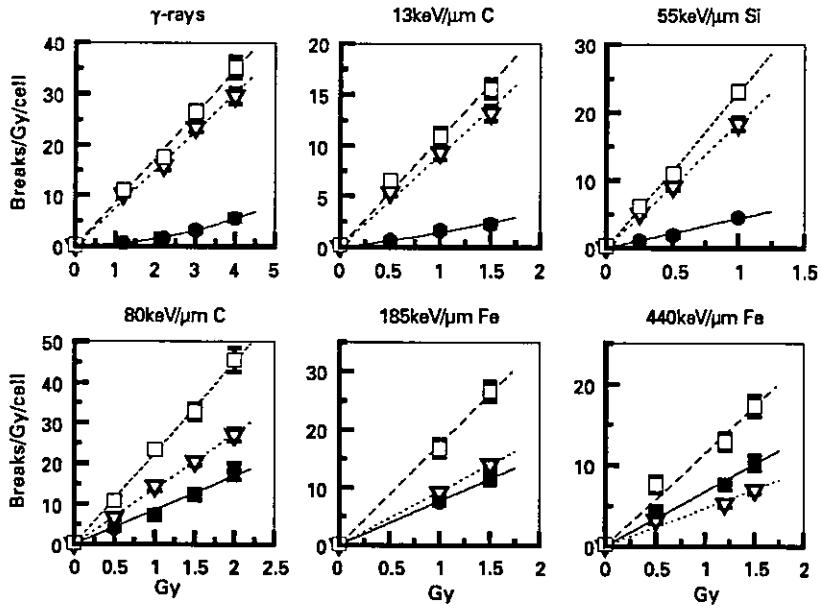

Fig. 2. Dose-response curves for the induction of chromatid-type breaks (▽), isochromatid-type breaks (●) and total chromatid breaks (□) after exposure to each type of radiation.

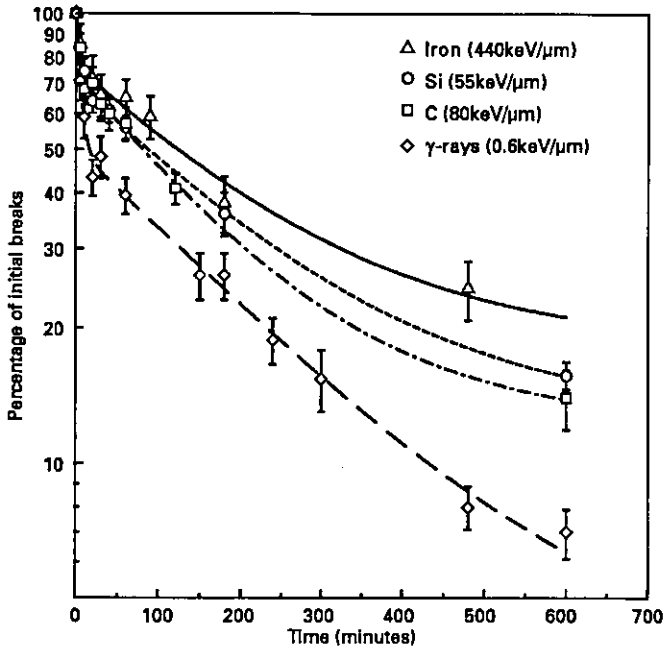

Fig. 3. Kinetics of rejoining of chromatid breaks following irradiation as a function of incubation time. Bars represent standard errors of the mean (data from Kawata et al., 2000).

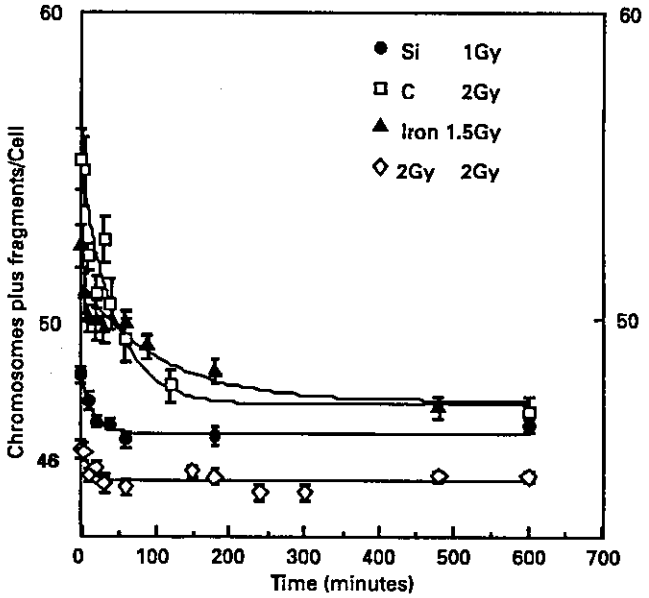

Fig. 4. Kinetics of rejoining of isochromatid breaks as a function of incubation times (Data from Kawata et al., 2001b).

