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臨床放射線

食道癌術後再発に対する放射線治療の検討

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食道癌術後再発に対する放射線治療の検討

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はじめに

食道癌治療戦略は進行度に応じた集学的治療の時代に入った。治療法では手術（3領域郭清を伴う食道切除）と放射線治療に加え，内視鏡的治療が新たに地位を確立した。さらに化学療法にも進歩が認められている。食道癌は治療成績の不良なイメージから脱皮しつつある[1-3]。すなわち，全国食道がん登録調査報告[4]によると，全切除例の5年生存率は，1988年症例では30.8%であったが，5年後の1993年症例では40.8%まで向上している。最近では，3領域郭清を伴う食道切除症例に限定すると50%の大台を超えて54%の成績が報告されている[5]。このように治療成績は確実に向上しているが，表在癌と比較するとT2以上の進行癌症例では今なお十分とはいえない。さらに術後再発症例においては，平均生存月数で5～10カ月とその治療成績はきわめて不良である[6][7]。再発食道癌を治癒させることが相当に困難であろうことは想像に難くない。そこで今回，筆者らが虎の門病院で放射線治療を行った術後再発症例を分析し，放射線治療の適応と長期生存を期待し得る必要条件について検討したので報告する。

1. 研究対象

1997年8月～2003年7月までの6年間に虎の門病院放射線科に登録された食道癌自験例は281例であった。このうち2領域または3領域郭清を伴う食道切除術後に再発を認め，放射線治療を施行した48例を対象とした。

内訳は男性43例，女性5例，登録時の年齢は41～83歳（中央値60歳），組織型はすべて扁平上皮癌，初回再発部位はリンパ節が最も多く33例，次いで骨7例，肝4例，腫瘍床3例，胸壁1例；再発腫瘍が比較的限局していた症例は28例，多発性20例，手術から再発（放射線治療）までの期間は1年未満が30例，1年以上18例であった。放射線治療では総線量で50Gy以上が33例（60Gy以上は19例），50Gy未満は15例であった。なお，化学療法は27例に併用されていた（表1）。

2. 研究方法

1）症例の分類

食道癌取扱い規約第9版[8]に従って臨床分類と病理分類を行った。

2）放射線化学療法

照射野は主癌巣部のみまたは隣接領域を含めたが，症例ごとに外科主治医と相談して決定した。照射方法は線量漸増照射法[9]をはじめ単純分割照射法や多分割照射法を用いたが，特に隣接領域を含めた場合にはField within a field（F-f）法を原則とし，主癌巣部（f）に対しては線量漸増法とした。この場合，最終の1回照射線量は

*1 A. Okazaki, A. Uki, H. Kurosaki, T. Tamaki, H. Maruno 虎の門病院放射線科 *2 H. Udagawa 同消化器外科
〔索引用語：食道癌，術後再発，放射線治療，放射線化学療法〕

表1　症例の内訳

初回再発部位	リンパ節				臓器			局所	総計
	頸部（鎖骨上部）	縦隔	上腹部	腹部傍大動脈	骨	肝	胸壁	腫瘍床	
	12	12	2	7	7	4	1	3	48
再発（照射）までの期間									
<6mos	2	2	0	1	1	0	0	0	6
6≦ <12	7	2	2	3	6	1	1	2	24
12≦ <18	1	5	0	2	0	3	0	1	12
18≦ <24	0	1	0	0	0	0	0	0	1
24≦	2	2	0	1	0	0	0	0	5
放射線治療									
<30Gy	0	1	0	0	0	0	0	0	1
30≦ <50	0	4	2	1	4	2	0	1	14
50≦ <60	4	1	0	4	3	1	0	1	14
60≦ <70	4	5	0	2	0	1	1	1	14
70≦	4	1	0	0	0	0	0	0	5
化学療法併用									
あり	11	5	1	4	0	3	1	2	27
なし	1	7	1	3	7	1	0	1	21

2.4Gyまたは2.6Gyであった。

一方，化学療法は27例に併用され，肝転移で動注化学療法を併用した2例以外はいずれもlow dose FP（CDDP 6mg/m²+5Fu 300mg/m²）で，放射線治療日に併用した。なお，low dose FPはIVH管理下で行い，CDDPは5時間，5Fuは24時間の持続注入方式によった。

3）症例の分析

予後調査は2004年11月に行い，1年以上生存症例について再発部位，再発（放射線治療）までの期間，再発時手術併用の有無，放射線化学療法とその効果を検討するとともに，全症例で放射線治療後の生存率をKaplan-Meier法により算出した。さらに，放射線治療で長期生存を期待しうる必要条件を考える上で示唆に富むと思われる症例を呈示した。

有害事象は，National Cancer Institute-Common Terminology Criteria for Adverse Events，Version 3.0を用いて急性反応を評価し，遅発性反応にはRTOG/EORTC Late Radiation Morbidity Scoring Schemeを用いた。

