表1　乳房切除後照射としての胸壁照射の方法

	1995~1997年	1999~2001年
1回線量の中央値（Gy）	2.0	2.0
総線量の中央値（Gy）	48	49
線質（6MV以下）	89 %	92 %
楔フィルタの使用頻度	23 %	20 %
ボーラスの使用頻度	13 %	3.6%
追加照射の施行率	9.6%	10 %

は改善傾向にあるが，いまだ6割以上の症例で固定具が使用されずに放射線治療が行われていた．

一方，1回線量や総線量，X線のエネルギー，楔フィルタの使用頻度，追加照射の施行率に関しては大きな変化は見られなかった（表1）．

3. 考　察

一般的に，診療ガイドラインは科学的根拠に基づくガイドラインと，コンセンサスを中心に作られるガイドラインとの二つに分けられる．2005年に日本乳癌学会が発表した乳癌診療ガイドラインは科学的根拠に基づくガイドラインとして作成されているため，わが国の現状を十分に反映しているものとは言えず，あくまでも信頼性の高いランダム化比較試験の結果やASCOのガイドラインなどを根拠に作成されている．わが国のガイドラインでも，ASCOのガイドライン同様に病理学的腋窩リンパ節4個以上を有する症例や局所進行期（T3，またはT4）である症例には術後照射を行うことが推奨されている．しかし，わが国の現状を顧みると，多くの外科医は乳房切除術後の胸壁再発の頻度の低さを考慮し，術後の放射線治療を省略する傾向が強い．一般臨床の現場と海外のエビデンスとの大きな開きが生じており，この乖離を解消するための何らかの処置が必要であると考えられる．わが国においても乳房切除術後の照射の意義を確認するランダム化比較試験を行うことも解決策のようにも思われるが，その結果が海外の結果と相反するものであった場合の解釈の仕方，また1,000例以上を要する前向き試験を組むことの困難さ，また生存率の向上が証明されている現在の状況において，非照射群に割り当てられる患者への倫理的配慮など，比較試験を実行するためには多くのハードルを越えなければならない．それよりは，遡及的解析とはなるが乳房切除術が施行され術後照射が行われなかった高リスク群の症例を大規模に調査し，わが国における非照射例の胸壁再発の頻度を求めていくのも一つの打開策となるかもしれない．

照射部位に関しては現在推奨されるものに近づきつつあるものの，胸壁および鎖骨上窩，傍胸骨リンパ節領域といった複数箇所を照射することは高い精度の放射線治療が要求される．しかし，安全性や有効性を確保するために必須と考えられる線量分布図を用いた評価が行われている症例が半数以下である現状は大きな問題と言わざるを得ない．米国においても全ての症例に三次元治療計画が行われているわけではないが，照射野中心面での線量分布図の作成（二次元での評価）はほぼ全ての症例で行われている[9]．今回は，線量分布図を用いた評価がなされた頻度を解析することでわが国の放射線治療の問題点を明らかにしたが，これ以外にも治療計画の際に肺や心臓といったリスク臓器への線量を低減させる配慮がなされているかを詳細に検討していく必要がある．1990年代までの臨床試験で乳房切除後照射の有効性を証明できなかった理由の一つとして，遅発性有害事象としての心毒性が多く発生したことが上げられている[1]．個々の症例の照射野や治療計画の内容を検討することが必要と考えられるが，膨大な資料のレビューとなりモニタリングに要する作業量の増加が懸念されることや，収集したデータをどう定量的に評価するかなどの問題も解決しなければならない．

また，単に診療の過程をモニタリングしていくだけではなく，改善の糸口を見つけ現実のものにしていかなければならない．例えば，患者の体位保持のための固定具も良い例である．日々の照射の際に重要となる照射野の再現性の問題を解決するための治具として患者固定具は重要である．使用率向上のためには，医療従事者の固定具の必要性に関する認識と，経済的支援の両方が必要である．固定具は比較的高価なものであり，それ自体

が病院収入を上げる機器ではないため，個々の施設で新たな予算立てが組まれることは困難な状況であり，大型機器の更新に併せての購入が最も良い機会となる．しかし，大型機器の購入は十数年に一度の機会であり，固定具の普及にもかなりの時間がかかる．補助金制度の導入や，診療保険制度への組み込みを行い，固定具使用による診療報酬の加算や使用しない場合の減点などにより各施設が固定具の購入を行いやすい方策を練る必要があるものと思われる．また，安全で有効な放射線治療を実現するためには，放射線腫瘍医の他に，放射線技師，物理士，品質管理士といった専門性の高い医療従事者の充実と，装置および周辺機器の整備が大きな鍵を握る．

今回は触れなかったが，複数の照射野を組み合わせる技術面（特に接合面）の問題点も，有害事象を減らすためには重要なポイントとなる．また，装置の日々の品質管理なども問題となるが，今回の調査では十分にまだ把握できていない．さらに，本調査の問題点としては，調査の対象規準を乳房温存療法と同じにしているため，多発病巣やびまん性の病変など乳房切除術が本来第一選択となる症例が一部調査から漏れている．これまでのわれわれが行ってきた乳癌診療における調査は，乳房温存療法と乳房切除後照射を同一規準でサンプリングしてきた．今後，わが国の診療ガイドラインが普及するにつれ徐々に乳房切除後照射の行われる症例が増えることが予想される．次回からの調査に当たっては，乳房温存療法施行例と同一の規準でデータ収集するのではなく，乳房切除後照射を行った症例の適格規準と除外規準を設けて乳房切除後照射を施行した症例の全体像が把握できるようにしなければならない．さらに，臨床的に把握しておくことが重要である事項に関しては適切なサンプルサイズを算出することも重要な課題となる．

海外の高い信頼性のエビデンスが報告され，徐々にわが国の診療にも変化が見られていることが伺えた．しかし，胸壁および領域リンパ節への放射線治療は緻密な放射線治療技術が要求されるものであり，安全な照射技術の向上が伴わない安易な知識の輸入は患者に不利益を与える可能性があり早急な是正が必要である．学会や研究会を通じて技術講習会を開くなど何らかの打開策を取らなければならない．また，機器の整備に当たっては診療報酬制度への働きかけなども重要となろう．近年，化学療法の進歩に伴い，進行期例の生命予後の改善が報告される現状の中，放射線治療が足を引っ張ることがないよう診療レベルの向上を顧ってやまない．

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胃悪性リンパ腫における照射方法の検討

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RADIATION TREATMENT PLANNING FOR GASTRIC LYMPHOMA

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Abstract: Purpose: To examine the methods of radiation treatment planning for gastric lymphoma.
Materials and Methods: Twenty-six patients who underwent radiotherapy for gastric lymphoma between February 2000 and April 2005 were included in the study. Radiation doses were 30–40.5 Gy (median: 30) with a daily fraction size of 1.5 Gy. We considered that the volume irradiated with 20 Gy or more in the bilateral kidneys (K-V20) may be reduced to 50% or less. Anterior-posterior/posterior-anterior parallel-opposed fields (AP/PA) were compared retrospectively with the 4-field technique in 12 patients whose simulation data could be reconstructed in the radiation treatment planning system.
Results: Twenty-four patients were treated with AP/PA, one patient with 4-field and one patient with 3-field. The predefined rules in margin-setting were not observed in 7 patients (27%) to reduce the irradiated volume of the kidney. Twenty-two patients achieved complete remission, and the overall 2-year survival rate was 95%. No late adverse events were seen. Our retrospective comparison of AP/PA with the 4-field technique in the radiation planning system indicated that K-V20 became more than 50% in 4 patients treated with AP/PA, but in none of those treated with the 4-field technique. In all 8 patients with K-V20 of less than 50% with AP/PA, the caudal side of the stomach was located above the mid-slice of the left kidney on abdominal CT.
Conclusion: The outcome of gastric lymphoma after radiotherapy is excellent. When the position of the stomach is low relative to that of the left kidney, the 3D-based 4-field technique may allow realization of optimal radiation therapy ensuring sufficient margins of the target and increased safety for the kidney.