Rejoining of chromatid breaks

The kinetics of total break (chromatid-type plus isochromatid-type), isochromatid break, and chromatid break rejoining were investigated after γ-rays, 13 keV/μm carbon, 55 keV/μm silicon, or 440 keV/μm iron particles (Kawata et al., 2000). The repair kinetics for total chromatid breaks showed a similar fast and slow time constant for both high-LET and γ-ray exposure (Fig. 3), and the half time for fast repair was about 4 min, regardless of radiation type. Iliakis and colleagues (Iliakis et al., 1993), using a combination of hypertonic treatment and fusion PCC technique, reported a half time of 1.5 min for repair of G1-phase CHO cells after exposure to X-rays. Durante and colleagues (Durante et al., 1998b), using the same technique with fluorescence in situ hybridization (FISH) analysis, also showed that γ-ray-induced chromosome breaks in G0 lymphocytes rejoined very quickly (half time of 5–6 min). Using the G2

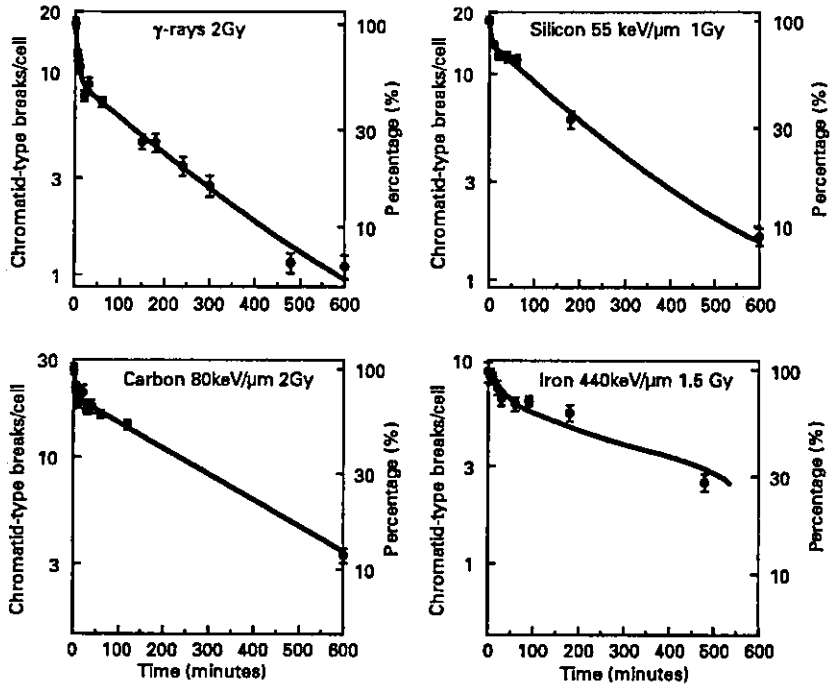

Fig. 5. Kinetics of rejoining of chromatid-type breaks as a function of incubation times (Data from Kawata et al., 2001b).

assay, Vral et al. (2002) demonstrated similar kinetics of disappearance of chromatid breaks following γ-rays and high-LET neutrons. These results suggest that the fast component of the repair process may be common throughout the cell cycle and independent of LET.

The percentage of residual breaks induced by high-LET exposure was from 4.2 to 6.2 times higher than γ-rays (Kawata et al., 2000), revealing an LET-dependent trend toward higher levels of residual chromatid breaks. Suzuki et al. (2001) also reported a higher frequency of residual chromatid breaks in human epithelial cells following high-LET iron particle exposure. Goodwin et al. (1994) demonstrated a clear LET-dependent trend in the percentage of excess residual fragments in CHO cells after helium (0.56 keV/μm), carbon (13.7 keV/μm), argon (115 keV/μm), and neon (183 keV/μm) particle exposure, with the reported percentage of residual excess fragments being 49% after 183 keV/μm neon particle exposure, compared to 11% after X-ray exposure. The higher rate of residual breaks induced by high-LET radiation may be due to the more clustered DNA damages induced by this type of exposure.

Kawata et al. (2001b) used calyculin-A-induced PCC method to examine the kinetics of isochromatid break rejoining, and found that high-LET radiation-induced isochromatid breaks rejoin quickly (Fig. 4). Since many more isochromatid breaks are produced by high-LET radiation, chromatid rejoining or exchange formation between isochromatid breaks is more likely to occur in these samples. During the isochromatid break rejoining or exchange formation process, a structural pattern similar to a simple chromatid-type break can be produced, which is therefore classified as residual chromatid-type break, leading to an increase in the number of chromatid-type breaks. This increase in chromatid breaks with repair time is not observed after low-LET radiation, since the initial yield of isochromatid breaks is much smaller. Therefore, the rejoining process of isochromatid breaks probably leads to the appearance of slower kinetics for chromatid-type break rejoining, especially for 440 keV/μm iron particles (Fig. 5).

Conclusion

High-LET radiation was found to be more effective at producing isochromatid breaks in the G2 phase of the cell cycle, and the repair process involved in the rejoining of these isochromatid breaks could explain why chromatid break yields remain higher after high-LET irradiation when compared with low-LET irradiation. The PCC technique with calyculin A proved very useful for analysis of the repair kinetics in G2 cells following low- or high-LET irradiation.

References

Cucinotta FA, Nikjoo H, Goodhead D: The effects of delta-rays on the number of particle-track traversals per cell in laboratory and space exposures. Radiat Res 150:115–119 (1998).

Durante M, Gialanella G, Grossi GF, Nappo M, Pugliese M, Bettega D, Calzolari P, Chiorda GN, Ottolenghi A, Tallone-Lombardi L: Radiation-induced chromosomal aberrations in mouse 10T1/2 cells: dependence on the cell-cycle stage at the time of irradiation. Int J Radiat Biol 65:437–447 (1994).

Durante M, Furusawa Y, Gotoh E: A simple method for simultaneous interphase-metaphase chromosome analysis in biodosimetry. Int J Radiat Biol 74:457–462 (1998a).

Durante M, George K, Wu HL, Yang TC: Rejoining and misrejoining of radiation-induced chromatin breaks. III. Hypertonic treatment. Radiat Res 149:68–74 (1998b).

Durante M, Furusawa Y, Majima H, Kawata T, Gotoh E: Association between G2-phase block and repair of radiation-induced chromosome fragments in human lymphocytes. Radiat Res 151:670–676 (1999).

Edwards AA, Finnon P, Moquet JE, Lloyd DC, Darroudi F, Natarajan AT: The effectiveness of high-energy neon ions in producing chromosomal aberrations in human lymphocytes. Radiat Prot Dosim 52:299–303 (1994).

George K, Wu H, Willingham V, Furusawa Y, Kawata T, Cucinotta FA: High- and low-LET induced chromosome damage in human lymphocytes: a time-course of aberrations in metaphase and interphase. Int J Radiat Biol 77:175–183 (2001).

Goodwin EH, Blakely EA, Tobias CA: Chromosomal damage and repair in G1-phase Chinese hamster ovary cells exposed to charged-particle beams. Radiat Res 138:343–351 (1994).

Gotoh E, Asakawa Y, Kosaka H: Inhibition of protein serine/threonine phosphatases directly induces premature chromosome condensation in mammalian somatic cells. Biomed Res 16:63–68 (1995).

Gotoh E, Kawata T, Durante M: Chromatid break rejoining and exchange aberration formation following γ-ray exposure: analysis in G-2 human fibroblasts by chemical-induced premature chromosome condensation. Int J Radiat Biol 75:1129–1135 (1999).

Griffin CS, Harvey AN, Savage JRK: Chromatid damage induced by ^{238}Pu α-particles in G2 and S phase Chinese hamster V79 cells. Int J Radiat Biol 66: 85–98 (1994).

Iliakis G, Okayasu R, Varlotto J, Shernoff C, Wang Y: Hypertonic treatment during premature chromosome condensation allows visualization of interphase chromosome breaks repaired with fast kinetics in irradiated CHO cells. Radiat Res 135:160–170 (1993).

Johnson RT, Rao PN: Mammalian cell fusion: induction of premature chromosome condensation in interphase nuclei. Nature 226: 717–722 (1970).

Kawata T, Gotoh E, Durante M, Wu H, George K, Furusawa Y, Cucinotta FA: High-LET radiation-induced aberrations in prematurely condensed G2 chromosomes of human fibroblasts. Int J Radiat Biol 76:929–937 (2000)

Kawata T, Durante M, Furusawa Y, George K, Takai N, Wu H, Cucinotta FA: Dose-response of initial G2-chromatid breaks induced in normal human fibroblasts by heavy ions. Int J Radiat Biol 77:165–174 (2001a)

Kawata T, Durante M, Furusawa Y, George K, Ito H, Wu H, Cucinotta FA: Rejoining of isochromatid breaks induced by heavy ions in G2-phase normal human fibroblasts. Radiat Res 156:598–602, (2001b).

Kawata T, Ito H, Motoori K, Ueda T, Shigematsu N, Furusawa Y, Durante M, George K, Wu H, Cucinotta FA: Induction of chromatin damage and distribution of isochromatid breaks in human fibroblast cells exposed to heavy ions. J Radiat Res 43: S169–S173 (2002).

Murray A, Hunt T: The cell cycle: an introduction (Freeman, New York 1993).

Napolitano M, Durante M, Grossi GF, Pugliese M, Gialanella G: Inactivation of C3H 10T1/2 cells by monoenergetic high LET alpha-particles. Int J Radiat Biol 61:813–820 (1992).

Raju MR, Eisen Y, Carpenter S, Inkret WC: Radiobiology of alpha particles. III. Cell inactivation by alpha-particle traversals of the cell nucleus. Radiat Res 128:204–209 (1991).

Ritter S, Kraft-Weyrather W, Scholz M, Kraft G: Induction of chromosome aberrations in mammalian cells after heavy ion exposure. Adv Space Res 12:119–125 (1992).

Ritter S, Nasonova E, Kraft-Weyrather W, Kraft G: Comparison of chromosomal damage induced by X-rays Ar ions with an LET of 1840 keV/μm in G1-phase V79 cells. Int J Radiat Biol 69:155–166 (1996).

Suzuki K, Suzuki M, Nakano K, Kaneko I, Watanabe M: Analysis of chromatid damage in G2 phase induced by heavy ions and X-rays. Int J Radiat Biol 58:781–789 (1990).