Key words: Gastric Lymphoma, Radiation therapy, Toxicity

はじめに

胃悪性リンパ腫は，消化管原発悪性リンパ腫の中で最も発生頻度が高い．組織型の多くは，いわゆるMALT（mucosa associated lymphoid tissue）リンパ腫，もしくはdiffuse large B-cell lymphoma（DLBCL）であり，過去の報告における両者の発生頻度は，ほぼ同等である[1)-2)]．低悪性度リンパ腫であるMALTリンパ腫と中・高悪性度リンパ腫であるDLBCLでは，異なった治療戦略がとられる．一般に限局期悪性リンパ腫に対する治療においては，化学療法と放射線治療が中心的な役割を担っているが[3)]，限局期胃原発MALTリンパ腫においては，局所療法として手術が行われてきた[4)]．しかし，Helicobacter pyloriの除菌により60～90％の症例で完全寛解を得られることが報告され[5)]，感染例には第一に除菌療法が行われるようになった．また，放射線治療による高い治療効果と安全性が報告され[6)]，除菌無効例，もしくは非感染例においては，放射線治療が有効な治療選択肢の１つとなっている．DLBCLに対しても，化学療法と放射線治療による保存的治療が多く試みられており，良好な成績が報告されている[7)-8)]．胃悪性リンパ腫に対する照射では，現在のところ，胃癌の放射線治療を参考にした照射方法が広く行われており[7)-9)]，X線シミュレータを用いて治療計画を行う前後対向２門照射法が主として用いられてきた．この際，胃の位置が日々異なることや，呼吸性移動などを考慮すると，確実に胃全体を照射野内に収めるためには十分な照射野マージンをつけることが必要であるが，腎臓への線量を考慮すると，十分な照射野マージンをとることが困難であることをしばしば経験する．今回われわれは，過去に行った胃悪性リンパ腫に対する根治的放射線治療における治療成績を検討するとともに，マージンの取り方やリスク臓器との関係を中心に照射野を再検討した．

対象と方法

当院において，2000年２月から2005年４月までに限局期胃原発悪性リンパ腫に対し放射線治療を行った26例を対象とした（Table 1）．Lugano staging system for gastrointestinal lymphomas[10)] に基づいて病期分類を行った．７例には，前治療としてCHOP療法（cyclophosphamide, doxorubicin, vincristine, predonisone）を３～６サイクル（中央値：６）行った．放射線治療は10 MVの超高圧X線を用い，１回線

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Table 1 Patients background

Age		45-80 (median: 69)
Gender		
male		16
Female		10
Stage		
I		21
II1		5
Histology		
	MALT lymphoma	20
	DLBCL	3
	MALT with DLBCL	3
Chemotherapy		
	CHOP	7

MALT: mucosa associated lymphoid tissue
DLBCL: diffuse large B-cell lymphoma
CHOP: cyclophosphamide, doxorubicin, vincristine, prednisone

量1.5 Gyで総線量30～40.5 Gy（中央値 30）を週 5 回の通常分割法にて投与した．MALTリンパ腫では30 Gyまで，DLBCLでは30 Gyを照射した後，照射野を縮小して総線量40.5 Gyまで投与した．照射野設定においては，空腹の状態で200W／V%の濃度のバリウムを50 ml程度内服し，透視下にて描出された胃全体，および腫大したリンパ節を照射開始時のCTV（clinical target volume）とし，呼吸性移動を加味したITV（internal target volume）に，さらに 2 cmのマージンを付加したものをPTV（planning target volume）とした．縮小照射野においては，化学療法前のgross tumor volumeに呼吸性移動を加味したITVに更に2 cm程度のマージンを付加したものをPTVとした．線量評価点は，中心軸上の体厚中心点，もしくは中心軸上の各ビームの交点とした．両側腎において，20 Gy以上照射される体積の割合（K-V20）が50%を超えないようにし，肝においては，20 Gy以上が照射される体積の割合（L-V20），30 Gy以上が照射される体積の割合（L-V30）がそれぞれ67%，50%を超えないように配慮した[7),11),12)]．各症例において安静吸気ー呼気間の胃角部大弯側，および胃底部の移動距離を調査し，より大きい値をその症例の呼吸性移動とした．空腹の状態で照射するため，朝食前あるいは昼食前に治療を行うようにした．放射線治療開始日を観察開始日とし，あらゆる原因による死亡をイベントとした全生存率をKaplan-Meier法を用いて算出した．算出にはStatView version 5.0（SAS Institute Inc., 米国）を用いた．完全寛解が得られた症例のうち，再び胃病変が出現したもの，および非完全寛解例においては残存病変が再増大したものを局所の再燃と定義した．

次に 3 次元治療計画が行われた12例において，前後対向 1 門照射法と前後左右 4 門照射法をCT治療計画装置上でシミュレーションし，両者の比較を行った．この際CTVはCT画像上の胃全体とし，CTVに 2 cmのマージンを付加し，さらに呼吸性移動として頭尾方向に 1 cmを付加したものをPTVとした．前後対向 2 門照射法，前後左右 4 門照射法，いずれにおいても各ビームの線量配分は均等とした．照射線量は30 Gy / 20回とし，K-V20およびL-V20，L-V30を算出した．CTはスライス厚 2 mmあるいは 5 mmを用いて非呼吸停止下に撮影した．治療計画装置はCadplan version 6.4.7（Varian Medical Systems, 米国）およびEclipse version 6.5（Varian Medical Systems, 米国）を用いた．前後対向二門照射法，前後左右四門照射法におけるK-V20，L-V20，L-V30を算出し比較した．統計学的検定にはStatView version 5.0（SAS institute Inc., 米国）にてStudentのt検定を用いた．

Table 2 Fields and 2-cm margin observation

Applied fields	Observed	Not observed	Total
AP/PA	18	6	24
4 fields	0	1	1
3 fields	1	0	1
Total	19	7	26

AP/PA: anterior-posterior/posterior-anterior parallel-opposed fields

結　果

1．全26例の治療成績

26例中24例で，対向 2 門照射が行われた．また 1 例が 3 門照射，1 例が 4 門照射であった．全症例中 7 例（27%）において 2 cmのマージンを付加できなかった（Table 2）．この 7 例中 5 例において，左腎が右腎よりも照射野に入る容積が多かった．胃の呼吸性移動は4.0～0.7 cm（中央値：2）であった．K-V20が50%を明らかに超えていたと思われる症例は，1 例のみであった．26例中22例（85%）に，照射終了時の判定で完全寛解が得られた．2 例が部分寛解，2 例が治療効果判定不能であった．全症例において，経過観察期間中に重篤な有害事象は見られなかった．2 年全生存率は95%（95%信頼区間：85～100）であった，経過中 2 例に局所の再燃を認め，2 例とも手術が行われた，うち 1 例はその後の経過が不明，もう 1 例は 1 年後に不明死した．

2．前後対向 2 門照射法と前後左右 4 門照射法の比較

前後対向 2 門照射法，前後左右 4 門照射法（Fig. 1）におけるK-V20は，それぞれ13～92%（平均値±SD：40.9±27.0），1～24%（平均値±SD：7.7±6.7）であり，前後左右 4 門照射法において有意に低下した（<0.001）．前後対向 2 門照射法においては，12例中 4 例でK-V20が50%以上となったが，前後左右 4 門照射法においては，全例でK-V20が50%未満となった．前後対向 2 門照射法，前後左右 4 門照射法におけるL-V20は，それぞれ11～47%（平均値±SD：22.2±9.9），6～52%（平均値±SD：26.5±11.9）で

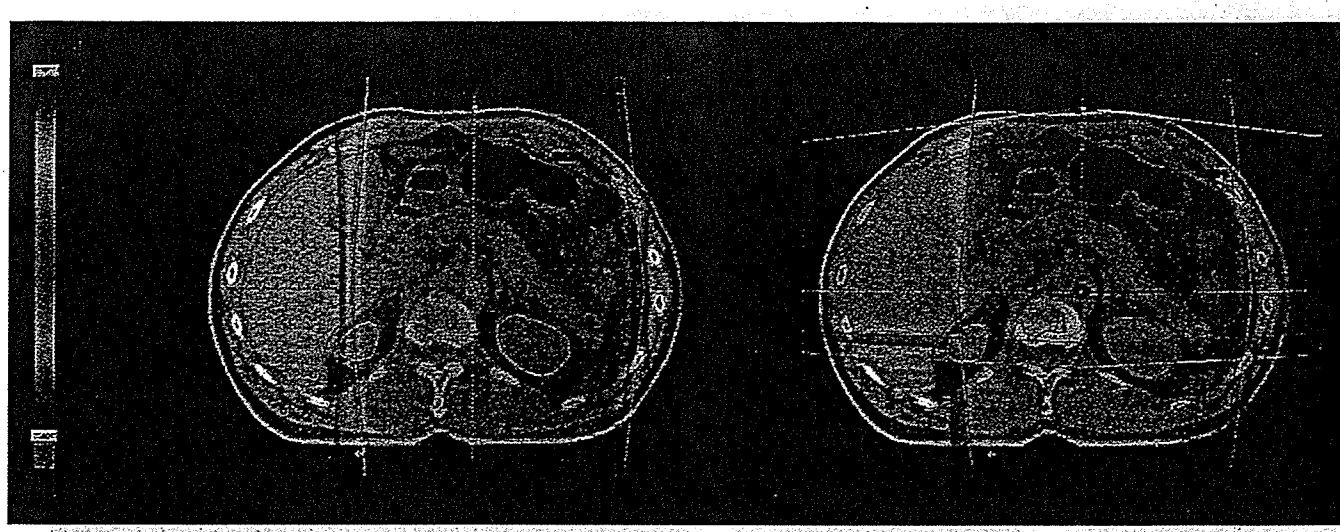

Fig. 1 An example of the dose distributions.
A: Anterior-posterior/posterior-anterior parallel-opposed fields.
B: Anterior-posterior/posterior-anterior/left-right/right-left fields.