Suzuki M, Watanabe M, Suzuki K, Nakano K, Kaneko I: Neoplastic cell transformation by heavy ions. Radiat Res 120:468–476 (1989).

Suzuki M, Piao C, Hall EJ, Hei TK: Cell killing and chromatid damage in primary human bronchial epithelial cells irradiated with accelerated 56Fe ions. Radiat Res 155:432–439 (2001)

Thacker J, Stretch A, Stevens MA: Mutation and inactivation of cultured mammalian cells exposed to beams of accelerated heavy ions. II. Chinese hamster V79 cells. Int J Radiat Biol 36:137–148 (1979).

Tsuboi K, Yang TC, Chen DJ: Charged-particle mutagenesis. 1. Cytotoxic and mutagenic effects of high-LET charged iron particles on human skin fibroblasts. Radiat Res 129:171–176 (1992).

Vral A, Thierens H, Baeyens A, De Ridder L: Induction and disappearance of G2 chromatid breaks in lymphocytes after low doses of low-LET gamma-rays and high-LET fast neutrons. Int J Radiat Biol 78: 249–257 (2002).

Yang TC, Graise LM, Mei M, Tobias CA: Neoplastic cell transformation by heavy charged particles. Radiat Res 8:S177–S187 (1985).

Available online at www.sciencedirect.com

SCIENCE DIRECT

Gynecologic Oncology 96 (2005) 335–340

Gynecologic Oncology

www.elsevier.com/locate/ygyno

Postoperative pelvic radiotherapy for cervical cancer patients with positive parametrial invasion

Takashi Uno[a,*], Hisao Ito[a], Koichi Isobe[a], Yuko Kaneyasu[b], Naotake Tanaka[c], Akira Mitsuhashi[c], Kiyomi Suzuka[c], Koji Yamazawa[c], Naoyuki Shigematsu[d], Jun Itami[e]

[a]*Department of Radiology, Chiba University, Graduate School of Medicine, Inohana 1-8-1, Chuou-ku, Chiba City, Chiba 260-8670, Japan*
[b]*Department of Radiology, Hiroshima University, Hiroshima, Japan*
[c]*Department of Obstetrics and Gynecology, Chiba University, Graduate School of Medicine, Chiba, Japan*
[d]*Department of Radiology, Keio University, School of Medicine, Tokyo, Japan*
[e]*Department of Radiation Therapy, International Medical Center of Japan, Tokyo, Japan*

Received 20 January 2004
Available online 13 November 2004

Abstract

Objective. To evaluate patterns of failure in cervical cancer patients with histopathologic parametrial invasion treated with postoperative pelvic radiation therapy.

Methods. Records of 117 stages IB–IIB cervical cancer patients with parametrial invasion treated with postoperative radiation therapy from 1985 to 2002 were retrospectively reviewed. Patients were divided into two groups based on status of pelvic lymph nodes. Patterns of recurrence and prognosis by status of pelvic lymph nods were statistically analyzed.

Results. Status of pelvic lymph nodes had significant impact on both recurrence and survival. Extrapelvic recurrence was observed in 23 of 66 node-positive patients compared with 6 of 51 node-negative patients ($P = 0.005$). Of 66 patients with a positive pelvic lymph node, 18 developed visceral metastases, whereas only three visceral metastases were noted in the 51 node-negative patients ($P = 0.003$). Five-year overall survival in node-positive and -negative patients was 52% and 89%, respectively ($P = 0.0005$). Corresponding rates for recurrence-free survival were 44% and 83%, respectively ($P = 0.0002$). The correlation between nodal metastasis and prognosis was enhanced when node-positive patients were stratified into two groups based on number of positive nodes ($n = 1$ and $n \geq 2$). Five-year recurrence-free survival rates for patients with negative, one positive, and two or more positive nodes were 83%, 61%, and 31%, respectively ($P = 0.0001$).

Conclusions. Extrapelvic recurrence was uncommon in node-negative patients with parametrial invasion. These findings do not support use of systemic therapy for cervical cancer patients with parametrial invasion if pelvic lymph node metastasis is negative.

Keywords: Cervical cancer; Parametrial invasion; Lymph node; Postoperative radiation therapy

Introduction

Adjuvant therapies for women with International Federation of Gynecology and Obstetrics (FIGO) stage IIB cervical cancer have not been widely examined in Western countries because these patients have mainly been treated initially with radical radiotherapy. On the other hand, in Japan, stage IIB cervical cancer patients have been predominantly treated surgically and receive postoperative adjuvant pelvic irradiation if histopathologic examination confirms parametrial involvement. Eligibility criteria of a recent clinical study for IB–IIA disease (which showed a positive survival effect for adjuvant concurrent cisplatin-based chemotherapy and radiation therapy) included parametrial tumor invasion [1]. Thus, it is now recommended that patients with parametrial invasion should receive postoperative concurrent chemotherapy and pelvic radiation therapy. However, this group of patients consists of those with and without pelvic lymph node metastasis. Status of

* Corresponding author. Fax: +81 43 226 2101.
E-mail address: unotakas@ho.chiba-u.ac.jp (T. Uno).