A | B

あり，前後左右 4 門照射法において有意に上昇した（p=0.03）が，前後左右 4 門照射法におけるL-V20の中で67％を超えるものは見られなかった．前後対向 2 門照射法，前後左右 4 門照射法におけるL-V30は，それぞれ 0～12％（平均値±SD：5.7±3.4），3～17％（平均値±SD：9.3±4.4）であり，前後左右 4 門照射法において有意に上昇した（p=0.002）が，前後左右 4 門照射法におけるL-V20の中で，50％を超えるものは見られなかった（Table 3）．前後対向 2 門照射法にてK-V20が50％未満であった 8 例は，治療計画CTにおける胃の最尾側のスライス位置がいずれも左腎の中央より頭側であったが，K-V20が50％以上であった 4 例中 3 例は尾側に位置していた（Fig. 2）．

考　察

限局期胃原発悪性リンパ腫に対する放射線治療は，良好な治療成績が報告されており，われわれの結果も諸家の報告と同様に良好であった[6),8)]．また，観察期間中に重篤な合併症は生じていなかった．

この治療では，次の二つの条件を満たすことが重要である．それは標的臓器である胃全体に十分な線量を投与すること，リスク臓器への線量が耐容線量を超えないようにすることである．Ishikuraらは，胃原発DLBCLに対する化学放射線療法に関する第 2 相試験において前後対向 2 門照射法を採用しているが，この試験において，腎への線量をプロトコル規定値以下に抑制するため，39％の症例で，標的臓器に付加する照射野マージンに関して規定が遵守されなかったと報告している[7)]．われわれの検討でも，安全性を確保するため予定したマージンを十分付加できなかった症例が少なからず見受けられた．こうした問題に対応するため，3 次元治療計画に基づいた多門照射法が模索されている．Biancaらは，前後対向 2 門照射法におけるPTV内に腎が入る場合，前後左右 4 門照射法を用いることで，胃への十分な線量を保ちながら腎への線量を軽減できると報告している[2)]．われわれが治療計画装置上で行ったretrospectiveな検討においても，前後対向 2 門照射法では1/3 の症例でK-V20が50％以上となったが，前後左右 4 門照射法では，全例でK-V20が50％未満となっており，腎への線量を軽減する手段として，前後左右 4 門照射法は有用であると考える．

しかしながら，前後左右 4 門照射法では照射される肝の体積が増大するという欠点がある．胃原発のMALT リンパ

Table 3 Retrospective comparison of AP/PA and 4 fields in 12 patients on the radiation treatment planning system

Case	AP/PA			4 fields		
	K-V20	L-V20	L-V30	K-V20	L-V20	L-V30
1	15	27	4	7	33	7
2	37	28	12	14	36	17
3	57	17	6	12	21	9
4	13	28	6	7	33	12
5	48	17	5	24	25	13
6	86	11	1	5	15	4
7	34	19	9	1	6	14
8	20	11	3	4	15	6
9	22	47	7	1	52	3
10	52	24	9	5	29	13
11	92	23	0	11	28	7
12	15	15	6	1	25	7

AP/PA: anterior-posterior/posterior-anterior parallel-opposed fields
4—fields: anterior-posterior/posterior-anterior/left-right/right-left fields
K-V20: rate of volume irradiated with 20 Gy or more in the kidneys (%)
L-V20: rate of volume irradiated with 20 Gy or more in the liver (%)
L-V30: rate of volume irradiated with 30 Gy or more in the liver(%)

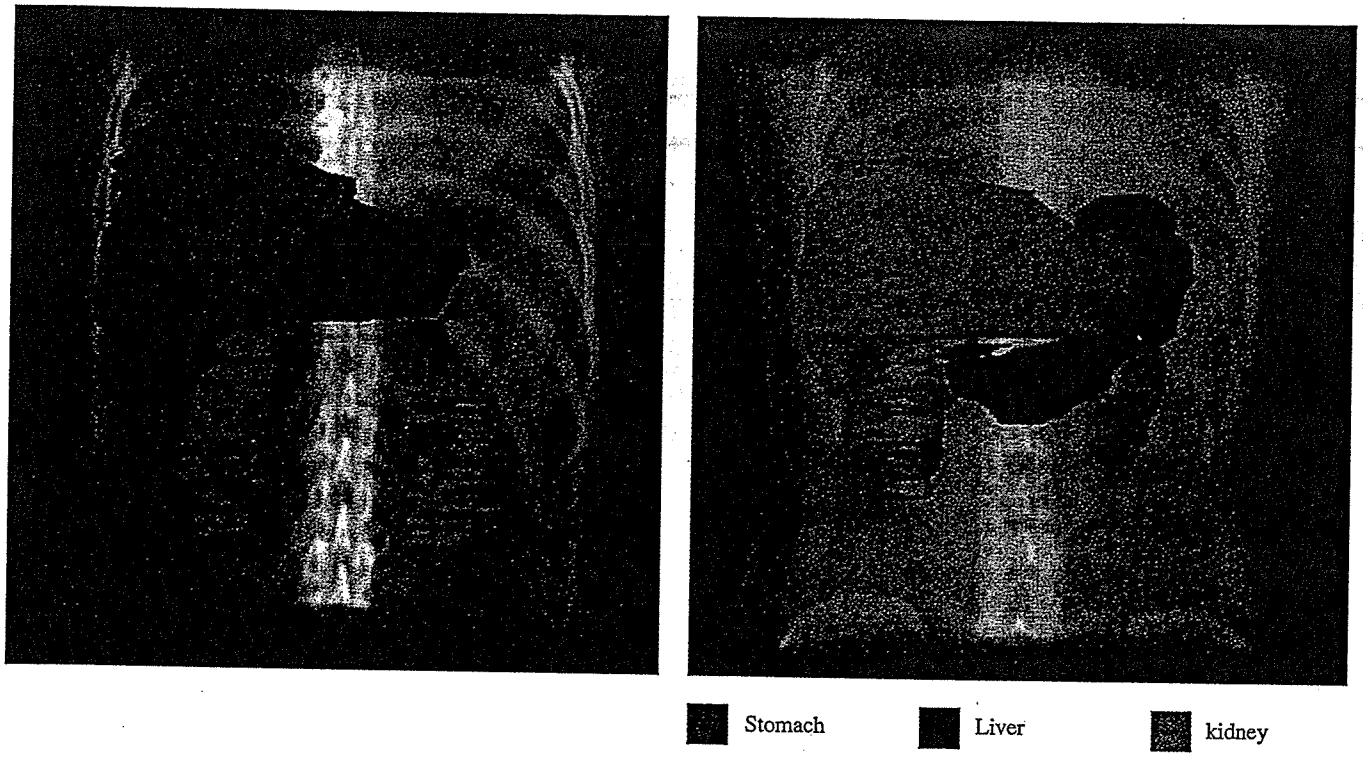

Fig. 2 Examples of the positions of the stomach and the risk organs.
A: The caudal side of the stomach was located above the mid-slice of the left kidney.
B: The caudal side of the stomach was located below the mid-slice of the left kidney.

腫に対する照射線量としては，30 Gy程度が一般的であり[4),12)-14)]，DLBCLの場合は，胃全体に30 Gy程度の照射を行った後に10 Gy程度のboost照射が加えられる[7),8)]．我々の結果からは，前後左右4門照射法を用いて胃全体へ30 Gy程度の照射を行っても，肝への照射線量が耐容線量を超える可能性は低いと考えられた[11)]．

Biancia ら[2)]は，胃と腎の位置関係が照射法を選択するうえにおいて重要であると述べている[2)]．彼らは，胃と腎が前後方向で重ならない場合は前後対向2門照射法を使用し，それ以外の場合は前後左右四門照射法を採用すべきであるとしている[2)]．この場合，前後対向2門照射法で治療される症例はごく一部に限られることになる．われわれの検討結果からは，CT上の胃の最尾側のスライス位置が左腎の中央よりも頭側に存在すれば，前後対向2門照射法でも安全に治療が行える可能性があり，前後対向2門照射法の適応は必ずしも胃と腎が前後方向で重ならない場合に限る必要はないと思われる．現在われわれの施設では，すべての患者で前後対向2門照射法，および前後左右4門照射法の3次元治療計画を作成し，双方のK-V20，L-V20，L-V30を比較して，実際行う照射方法を決定している．

胃に対する照射方法は他にも，さまざまな方法が考案されている．Tsang ら[2)]は，胃の頭側を前後対向2門照射法で，尾側を左右対向2門照射法で照射する方法を提唱しており，これによりリスク臓器である肝および腎への照射線量を低減できるとしている[12)]．

現在のところ，胃悪性リンパ腫に対する最適な照射方法は確立していない．しかし，3次元治療計画装置の発達により，さまざまな方法が実行可能となっている．今後，更なる研究により，胃悪性リンパ腫に対する放射線治療の最適化が望まれる．

結　論

胃悪性リンパ腫における放射線治療後の成績は良好であった．多くの症例では，前後対向2門照射法による対応が可能であったが，腎臓への線量を考慮し，約1/3の症例で照射野マージンの変更や多門照射法などの工夫が必要であった．胃の位置が左腎に対し相対的に低く，前後対向二門照射法が困難である場合，3次元治療計画に基づいた前後左右4門照射法を用いることで，十分なマージンを保ちつつ，腎への合併症を増加させない治療を行える可能性が示唆された．