0090-8258/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.ygyno.2004.09.061

pelvic lymph nodes is considered to be one of the most important prognosticators [2–7]. In addition, it is still unclear whether patients with all stages and extents of disease equally benefit from chemotherapy. Therefore, it is still unknown whether this heterogeneous patient group should be uniformly treated with concurrent chemoradiation. Results of our previous study, which included 45 patients with pathologic T2b (pT2b) disease by TNM classification, showed that lymph node status had an obvious impact on development of distant metastasis [8] and thus did not support use of chemotherapy for patients without lymph node metastasis. In order to examine this issue further, in the current study, we reevaluated patterns of failure in stages IB–IIB cervical cancer patients with histopathologic parametrial invasion treated with postoperative pelvic radiotherapy in a larger patient group. The main objective of the present study was to validate or refute our previous speculation that status of pelvic lymph nodes determines the recurrence pattern in patients with parametrial invasion.

Patients and methods

Between April, 1985, and March, 2002, 327 patients with FIGO IB-IIB carcinoma of the cervix received postoperative pelvic radiotherapy at the Chiba University Hospital and three affiliated institutions. Eligibility criteria for the present study included (1) radiotherapy preceded by a class III radical hysterectomy with bilateral pelvic lymphadenectomy; (2) squamous cell carcinoma; (3) histopathologically confirmed parametrial invasion (pT2b); and (4) dose of pelvic radiotherapy ≥40 Gy. A total of 117 patients with pT2b uterine cervical cancer according to the UICC-TNM classification were entered into this study. Patient characteristics are shown in Table 1. Median age was 53 years (range, 27–79). Preoperative FIGO clinical stage was IB for 17 patients, IIA for 6, and IIB for 94. After surgery, a total of 66 patients (56%) were positive for pelvic lymph node metastasis, 8 of 17 (47%) stage IB patients, 4 of 6 (67%) stage IIA patients, and 54 of 94 (57%) stage IIB patients. Of the 66 node-positive patients, 29 had only one positive node and the remaining 37 had two or more positive nodes. A microscopically positive surgical margin was observed in 32 of 117 (27%) patients. The majority of patients were found to have some degree of lymph-vascular space invasion. The retrospective and multicenter nature of the current study placed some limitations on data available for analysis. In general, preoperative bimanual examination has been performed without any anesthesia in Japan, which limited findings for some patients, especially those for whom the exam was painful or otherwise difficult. In addition, preoperative work-up did not necessarily include magnetic resonance imaging (MRI), especially in the early part of the study period. Furthermore, lesion size was not always accurately cited in the pathology report and variability existed in the direction of sectioning for slide preparation. Thus, it was impossible to determine the greatest tumor diameter objectively. Patients with grossly positive nodes were not included in the present study. However, patients with questionable abnormalities by pelvic CT or those with unknown lymph node status before surgery were eligible.

Table 1
Patient characteristics

No. of patients	117
Age	
Median	53
Range	27–79
Clinical stage	
IB[a]	17
IIA	6
IIB	94
Surgical margin	
Negative	85
Positive	32
Lymph node metastasis	
Negative	51
Positive	66
Dose of irradiation (Gy)	
Median	50
Range	40–56

[a] Includes four patients with IB2 disease diagnosed after 1995.

The radiation therapy techniques have been described previously [8], and they were similar at each institution. In brief, patients were treated with 10–18 MV X-rays from a linear accelerator using anterior and posterior opposing techniques, with the fields encompassing the whole pelvis extending from the lower margin of the obturator foramen to the upper margin of the fifth lumbar vertebra and laterally to at least 1.5 cm outside of the true pelvis. After implementation of a computed tomography (CT) simulator with three-dimensional treatment planning system, patients were predominantly treated with four-field box technique. Anterior and posterior borders of the lateral fields were carefully determined based on preoperative diagnostic imaging studies such as CT and MRI, with an adequate coverage of the pelvic lymph node area and the primary tumor bed. Typically, the anterior margin was placed just anterior to the symphysis pubis and the posterior margin included the anterior aspect of the sacrum. No attempt was made to irradiate paraaortic lymph nodes. A fractional daily dose of 1.8–2.0 Gy at midpoint of the central axis or at beam intersection of central axes to a median total dose of 50 Gy (range, 40–56 Gy) was delivered. Patients with a microscopically positive surgical margin at the lateral parametrium could be treated with a boost field up to a dose of 60 Gy. Brachytherapy was applied for women with microscopic tumor cut-through at the vaginal stump at the discretion of the attending physician. In general, a prescribed dose of 500–1200 cGy at the submucosa 5 mm in one to two fractions was delivered by high-dose-rate machines. No patient received systemic chemotherapy

adjunctively. Only six node-positive patients who were treated after 1998 received weekly or daily cisplatin concurrently with pelvic radiotherapy.

Patients were followed every one to 3 months. Mean follow-up of surviving patients was 72 months (range, 6–237 months). Patients were, in general, examined clinically at 1- to 3-month intervals during the first 2 years, at 1- to 6-month intervals for the next 3 years, and yearly thereafter. The diagnosis of recurrence was predominantly based on clinical and radiological findings, with histological confirmation in cases of supraclavicular lymph node metastasis or central vaginal stump recurrence.

Sites of recurrent were divided into pelvis and extrapelvis. Pelvic recurrence was further divided into central and peripheral pelvic wall. Extrapelvic recurrence included paraaortic node recurrence as well as other sites such as supraclavicular lymph nodes and visceral recurrence. For analysis of recurrence pattern, only the site of the first failure, which emerged more than 1 month earlier than recurrence at any other site, was counted. Impact of clinical factors on development of recurrence was examined by chi-square test. A P value of less than 0.05 was considered statistically significant.

Overall survival (OS) was measured from date of surgery to death from any cause, with surviving patient follow-up data censored at the last contact date. OS and recurrence-free survival (RFS) were estimated using the method of Kaplan and Meier. Time-to-event distributions were compared using the log-rank test with a statistical significance level of 0.05. All estimated P values were two tailed. Late bladder and intestinal complications were graded according to the RTOG/EORTC late radiation morbidity scoring system [9]. Probability of developing leg edema was graded by LENT-SOMA scale [10] and was calculated actuarially. Patients who died of intercurrent disease without experiencing leg edema were censored at the time of death. In calculating leg edema rates, patients who developed pelvic recurrence were excluded.

Results

Patterns of recurrence and impact of clinical factors on recurrence

Thirty-five patients developed recurrent disease in a total of 40 sites. Pelvic recurrence developed in 10 patients, and extrapelvic recurrence developed in 29 patients. Four patients are counted in both categories because they developed recurrent disease in both pelvic and extrapelvic sites simultaneously. None of the clinical factors such as FIGO stage, surgical margin status, and pelvic node status influenced development of pelvic recurrence. Neither FIGO stage nor surgical margin status influenced development of extrapelvic recurrence. In contrast, pelvic node status had significant impact on development of extrapelvic recurrence. Sites of recurrence according to pelvic node status are shown in Table 2. Extrapelvic recurrence was observed in 23 of 66 (35%) node-positive patients as opposed to 6 of 51 (12%) node-negative patients ($P = 0.005$). Notably, 18 of 66 (27%) patients with a positive pelvic lymph node developed visceral metastases, whereas only three visceral metastases were noted in 51 node-negative patients (6%) ($P = 0.003$).

Survival and clinical factors

The 5-year OS and RFS rates for all patients were 69% and 61%, respectively. Surgical margin status did not influence either OS or RFS. Clinical FIGO stage (IB–IIA vs. IIB) had marginal impact on both OS and RFS. Five-year OS rates were 80% and 66% in patients with IB–IIA and IIB disease, respectively ($P = 0.056$). Corresponding figures for RFS were 77% and 58% ($P = 0.067$). Pelvic lymph node metastasis had an obvious impact on both OS and RFS. Five-year OS rates for patients with and without pelvic lymph node metastasis were 52% and 89%, respectively (Fig. 1, $P = 0.0005$). Corresponding figures for RFS were 44% and 83% ($P = 0.0002$). This correlation between status of pelvic lymph nodes and prognosis was enhanced when node-positive patients were classified into two groups based on number of positive nodes ($n = 1$ or $n \geq 2$). Five-year RFS rates for patients with negative, one positive, and two or more positive lymph nodes were 83%, 61%, and 31%, respectively (Fig. 2, $P = 0.0001$). Corresponding figures for OS were 89%, 61%, and 46%, respectively ($P = 0.0011$).

Toxicity

No patient developed a severe life-threatening complication that required surgical intervention during radiotherapy. As for late bladder complications, grade 2 complications were observed in three patients and a grade 3 complication in one patient. Grade 2 intestinal complications requiring conservative treatment occurred in three patients. Grade 3 intestinal complications requiring surgical intervention occurred in two patients. Use of brachytherapy did not influence development of complications. The most

Table 2
Sites of recurrence based on status of pelvic lymph nodes

Node status	Pelvis		Extrapelvis		Total
	Central	Peripheral	PAN	Visceral recurrence	
Negative ($n = 51$)	1	3[a]	3	3	10
Positive ($n = 66$)	2[a]	4[b]	6	18[c]	30
Total	3	7	9	21	40

PAN, paraaortic lymph nodes.
[a] One patient had simultaneous extrapelvic recurrence.
[b] Two patients had simultaneous extrapelvic recurrence.
[c] One patient also had PAN metastasis.

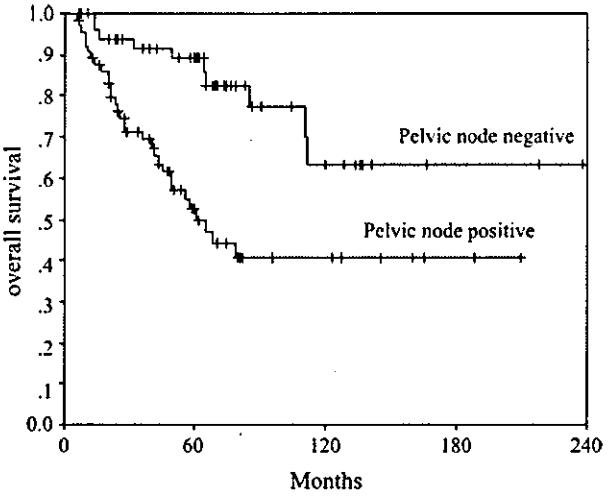

Fig. 1. Kaplan–Meier estimates of overall survival for cervical cancer patients with parametrial invasion based on status of pelvic lymph nodes.

common complication was lymphedema. Because of limitations due to this study's multi-institution retrospective setting, leg edema could be assessed in only 57 patients. Of those, 12 patients developed leg lymphedema with symptomatic edema (grade 2) in four patients and secondary dysfunction (grade 3) in eight. The actuarial probability of suffering leg edema at 3 years was 26%.