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要旨:【目的】胃悪性リンパ腫に対する放射線治療後の治療成績を解析するとともに、照射方法を検討する。
【対象と方法】2000年2月から2005年4月までに限局期胃原発悪性リンパ腫にて放射線治療を行った26例を対象とした。放射線治療は一回線量1.5Gyにて30~40.5Gy(中央値30)が投与された。両側腎に20Gy以上の照射される体積の割合(K-V20)が50%以下となるように配慮した。また、3次元治療計画が行われた12例では前後対向2門照射法と前後左右4門照射法を用いた仮想の治療計画を立て、両照射法のK-V20の比較を行った。
【結果】26例中24例に前後対向2門照射、1例に前後左右4門照射、1例に3門照射が行われた。胃への線量を軽減するため、規定した照射野マージンを立てできなかった症例が7例(27%)見られた。照射は全例に22例が完全寛解し、全症例の2年全生存率は95%であった。臨床的に問題となる晩期有害事実はなかった。3次元治療計画で比較が可能であった12例のうち、前後対向2門法では4例においてK-V20が50%以上となったが、前後左右4門法においては全例でK-V20が50%未満となった。また、前後対向2門法にてK-V20が50%未満であった8例は、治療計画CTにおける胃の最尾側のスライス位置がいずれも左腎の中央より頭側であった。
【結論】放射線治療後の成績は良好であった。胃の位置が左腎の位置に対し相対的に低い場合、前後左右4門法を用いることで、十分な照射野マージンを保ちつつ、腎への線量を軽減した治療が可能と考えられた。

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Initial Experience with the Quality Assurance Program of Radiation Therapy on behalf of Japan Radiation Oncology Group (JAROG)

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Background: We evaluated the efficacy of our quality assurance (QA) program of radiation therapy (RT) in a prospective phase II study. This is the first description of the experience of the Japan Radiation Oncology Group (JAROG) with this program.
Methods: Clinical records, all diagnostic radiological films or color photos that depicted the extent of disease of 37 patients with stage IEA extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) were collected for review. Radiation therapy charts, simulation films or digitally reconstructed radiographs, portal films and isodose distributions at the central axis plan were also reviewed. All documents were digitally processed, mounted on Microsoft PowerPoint, and for security returned from researchers by mail in CD-ROM format. The QA committee members reviewed all documents centrally, utilizing the slide show functionality.
Results: All patients were prescribed their specified dose to the dose specification point in accordance with the protocol. Three patients were regarded as deviations, because of a smaller margin than that specified in the protocol ($n = 2$) or a prolonged overall treatment time ($n = 1$). No violations were observed in this study.
Conclusions: This is the first report with regard to the QA program in MALT lymphoma. We demonstrated that our QA program was simple and inexpensive. We also confirmed that the radiation oncologists in Japan adhered closely to the protocol guidelines.

Key words: MALT lymphoma – quality assurance – QA program – radiation therapy

INTRODUCTION

It has been estimated that about 170 thousand cancer patients will be treated with radiation therapy (RT) either as part of their primary treatment or in connection with recurrences or palliation in 2005 in Japan (1). It is anticipated that RT will play an increasingly important role because of the improvements of early detection of and screening for cancer. Furthermore, other factors will also prompt the use of RT: the trend toward less drastic organ-conserving surgery combined with adjuvant RT; the improvement in identification of patients with high risk of developing loco-regional recurrences following surgery; and the aging population of Japan. It is undeniable that the deleterious consequences of poor quality treatment contribute not only to the rise of complications but also to deterioration of outcomes. They also lead to both an increase in health care costs and a decrease in the

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quality of life. Thus, it has long been recognized that quality assurance (QA) in RT is vital to guarantee provision of safe and effective treatments (2–12).

The Radiation Therapy Oncology Group (RTOG) and European Organisation for Research and Treatment of Cancer (EORTC) are the two largest working organizations presenting the models for the application of valid QA procedures in radiation oncology trials. Both organizations have funding for centralized data collection, inter-institutional dosimetry programs and regular site visits, utilizing medical, dosimetric and physics staff. For the data to be useful with regard to RT, a rigorous review process must be implemented to document the radiation used, volume irradiated, fraction size and dose delivered to comply with the designated therapeutic protocol. This is the most accurate way to confirm the uniformity of the treatment and usefulness of the outcome data.

The Japan Radiation Oncology Group (JAROG) conducted a QA program to guarantee the treatment quality of RT in a phase II study. This study evaluated the efficacy and toxicity of moderate dose RT for patients with extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma). In pursuing the project, the JAROG were faced with a difficult situation in order to ensure that the clinical and technical compliance to the specified protocol was satisfactory, without having the financial, structural or personnel resources to conduct a comprehensive clinical QA program. Thus, we developed a simple and less expensive computer based method to easily execute our QA program.

Our QA program was based on a central radiation oncological review of all patients' diagnostic imaging, color photographs and clinical findings. Additionally, an individual RT prescription for every patient was provided. All of these documents were digitally processed, and were mailed to researchers in CD-ROM format. The purpose of the present study was to assess the feasibility of such a procedure in multicenter trials and its impact on the definition of the extent of disease and patients' treatment among Japanese radiation oncologists. This is the first report describing the QA program in MALT lymphoma.

METHODS

Study Design

From April 2002 to November 2004, 37 eligible patients with stage IEA MALT lymphoma received RT. The protocol specified three different total doses of RT, which were dependent on the tumor location and its maximum diameter. Patients with orbital disease or those who had minimal residual disease after surgical removal received 30.6 Gy. Patients with tumors that were less than 6 cm received RT with 36 Gy, and those with ≥ 6 cm of disease were treated with 39.6 Gy. A fraction size was 1.8 Gy in every setting. The clinical target volume (CTV) was defined as an entire involved organ (orbit, thyroid, salivary gland, breast) or gross tumor volume (GTV) with a margin of at least 20 mm. We did not intend to treat the adjacent first echelon lymph node region. A lens shield was placed to prevent this except where the block compromised tumor coverage. Radiation doses were specified according to the report of ICRU 50. In electron beam therapy, doses were specified at the peak dose on the beam axis reached.

Procedure of Quality Assurance Program

Clinical records, all diagnostic radiological films or color photos that depicted the extent of disease of all patients were collected for review. Radiation therapy charts, simulation films or digitally reconstructed radiographs, and portal films were reviewed. In cases of patients who received electron beam RT, color photos demonstrating the treatment position in the treatment room were assessed. The isodose distributions at the central axis were also submitted for review. In addition to the evaluation of adherence of the protocol, an evaluation of the response assessment was examined by reviewing the clinical records, diagnostic radiological films and color photos. All documents were digitally processed, and mounted using Microsoft PowerPoint. Each researcher de-identified all materials before submission. Afterwards, each researcher returned the data via a CD-ROM, and the QA committee member reviewed it using the slide show functionality. The patient data was not delivered via the internet for reasons of security. Figure 1 shows an example of the PowerPoint template.

Our QA programs included evaluation of the fraction size, the elapsed days, the prescribed dose to the reference point, the relationship between GTV, CTV and radiation field, and the difference between simulation film and portal film. The isodose distributions were also examined as reference data.

Definition of Protocol Violations and Protocol Deviations

Protocol violations were defined as a fractional dose less than 1.5 Gy, a total dose to the reference point either <90% or >110% of the dose prescribed in the protocol, the incomplete coverage of GTV, and more than 1 cm of difference between simulation film and portal film. In addition, protocol deviations were defined as an overall treatment time either <three weeks or ≥six weeks, the difference between simulation film and portal film >5 mm, the field border <20 mm away from CTV, and a dose to the reference point either <95% or >105% of the dose prescribed in the protocol.

RESULTS

We held the QA committee meeting on 19 March 2005. There were no missing data for any patients, and all documents were of adequate quality for review. Table 1 shows the relationship between the RT technique and primary site.

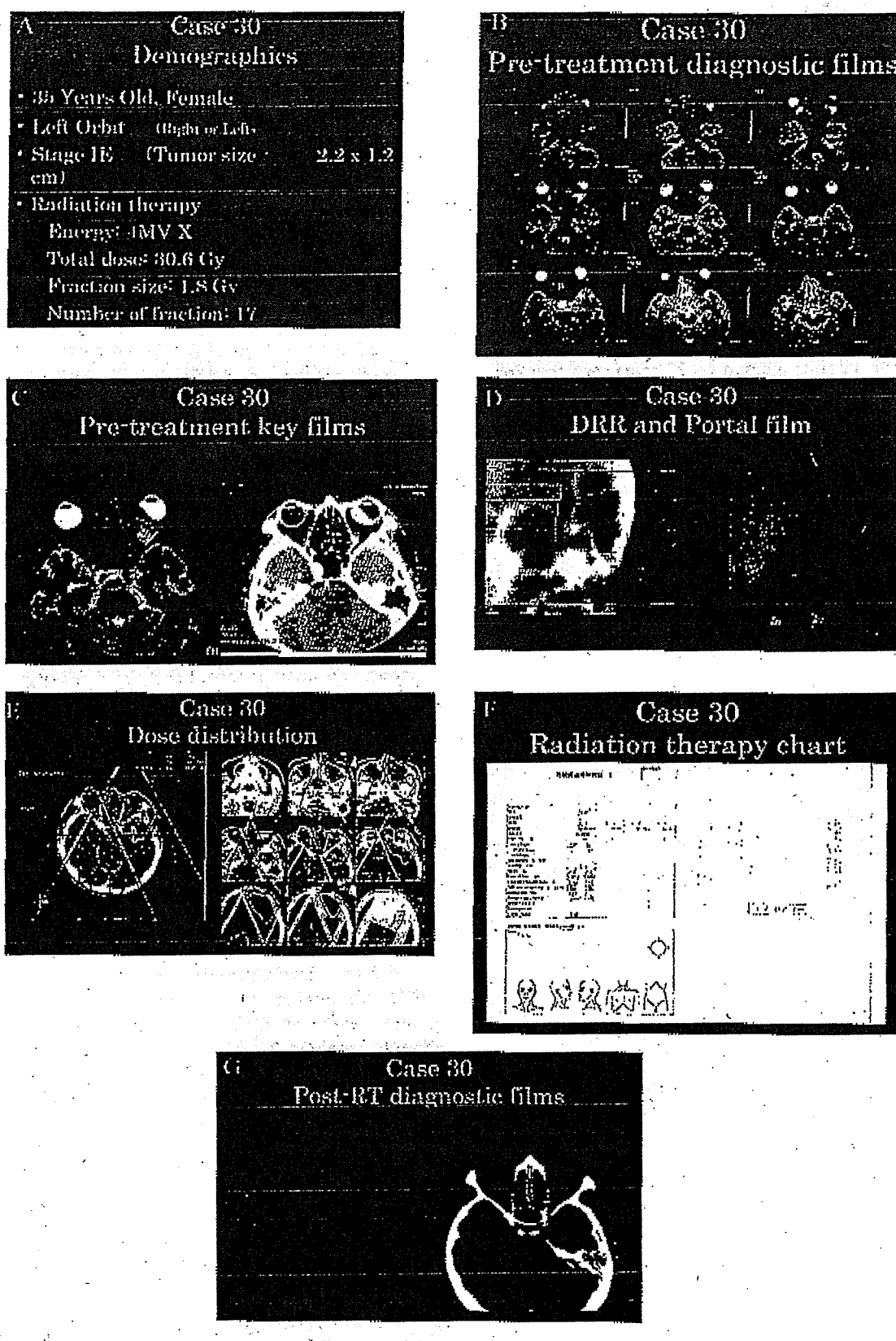

Figure 1. Examples are shown of the types of data that were used in this template. (A) a patient demographics, (B) pretreatment diagnostic films, (C) pretreatment key films, (D) digitally reconstructed radiograph (DRR) and portal film, (E) dose object, (F) radiation therapy chart, and (G) post treatment diagnostic films. The original documentation was written in Japanese. (Please note that a colour version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org).

The most common field arrangement was a single anterior–posterior field (41% of patients), and two oblique fields follow (30%). Two anterior–posterior or lateral opposing field techniques were employed in nine patients (24%). No patient received RT with a 3D conformal technique or intensity modulated radiation therapy (IMRT). All patients were prescribed their specified dose to the dose specification point in accordance with the protocol. No patients received RT with a fraction size other than 1.8 Gy. Only one patient required an overall treatment time more than 6 weeks, which was defined as deviation. The cause of this prolonged treatment time was merely personal. Adequate tumor coverage was achieved in 95% of the patients. Although CTV was covered enough in the treatment volume, the field border was placed with smaller margin (<20 mm) than that specified in the protocol in the remaining two patients. These two cases were defined as deviations. The isodose distributions at the central axis plan were acceptable in all patients. Overall, deviations were observed in three patients and the QA committee concluded that 92% of patients received RT as specified by the protocol. No protocol violations were observed in this study.

Because all documents were digitally processed in this study, the cost per patient, including CD-ROM and postage, was about ¥150 (i.e. about US$1.30). It took about an hour to prepare each patient data for review.

DISCUSSION

This report described our initial experience with a QA program in a multi-institutional prospective study. Our program is very simple and inexpensive. Ishikura et al. (13) investigated the quality of RT in a Japanese clinical trial and found that 60% of patients received less satisfactory RT in 2001. They extended their research to 2005 and demonstrated that protocol violation decreased dramatically to less than 5%. The early RTOG study also showed that the frequency of major and minor deviation was as high as between 60 and 70%. They reported that the appropriateness rate rose over time, because the participating radiation oncologists became familiar with the protocol (2). The Trans-Tasman Radiation Oncology Group (TROG) also demonstrated an improvement in QA over time (14). Our observation that 92% of patients received RT per protocol specification was very promising for the initial QA experience. In addition to the decrease of protocol violation over time, Halperin et al. (15) reported that institutional experiences affected the incidence of major deviations. RTOG also found that the QA performance was significantly better at principal centers compared with satellites. We were not able to assess institutional difference, because only three patients were judged as being a violation of protocol guidelines.

It has long been realized that the quality of treatment seriously affects the outcome of clinical trials. Several groups have evaluated the relationship between violation and staging, treatment strategies, and outcome. The German Hodgkin's Study Group (GHSG) evaluated the quality of RT for early stage HL (Hodgkin's lymphoma) and found that freedom from treatment failure (FFTF) was significantly influenced by the quality of RT. Those who received RT as per protocol obtained 82% of FFTF, and those with violation demonstrated only 70% of FFTF after five years (16). Furthermore, they observed that the disease extent recorded on the case report forms was significantly different from that shown on diagnostic CT, which resulted in a change of disease stage, treatment group allocations, and treatment volume (17,18). As these misinterpretations lead to protocol violations, they recommended an early central prospective review. Dieckmann and colleagues (19) also concluded that an up-front centralized review of patient data and consecutive set-up and delivery of individualized treatment proposals for every patient are feasible within a large multicenter trial involving pediatric HL.

However, two groups have concluded that violation did not lead to a detrimental treatment outcome. The EORTC 20884 trial evaluating the efficacy of involved field RT in patients with advanced HL demonstrated that 47% of patients received RT with major violation (20). However, their conclusion was that the outcome was not influenced by violation of the radiotherapy protocol. In another multicenter trial involving pediatric medulloblastoma, 57% of the fully evaluable patients had one or more major deviations in their treatment schedule (21). Major deviations regarding the treatment site were also found in more than 40% of patients. Despite these high major deviation rates, underdosage or geographical misses were not associated with a worse outcome. Although these two groups did not demonstrate a relationship between violation and treatment outcome, it is assumed that these high violation rates make it difficult to correctly understand the true message of clinical trials. With respect to violation rates, our present trial was satisfactory and the outcome data are robust.

Table 1. Primary site and RT technique

Primary site	RT technique			
	AP	Oblique	Opposing field	Others
Orbit	15	6	3	0
Thyroid	0	3	1	0
Salivary gland	0	2	2	0
Waldeyer's ring	0	0	2	0
Prostate	0	0	0	1
Lung	0	0	0	1
Cecum	0	0	1	0
Total	15	11	9	2

RT, radiation therapy; AP, single anterior-posterior field; Opposing field, two anterior-posterior or lateral opposing field techniques.

Advances in imaging and other technology have enhanced our ability to create complete anatomic and functional 3D data for each patient that facilitates the use of advanced technology RT delivery tools, including 3D conformal RT, intensity modulated RT, stereotactic RT and radiosurgery, and image-guided RT. Implementing these advanced technologies safely in clinical practice will require innovative and efficient methodologies for clinical QA. For example, Palta et al. (22) introduced the new web-based QA program to allow the rapid peer review of radiotherapy data through a simple personal computer-based web browser. RTOG has already developed a web-based QA program, and EORTC will also adopt a similar system to facilitate their QA program.

This is the first report that evaluates the QA program in MALT lymphoma. The technical deviation rate, technical data quality and completeness of this phase II trial were acceptable, and in addition our QA procedures were inexpensive and not time consuming. Furthermore, in multi-institutional studies, this analysis continues to lend credence to efforts related to QA for RT.

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Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION **Cervix**

MULTI-INSTITUTIONAL STUDY OF RADIATION THERAPY FOR ISOLATED PARA-AORTIC LYMPH NODE RECURRENCE IN UTERINE CERVICAL CARCINOMA: 84 SUBJECTS OF A POPULATION OF MORE THAN 5,000

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Purpose: Most patients who had any recurrent sites of cancer have been considered to be in their last stage of life. However, recent advances of clinical research reveal some patients achieve long-term survival even in recurrence. Furthermore, for patients who had only one recurrent region, radiation therapy could play an important role. As for uterine cervical carcinoma, the most common recurrent site other than the pelvis is the para-aortic lymph nodes. Thus we conducted the current study.

Patients and Methods: Between 1994 and 2003, more than 5,000 uterine cervical carcinoma patients were treated with curative intended treatments at 13 Japanese hospitals. Of these patients, 84 developed para-aortic lymph node recurrence as the only site of initial tumor progression. These patients were treated with external beam radiation therapy. Radiation therapy protocol was as follows: 1.7–2.0 Gy per fraction, 5 fractions per week, and the mean total dose was 50.8 Gy (25–60 Gy).

Results: Three- and 5-year overall survival rates of all patients were 49.5% and 31.3%, respectively. Stratified by symptom sign, 3-year overall survival rate of symptom positive was 27.6% and those of the negative was 56.1% ($p = 0.018$). Three-year overall survival rates of the total dose ≥51 Gy and that of ≤50 Gy were 58.0% and 42.8%, respectively ($p = 0.07$). As for morbidity, no patients received Grade 3 or greater late toxicity.

Conclusions: The current study suggested that radiation therapy for isolated para-aortic lymph node recurrence in uterine cervical carcinoma could have a significant impact on survival. © 2006 Elsevier Inc.

Uterine cervical carcinoma, Isolated para-aortic lymph node recurrence, Radiation therapy, Oligo-recurrence.

INTRODUCTION

Most patients who have any recurrent sites of cancer are considered to be in their last stage of life. However, recent advances of clinical research reveal some patients achieve long-term survival even with recurrent cancers, a term we first defined as oligo-recurrence in our previous study (1). Furthermore, for patients who have only one recurrent region, radiation therapy could play an important role.