Discussion

Women with FIGO stage IIB cervical cancer are considered to have advanced lesions. Even if they can be surgically treated, postoperative histological examination typically reveals various risk factors for recurrence that mandate additional local and/or systemic therapies for the majority of cases. The Milan trial, which compared survival outcome for patients with stages IB–IIA cervical cancer randomized to radiation or radical surgery with selective adjuvant postoperative radiotherapy, showed that the rate of late complications was highest among patients undergoing combined modality therapy with identical survival outcome. Patients staged greater than IIA are not candidates for initial surgery in the United States and Europe because the majority will need postoperative radiotherapy that increases the probability of developing late complications. However, initial surgery for IIB disease is the usual practice in Japan and we believe this practice pattern will continue. Because Japanese women present first at gynecologic clinics, it is gynecologists in most institutions who determine treatment strategy without additional input from radiation oncologists. Most gynecologists consider surgical treatment to be superior to radiotherapy; as a result, the majority of patients with stage IIB cervical cancer have been treated with radical hysterectomy and lymphadenectomy. These patients have also typically received postoperative pelvic irradiation if histopathological examination confirmed pT2b disease or other risk factors.

The concept of postoperative pelvic radiotherapy, therefore, is quite different between the United States/Europe and Japan. In the United States/Europe, postoperative radiotherapy means "adjuvant pelvic radiotherapy for completely resected stages IB–IIA disease" whereas, in Japan, it simply means "radiotherapy after surgery." Thus, most Japanese postoperative studies include patients with initial FIGO stage IIB disease, for whom initial chemoradiation is now the treatment of choice in the United States/Europe. Comparison of the two different approaches, initial chemoradiotherapy versus surgery followed by adjuvant radiotherapy, is beyond the scope of the present study. One benefit of the latter strategy is that surgical lymph node staging might select the subpopulation of patients who can safely skip chemotherapy.

Based on five recent randomized trials, it has become increasingly clear that concurrent chemoradiation is more effective than radiation alone for most clinical stages of cervical cancer [1,11–14]. Concurrent cisplatin-based chemotherapy with radiation therapy has become the standard of care in advanced cervical cancer and a standard for some patients receiving adjuvant therapy after initial surgery. Eligibility criteria of the adjuvant chemoradiation trial included parametrial invasion [1]. Results of that study suggest that patients with parametrial invasion should undergo postoperative concurrent chemotherapy and pelvic radiation therapy. In the present study, extrapelvic recurrence was dominant in patients with positive pelvic lymph nodes. Thus, systemic therapy should be offered for patients with node-positive pT2b disease.

Many investigators have shown that survival after radical hysterectomy is affected by lymph node status [2–7]. Patients with positive pelvic lymph nodes were placed in the high-risk group in the Gynecologic Oncology Group (GOG) study. Despite the finding that extrapelvic recurrences were dominant in the node-positive group, this did not translate into a decreased survival outcome in our

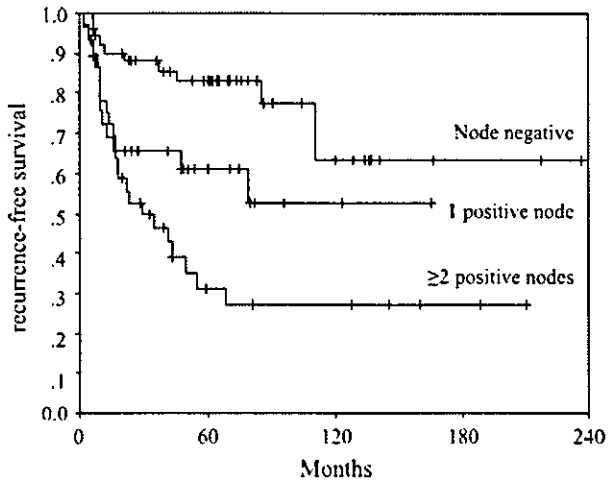

Fig. 2. Kaplan–Meier estimates of recurrence-free survival for patients with negative, one positive, or two or more positive pelvic lymph nodes.