As for uterine cervical carcinoma, the most common

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recurrent site other than pelvis is the para-aortic lymph nodes. Furthermore, improvement of diagnostic imaging enables us to detect more frequently isolated para-aortic lymph node recurrence. In Japan, the largest population-based study of the frequency of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma has been recently reported (1). Sixty-seven patients of 3,137 uterine cervical carcinoma (Stage Ia-IVa) treated with curative treatment have recurred in isolated para-aortic lymph node regions (2.1%). Moreover, Singh *et al.* recently reported that isolated para-aortic lymph node recurrence in uterine cervical carcinoma treated with concurrent chemoradiotherapy achieved 100% of 5-year survival according to Kaplan-Meier method, although this study consisted of only 7 patients, and only 1 patient achieved actual 5-year survival (2). Regions in Asia have the highest incidence of uterine cervical carcinoma. Kim *et al.* in Korea recently reported that 3-year overall survival rate of isolated para-aortic lymph node recurrence in uterine cervical carcinoma patients treated with hyperfractionated radiation therapy totaling 60 Gy combined with concurrent chemotherapy was 19% (3). Chou *et al.* in Taiwan reported that the 5-year survival rate for isolated para-aortic lymph node recurrence treated with concurrent chemoradiotherapy was 51.2% (4). Hong *et al.* in Taiwan reported 34% of 5-year survival (5). In Japan, 38% of 5-year survival was reported for these patients treated by radiation therapy or radiation therapy combined with chemotherapy (6).

However, no studies such as these have been performed on a large population. Thus we conducted a multi-institutional study for isolated para-aortic lymph node recurrence in uterine cervical carcinoma of a population of more than 5,000.

Table 1. Patient characteristics

Mean age	
at the initial treatment	54.8 years (25–80 years)
at the recurrence	56.4 years (26–81 years)
Histopathology	
SCC	74
Adenocarcinoma	5
Adenosquamous cell carcinoma	5
Clinical stage at the initial treatment	
Ia	0
Ib	16
IIa	3
IIb	15
IIIa	1
IIIb	42
IVa	7
The mean serum SCC level	
at the initial treatment	17.8 ng/dL (0.5–100 ng/dL)
at the recurrence	7.0 ng/dL (0.4–92.8 ng/dL)
Symptom	
None	66
Lumbago	12
Edema of lower extremities	4
Pain of lower extremities	2

Abbreviation: SCC = squamous cell carcinoma.

Table 2. Treatment characteristics

Initial treatment	
Radiation therapy alone (combination of external beam radiation therapy with intracavitary irradiation)	42
Chemoradiotherapy (radiation therapy as above)	16
Surgery with radiation therapy	11
Surgery with chemoradiotherapy	6
Surgery alone	9
Mean total dose for isolated PAN	50.8 Gy (25–61 Gy)
Chemotherapy regimens	
BOMP	8
UFT	8
CDDP	5
Others	11

Abbreviations: PAN = para-aortic lymph node recurrence; BOMP = bleomycin, Oncovin, mitomycin C, cisplatin; UFT = uracil-tegafur; CDDP = cisplatin.

PATIENTS AND METHODS

More than 5,000 uterine cervical carcinoma patients (Ia-Iva) were treated with curative treatment such as surgery, radiation therapy, or a combination of these treatments in 13 major Japanese hospitals. Of these, 84 patients, who recurred in isolated para-aortic lymph node, were treated with radiation therapy for para-aortic regions between 1994 and 2003. These patients are analyzed in the current study. Patient characteristics are listed in Table 1. The mean age at the initial treatment (pelvis) was 54.8 years (range, 25–80 years). On the other hand, the mean age at the isolated para-aortic recurrence was 56.4 years (range, 26–81 years). The mean duration time was 22.0 months (range, 1–103 months). The clinical stage at the initial treatment was as follows: 0 were Stage Ia, 16 were Stage Ib, 3 were Stage IIa, 15 were Stage IIb, 1 was Stage IIIa, 42 were Stage IIIb, and 7 were Stage IVa. The mean serum squamous cell carcinoma (SCC) antigen level at

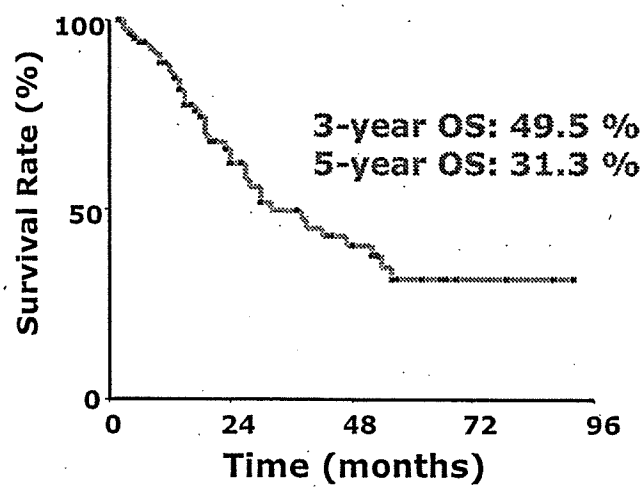

Fig. 1. Overall survival (OS) curve of all patients is demonstrated. Five-year overall survival of all patients was 31.3%.

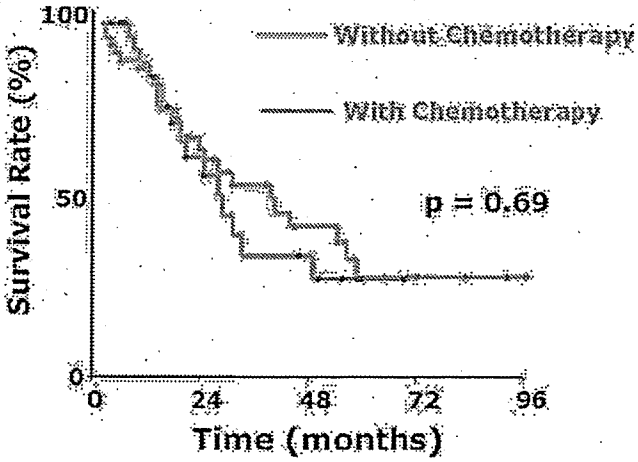

Fig. 2. Overall survival curves with and without chemotherapy were demonstrated; they are almost the same curves ($p = 0.69$).

the initial treatment was 17.8 ng/dL (range, 0.5–100.0). The mean serum SCC antigen level at the isolated para-aortic recurrence was 7.0 ng/dL (range, 0.4–92.8). Eighteen patients had symptoms at the isolated para-aortic recurrence, 12 patients had lumbago, 2 patients had pain of the lower extremities, 4 patients had edema of the lower extremities, and 1 had other symptoms.

As for treatment characteristics (Table 2), the initial treatment was as follows: radiation therapy (the combination of external beam radiation therapy with intracavitary irradiation) was performed in 42 patients. The combination of radiation therapy (the combination of external beam radiation therapy with intracavitary irradiation) with chemotherapy was performed in 16 patients, combination of surgery with radiation therapy was performed in 11 patients, and combination of surgery with chemoradiotherapy was performed in 6 patients. Surgery was performed in 9 patients. As for the isolated para-aortic lymph node recurrence, all patients received external beam radiation therapy. The mean total dose was 50.8 Gy (range, 25–61 Gy). Thirty-two patients received chemotherapy (8 BOMP, 8 UFT, 5 CDDP, 11 other).

As for statistical analysis, survival curves were constructed by Kaplan-Meier method and the log–rank test was performed to compare between clinicopathologic valuables. Statistical

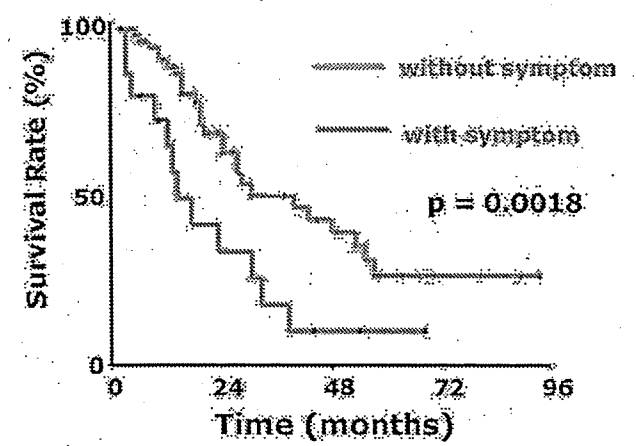

Fig. 3. Overall survival curves by symptom sign were demonstrated. Those without symptoms were significantly superior to those without symptoms ($p = 0.0018$).

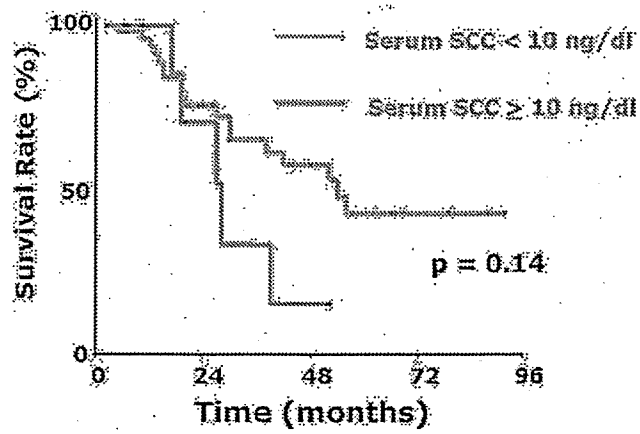

Fig. 4. Overall survival curves by serum squamous cell carcinoma (SCC) level were demonstrated. That of high SCC had a tendency to be superior to that of low SCC ($p = 0.14$).

significance was assumed for a two-tailed p value less than 0.05.

RESULTS

Median follow-up time of all patients from the initiation of radiation therapy for isolated para-aortic lymph node recurrence was 20 months (2–92 months). Three-year and 5-year overall survival rates of all patients were 49.5% and 31.3%, respectively (Fig. 1).

Stratified by patients with or without chemotherapy, 3-year overall survival rate of patients with chemotherapy group was 37.7% and those without was 56.7% ($p = 0.69$) (Fig. 2).

Moreover, stratified by symptom sign, 3-year overall survival rate of symptom positive group was 27.6% and those in the symptom negative group was 56.1% ($p = 0.018$) (Fig. 3).

Furthermore, stratified by serum SCC antigen level (≥10 ng/dL) at the isolated para-aortic recurrence, 3-year overall

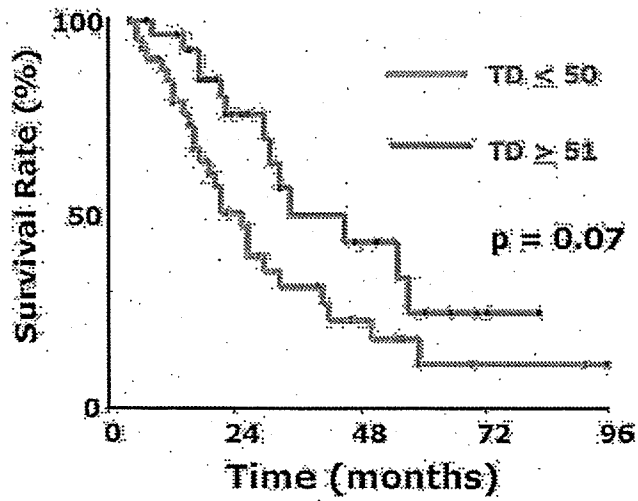

Fig. 5. Overall survival curves by total dose (TD) were demonstrated. That of ≥51 Gy had a tendency to be superior to that ≤50 Gy ($p = 0.07$).

survival rate of high SCC levels was 35.7%, and those with low levels was 66.5% ($p = 0.14$) (Fig. 4).

Three-year overall survival rates of the total dose ≥51 Gy and that of ≤50 Gy were 58.0% and 42.8%, respectively ($p = 0.07$) (Fig. 5).

As for morbidity, no patients received Grade 3 or greater late toxicity (National Cancer Institute-Common Terminology Criteria for Adverse Events version 3.0).

DISCUSSION

We defined one or several sites of recurrence as "oligo-recurrence" in our previous article (1), based on the many published reports on this recurrent pattern. Recently, oligo-recurrence was easily and frequently found owing to the improvements of biochemical markers for malignancies and diagnostic imaging. However, no current strategy, differing from systemic chemotherapy, has been established to cope with oligo-recurrence.

Isolated para-aortic lymph node recurrence in uterine cervical carcinoma is considered to be a regional disease rather than systemic disease of this oligo-recurrence (1). Singh *et al.* recently reported that isolated para-aortic lymph node recurrence in uterine cervical carcinoma treated with chemoradiotherapy achieved 100% of 5-year survival, although their method of chemotherapy did not have sufficient power systemically. Many reports other than Singh *et al.* have been performed on the survival benefit of radiation therapy of isolated para-aortic lymph node recurrence in uterine cervical carcinoma (3–6). Furthermore, 1.7–3.6% of uterine cervical carcinoma treated with curative treatment reportedly resurfaces as isolated para-aortic lymph node recurrence in large population-based studies (1, 3–5).

In the current large population-based study from Japan, 5-year overall survival was 31.3%, which was similar to 38% of 5-year overall survival in a small population-based study also from Japan (6). Survival benefit of chemotherapy in the current multi-institutional retrospective study could not be demonstrated. However, until now no phase III trial comparing radiation therapy alone vs. chemoradiotherapy for the isolated para-aortic lymph node recurrence in uterine cervical carcinoma has been performed. Furthermore, the chemoradiotherapy group in the current study consisted mostly of sequential, nonconcurrent chemoradiotherapy, such as radiation therapy followed by several courses of BOMP. Thus the survival benefit of up-to-date concurrent chemoradiotherapy is a challenge for future study.

In this study, patients with symptoms of recurrent cancer in an isolated para-aortic lymph node had much worse prognoses than those without symptoms. These findings concur with previous small-population studies (3, 7). These facts indicate that early detection of isolated para-aortic lymph node recurrence has great importance. Our previous study on characteristics of isolated para-aortic lymph node recurrence in uterine cervical carcinoma indicated that serum SCC antigen level at the initial curative treatment for pelvic tumors correlated with that at recurrence ($r = 0.492$, $p = 0.01$) (1), which indicated that the monitoring of serum SCC antigen level was useful to detect isolated para-aortic lymph node recurrence regardless of symptoms. Moreover, lower serum SCC antigen level at the detection of recurrence brought better prognosis in the current study. Thus if the primary region has no recurrence when serum SCC antigen level increases, oncologists are strongly recommended to perform abdominal computed tomography to examine whether para-aortic lymph node recurrence exists or not.

As for the total dose, the current study indicated that 51 Gy or more irradiation tended to have a better prognosis than 50 Gy or less. Thus higher irradiation (51 Gy or more) is recommended.

As for morbidity, severe late morbidity was not seen in the current study. Thus 51–60 Gy irradiation to para-aortic lymph node recurrence is considered a feasible dose using a suitable irradiation technique.

In conclusion, radiation therapy for isolated para-aortic lymph node recurrence is safe and effective indicating this method should be strongly recommended for such patients.

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Frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma in Japan: A multi-institutional study

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Abstract

Objective. In most cases of uterine cervical carcinoma recurrence, the first site of distant metastasis or recurrence is reported to be the para-aortic region. Some reports have demonstrated that, in cases of isolated para-aortic lymph node recurrence treated by radiation therapy, patients survived for a long period, which suggests that isolated para-aortic lymph node recurrence in uterine cervical carcinoma is a regional disease rather than systemic disease. Determining the predictive characteristics of isolated para-aortic lymph node recurrence in patients at the time of the initial treatment for primary uterine cervical carcinoma is important, so we conducted the current multi-institutional study.

Patients and methods. Patients (n=3137) with uterine cervical carcinoma of stages Ia to IVa were treated in twelve Japanese hospitals between 1994 and 2003. The current study investigated the frequency and characteristics of patients with isolated para-aortic lymph node recurrence as well as the characteristics of clinical stage, histopathology, serum squamous cell carcinoma antigen level, the treatment method at the initial treatment, the duration between the initial treatment and the recurrence, and the serum squamous cell carcinoma antigen level at the recurrence.

Results. Of the 3137 patients with uterine cervical carcinoma in stages Ia–IVa, 67 (2.1%) experienced recurrence in isolated para-aortic lymph nodes. Stratified by clinical stage, none of the 613 patients with stage Ia experienced recurrence in isolated para-aortic lymph nodes. However, recurrence was experienced by 14 (1.4%) of the 966 patients with stage Ib, 7 (3.5%) of the 199 patients with stage IIa, 14 (2.3%) of the 613 patients with stage IIb, 1 (2.1%) of the 48 patients with stage IIIa, 26 (4.6%) of the 538 patients with stage IIIb, and 5 (5%) of the 100 patients with stage IVa. The mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months (range, 2–49 months). The correlations between duration time and the clinico-pathological factors (clinical stage, histopathology, serum squamous cell carcinoma antigen level, and treatment method) at the initial treatment were investigated. No statistically significant factors have been revealed in the current study.

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Conclusions. The frequency of isolated para-aortic lymph node recurrence was 2.1% and increased with increasing clinical stage at the initial treatment (stage IVa: 5%) in the current study.

Keywords: Isolated para-aortic lymph node recurrence; Uterine cervical carcinoma; Radiation therapy

Introduction

Recently, oligo-metastasis/oligo-recurrence has been one of the most important concerns of oncology, especially in radiation oncology [1]. Advances of diagnostic imaging and biochemical diagnosis for various carcinomas have enabled us to detect isolated metastasis or recurrence, although some decades ago, metastasis and recurrence meant systemic disease in almost all cases. However, no strategy has been established for treating oligo-metastasis/oligo-recurrence in any kind of carcinoma. Most oncologists select systemic chemotherapy for these patients as a community standard. Nonetheless, oligo-metastasis/oligo-recurrence, especially isolated metastasis or recurrence, is considered to not always mean systemic disease. Singh et al. reported that patients with isolated para-aortic lymph node recurrence in uterine cervical carcinoma achieved 100% of 5-year survival when the recurrent site was treated with chemoradiotherapy [2]. Niibe et al. reported that the survival rates of patients with metastatic brain tumors with controlled primary lesions and no other distant metastasis were 88.9% after 1 year and 51.9% after 3 years respectively [3]. These findings suggested that some oligo-metastasis/oligo-recurrence patients could survive for as long a period as the patients with primary carcinoma. Thus, these patients must be treated curatively.