previous study, probably due to the small number of patients [8]. In the present study, which had a larger patient population, pelvic lymph node metastasis had a significant impact on both OS and RFS. There are other primary tumor-related risk factors such as lesion size, depth of stromal invasion, and capillary-lymphatic space invasion. Thomas and Dembo postulated that women with negative nodes but primary tumor-related poor prognostic factors were more likely to develop recurrent disease in the pelvis and therefore might benefit from pelvic irradiation [15]. The randomized study conducted by the GOG demonstrated the efficacy of postoperative pelvic irradiation for patients with IB disease with tumor-related pathologic risk factors other than pelvic lymph node metastasis [16]. Two-year recurrence-free rate in the study was 88% in patients who received pelvic radiotherapy compared with 79% in the surgery alone group ($P = 0.008$). In the present study, only 10 patients developed pelvic recurrence. Although the majority of patients belonged to stage IIB, pelvic control in the present study appears to be identical with findings from other studies that mainly treated patients with stages IB–IIA lesions [1,16–20]. According to the GOG criteria, all node-negative patients in the present study can be allocated to the intermediate-risk group. Therefore, it may be a reasonable extrapolation that adjuvant pelvic irradiation effectively reduces the number of recurrences in women with node-negative pT2b disease. The present results suggest that parametrial invasion per se is not a definitive indication for combined systemic chemotherapy and radiotherapy. Only 6 of 51 node-negative patients developed extrapelvic recurrence as opposed to 23 of 66 node-positive patients. Notably, only 3 of 51 node-negative patients developed visceral metastases. From these data, it appears that parametrial involvement without pelvic lymph node metastasis should not be overestimated as a risk factor for recurrence outside the pelvis. Because the superiority of combined modality therapy in the adjuvant setting was mainly demonstrated in patients with stages IB–IIA disease with lymph node metastasis, there are no relevant data for IIB disease treated with initial radical surgery. Treatment strategies for histopathologically confirmed parametrial invasion in several Eastern countries such as Japan, where patients with IIB cervical cancer are predominantly treated with initial surgery, require further investigation. Results of the present study suggest that adjuvant therapy for pT2b should be tailored according to pathological lymph node status, although this should be confirmed with a prospective study.

In conclusion, the results of the present study strongly support the use of concurrent chemoradiation in node-positive pT2b patients. However, the role of systemic chemotherapy for patients without lymph node metastasis remains questionable. For patients with parametrial involvement without lymph node metastasis, postoperative pelvic radiotherapy can offer both sufficient pelvic control and survival.

References

[1] Peters III WA, Liu PY, Barrett II RJ, Gordon Jr W, Stock R, Barek JF, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000;18:1606–13.

[2] Fuller AF, Elliott N, Kosloff C, Hoskins WJ, Lewis Jr JL. Determinants of increased risk for recurrence in patients undergoing radical hysterectomy for stage IB and IIA carcinoma of the cervix. Gynecol Oncol 1989;33:34–9.

[3] Piver MS, Chung WS. Prognostic significance of cervical lesion size and pelvic node metastasis in cervical carcinoma. Obstet Gynecol 1975;46:507–10.

[4] Sevin BU, Lu Y, Bloch DA, Nadji M, Koechli OR, Averette HE. Surgically defined prognostic parameters in patients with early cervical carcinoma. A multivariate survival tree analysis. Cancer 1996;78:1438–46.

[5] Snijders-Keilholz A, Hellebrekers BW, Zwinderman AH, van de Vijver MJ, Trimbos JB. Adjuvant radiotherapy following radical hysterectomy for patients with early-stage cervical carcinoma (1984–1996). Radiother Oncol 1999;51:161–7.

[6] Soisson AP, Soper JT, Claarke-Pearson DL, Berchuck A, Montana G, Creasman WT. Adjuvant radiotherapy following radical hysterectomy for patients with stage IB and IIA cervical cancer. Gynecol Oncol 1990;37:390–5.

[7] Stock RG, Chen AS, Flickingeer JC, Kalnicki S, Seski J. Node-positive cervical cancer: impact of pelvic irradiation and patterns of failure. Int J Radiat Oncol Biol Phys 1995;31:31–6.

[8] Uno T, Ito H, Itami J, Sato T, Minoura S, Yasuda S, et al. Adjuvant pelvic irradiation in patients with pathologic T2b carcinoma of the cervix. Int J Gynecol Cancer 2001;12:187–91.

[9] Perez CA, Brady LW. Quantification of treatment toxicity. In: Perez CA, Brady LW, editors. Principles and Practice of Radiation Oncology. Second ed. Philadelphia: JB Lippincott; 1992 p. 51–5.

[10] LENT/SOMA tables. Radiother Oncol 1995;35:17–60.

[11] Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. N Engl J Med 1999;340:1154–61.

[12] Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. N Engl J Med 1999;340:1137–43.

[13] Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999;340:1144–53.

[14] Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler Jr WC, et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stages IIB–IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group Study. J Clin Oncol 1999;17:1339–48.

[15] Thomas GM, Dembo AJ. Is there a role for adjuvant pelvic radiotherapy after radical hysterectomy in early stage cervical cancer. Int J Gynecol Cancer 1991;1:1–8.

[16] Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group Study. Gynecol Oncol 1999;73:177–83.

[17] Hart K, Han I, Deppe G, Malviya V, Malone Jr. J, Christenseen C, et al. Postoperative radiation for cervical cancer with pathologic risk factors. Int J Radiat Oncol Biol Phys 1997;37:833–8.

[18] Lai CH, Hong JH, Hsueh S, Ng KK, Chang TC, Tseng CJ, et al. Preoperative prognostic variables and the impact of postoperative