Uterine cervical carcinoma was reported to spread more by the lymphatic route than by the hematogenous route [4]. In most cases, the first site of distant metastasis or recurrence is the para-aortic region. As mentioned above, Singh et al. reported the long-term survival of patients with isolated para-aortic lymph node recurrence, which meant that isolated para-aortic lymph node recurrence in uterine cervical carcinoma is a regional disease rather than a systemic disease. Determining the characteristics of isolated para-aortic lymph node recurrence in patients at the time of the initial treatment for primary uterine cervical carcinoma is important.

Thus, we conducted the current multi-institutional study to reveal the frequency and characteristics of isolated para-aortic lymph node recurrence in uterine cervical carcinoma.

Patients and methods

Patients (n=3137) with uterine cervical carcinoma of stages Ia to IVa were treated in twelve Japanese university hospitals, cancer centers, and major general hospitals between 1994 and 2003. The current study investigated the frequency and characteristics of isolated para-aortic lymph node recurrence as well as the clinical stage, histopathology, serum squamous cell carcinoma (SCC) antigen level, initial treatment method, duration between the initial treatment and the recurrence, and serum SCC antigen level at the time of recurrence (Table 1).

Data were collected on data sheets from these twelve hospitals. Data sheets included patient age, serum SCC antigen level, treatment method, and the date at the initial treatment and patient age, serum SCC antigen level, and the date at the time of detection of isolated para-aortic recurrence. A data center was established at the Department of Radiology, Kitasato University Hospital.

Results

Of the 3137 patients with uterine cervical carcinoma in stages I–IVa, 67 (2.1%) experienced recurrence in isolated para-aortic lymph nodes. Stratified by clinical stage, none of the 613 patients with stage Ia experienced recurrence in isolated para-aortic lymph nodes. However, recurrence was experienced by 14 (1.4%) of the 966 patients with stage Ib, 7 (3.5%) of the 199 patients with stage IIa, 14 (2.3%) of the 613 patients with stage IIb, 1 (2.1%) of the 48 patients with stage IIIa, 26 (4.6%) of the 538 patients with stage IIIb, and 5 (5%) of the 100 patients with stage IVa. These results suggested that patients with more locally advanced stages (IIIb and IVa) were more likely to experience recurrence in isolated para-aortic lymph nodes than patients with early locally invasive stages (I–II).

Other patients characteristics are summarized in Table 2. The mean age was 55.7 years (range, 25–86 years). The mean duration time between the initial treatment and isolated para-aortic recurrence was 20 months (range, 2–49 months) (Fig. 1). As for the initial treatment, 32 patients underwent external radiation therapy combined with intracavity radiation therapy alone; 20 patients underwent surgery combined with external radiation therapy; 12 patients underwent concurrent chemo-radiation therapy (radiation therapy: external radiation therapy combined with intracavity radiation therapy); and 3 patients underwent surgery only. As for histopathology, 56 patients were found to have squamous cell carcinoma; 5 patients had adenocarcinoma; 5 patients had adenosquamous cell carcinoma; and 1 patient had a malignancy that was unclassified. The mean serum SCC antigen level at the start of the initial treatment was 17.3 ng/dl (range, 0.5–100 ng/dl), and the mean serum SCC antigen level at the time of isolated para-aortic lymph node recurrence was 9.5 ng/dl (range, 0–120 ng/dl). These results indicate that the serum SCC antigen level at the time of isolated para-aortic lymph node recurrence tended to be lower than that at the initial treatment. As for symptoms of the isolated para-aortic lymph node recurrence, 20 patients had symptoms with recurrence (Table 3). Lumbago was the most frequent symptom,

Table 1
The frequency of isolated para-aortic lymph node recurrence

Clinical stage	Frequency of isolated para-aortic lymph node recurrence
Ia	0/613 (0%)
Ib	14/966 (1.4%)
IIa	7/199 (3.5%)
IIb	14/613 (2.3%)
IIIa	1/48 (2.1%)
IIIb	26/538 (4.6%)
IVa	5/100 (5%)
Ia–IVa	67/3137 (2.1%)

Table 2
Patients characteristics of isolated para-aortic lymph node recurrence

Mean age	55.7 years (range; 25–86 years)
Histopathology	
Squamous cell carcinoma	56
Adenocarcinoma	5
Adenosquamous cell carcinoma	5
Unclassified	1
Initial treatment	
Radiation therapy alone	32
Chemoradiation therapy	12
Surgery followed by radiation therapy	20
Surgery alone	3
Mean serum SCC level	
Initial treatment	17.3 ng/dl (range; 0.5–100 ng/dl)
Recurrence	9.5 ng/dl (range; 0–120 ng/dl)
Mean DT[a]	20 months (range; 2–49 months)

[a] Mean DT: the mean duration time between the initial treatment and isolated para-aortic recurrence.

Table 3
Symptom at the isolated para-aortic recurrence

Symptom	Number of patients
Lumbago	14
Edema of lower extremities	3
Pain of lower extremities	3

seen in 14 patients. Three patients experienced edema of the lower extremities, and three patients experienced pain in the lower extremities. The correlations between duration time and the clinico-pathological factors (clinical stage, histopathology, serum SCC antigen level, and treatment method) at the initial treatment were investigated. No statistically significant factors have been revealed in the current study.

The correlation between serum SCC antigen level at the initial treatment and that at the time of isolated para-aortic lymph node recurrence was statistically significant ($r = 0.492$, $P = 0.01$) (Fig. 2).

The correlation between higher serum SCC antigen level (>10 ng/dl) at the time of isolated para-aortic lymph node recurrence and coexisting symptoms at the time of recurrence was statistically significant ($P = 0.05$).

Discussion

Some patients with uterine cervical carcinoma and isolated para-aortic lymph node recurrence were reported to survive for a long period and were considered to be cured [2,5–7]. Singh et al. reported that 100% of patients with uterine cervical carcinoma and isolated para-aortic lymph node recurrence treated with concurrent chemoradiotherapy achieved 5-year survival, although patients treated with only chemotherapy died within 1.5 years [2]. Niibe et al. reported that, in cases of advanced uterine cervical carcinoma with isolated para-aortic lymph node recurrence or metastasis treated with radiation therapy, 38% of patients achieved 5-year survival and the authors pointed out that c-erb B-2/HER2 expression in tumor tissues had prognostic significance, suggesting that anti-c-erb B-2/HER2 therapy, molecule-targeting therapy, such as with tratsuximab, might have an influence on survival [5]. These findings indicated that isolated para-aortic lymph node recurrence in uterine cervical carcinoma was not considered to be a systemic disease but to be a loco-regional disease. The detection of isolated para-aortic lymph node recurrence is important, so we investigated the frequency and characteristics of isolated para-aortic lymph node recurrence in patients with uterine cervical carcinoma.

The current multi-institutional study revealed that 2.1% of patients with uterine cervical carcinoma treated with curative therapy (including radiation therapy, chemoradiation therapy, surgery, and combined therapy) experienced recurrence in isolated para-aortic lymph nodes. This is the clinical demonstration in the largest population ($n=3137$). Others report on this theme in a large population as follows. Chou et al. reported in 2001 that 26 out of 867 patients (3%) who received pelvic radiotherapy after the diagnosis of primary cervical carcinoma were found to have isolated para-aortic lymph node recurrence in Taiwan [7]. Hong et al. reported in 2004 that 46 out of 1292 patients (3.6%) with uterine cervical carcinoma who underwent curative intended radiation therapy were found to have para-aortic lymph node recurrence in Taiwan [8]. Tsai et al. reported

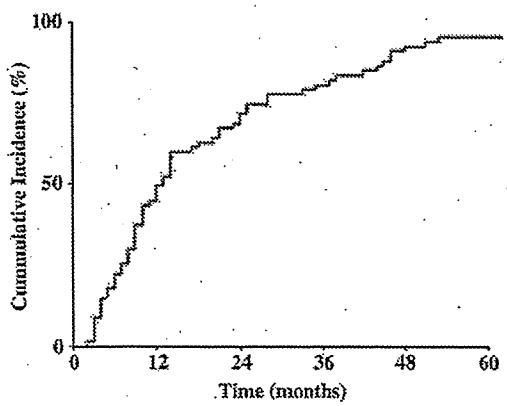

Fig. 1. The cumulative mean duration time between the initial treatment and isolated para-aortic lymph node recurrence was demonstrated. The mean duration was 20 months (range, 2–49 months).

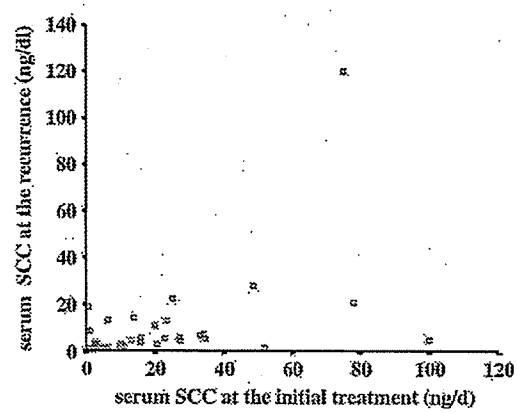

Fig. 2. The correlation between serum SCC antigen level at the start of the initial treatment and serum SCC antigen level at the isolated para-aortic lymph node recurrence. The positive correlation was recognized ($r = 0.492$, $P = 0.01$).