3. 結　果

1）1年以上生存症例（表2）

生存中と死亡例を合わせると48例中13例（27%）が1年以上生存していた。このうち生存中は4例で，いずれも放射線化学療法後2年以上（25～60カ月）の経過を有していた。一方，死亡（癌死）44例中9例（20%）が1年以上（12～43カ月）生存した。生存中の4例をみると3例で転移リンパ節を郭清または摘出した後に放射線治療を施行していた。なお，死亡症例で再発時にリンパ節郭清が行われた症例は1例にとどまっていた。一方，手術は困難と判断され放射線治療（化学療法併用は8例）が行われた9例中8例は，最長31カ月までの観察期間で明らかな再増大は認められていない。これらの症例ではいずれも線量漸増照射法で総線量60Gy以上の放射線治療が行われていた。

2）予後（図1）

放射線治療後の生存期間は2カ月～60カ月で中央値6.5カ月，平均12.2カ月であった。累積生存率は1年25%，2年19%，3年8%，4年5%，5年

表2　1年以上生存症例の分析

症例				術後再発		放射線治療		化学療法	特記事項	再増大有無
No.	年齢	性	生存期間 (month)	部位	期間	照射方法	総線量 (Gy)			
生存4例										
1	54	男	25	縦隔	22	D-i/F-f	66.6	FP		無
2	58	男	26	頸部	11	D-i/F-f	59.6	FP	LN摘出	無
3	47	男	52	腹部	11	H-f	50.2	FP	LN郭清	無
4	53	女	60	頸部	6	D-i/F-f	51.4	FP	LN郭清	無
死亡44例中9例										
1	64	女	12	頸部	12	H-f/D-i/F-f	64.6	FP		無
2	67	男	13	肝	31	D-i	52.0	動注		無
3	58	男	18	縦隔	24	H-f/D-i	72.6	FP		無
4	75	男	20	頸部	9	D-i /F-f	70.9	FP		無
5	73	男	31	鎖骨上部	8	H-f/D-i/F-f	67.2	FP		無
6	52	男	31	腹部	13	D-i /F-f	61.0	FP		無
7	55	男	31	頸部	28	H-f/D-i/F-f	71.8	FP		無
8	56	男	35	腹部	76	D-i/F-f	61.6	FP		?
9	63	男	43	頸部	16	H-f/D-i	55.6	FP	LN郭清	無

D-i（Dose increment）：線量漸増，H-f（Hyperfractionation）：多分割，F-f：Field within a field，
LN：Lymph Node

5%であった。

3）症例呈示

放射線治療で長期生存を期待しうる必要条件を考える上で示唆に富む3症例の経過を概説し，それぞれ図2に手術時の原発巣とリンパ節転移部位および初回再発部位を示した。

〔症例1〕53歳，女性（表2　生存症例No.4）

表在癌（Ut-Mt，triple ca.，T1bN1M0 Stage II）で1999年3月に3領域郭清を伴う手術が行われ，pT1bpN1（1/98，#101）と診断された。6カ月後に右頸部食道傍リンパ節（#101）領域に再発が疑われ，同部の郭清術が行われた。その結果，リンパ節転移が確認されたため1999年11月に両鎖骨上部と頸部（#101，102-mid，104）に多分割・線量漸増法で総線量51.4Gyの放射線化学療法を施行した。5年後の現在，新たな再発もなく生存している。本例は術後間もない時期の再発であり，慎重な経過観察と定期的頸部超音波検査でリンパ節転移再発を郭清可能な時点で発見できた症例であった。

〔症例2〕47歳，男性（表2　生存症例No.3）

進行食道癌（Ae,8cm,2型全周,T3N1-4M0，Stage IVa）で，リンパ節転移が広汎であったため手術の前後で化学療法が行われた。3領域郭清術による病理組織学的進行度はpT3pN1-4であった。6カ月後に腹部リンパ節転移が疑われ，再度郭清術が施行された。その結果，大動脈周囲リンパ節（#16）に転移が確認されたため，上腹部（#9，16領域）に多分割で総線量50.2Gyの放射線化学療法を施行した。4年4カ月後の現在，新たな再発はなく生存している。本例も術後間もな

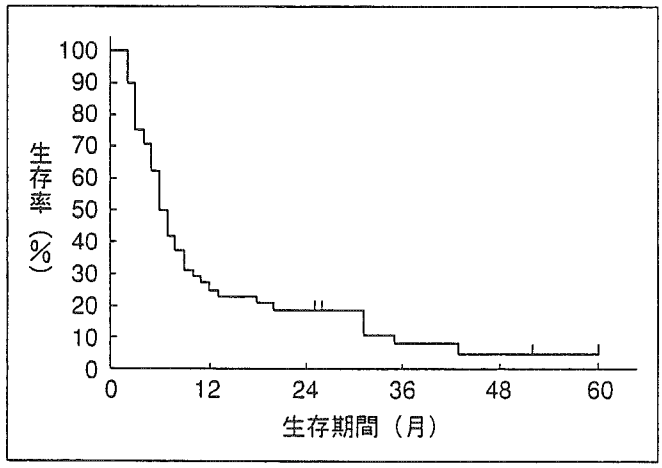

図1　術後再発に対する放射線治療後の生存率

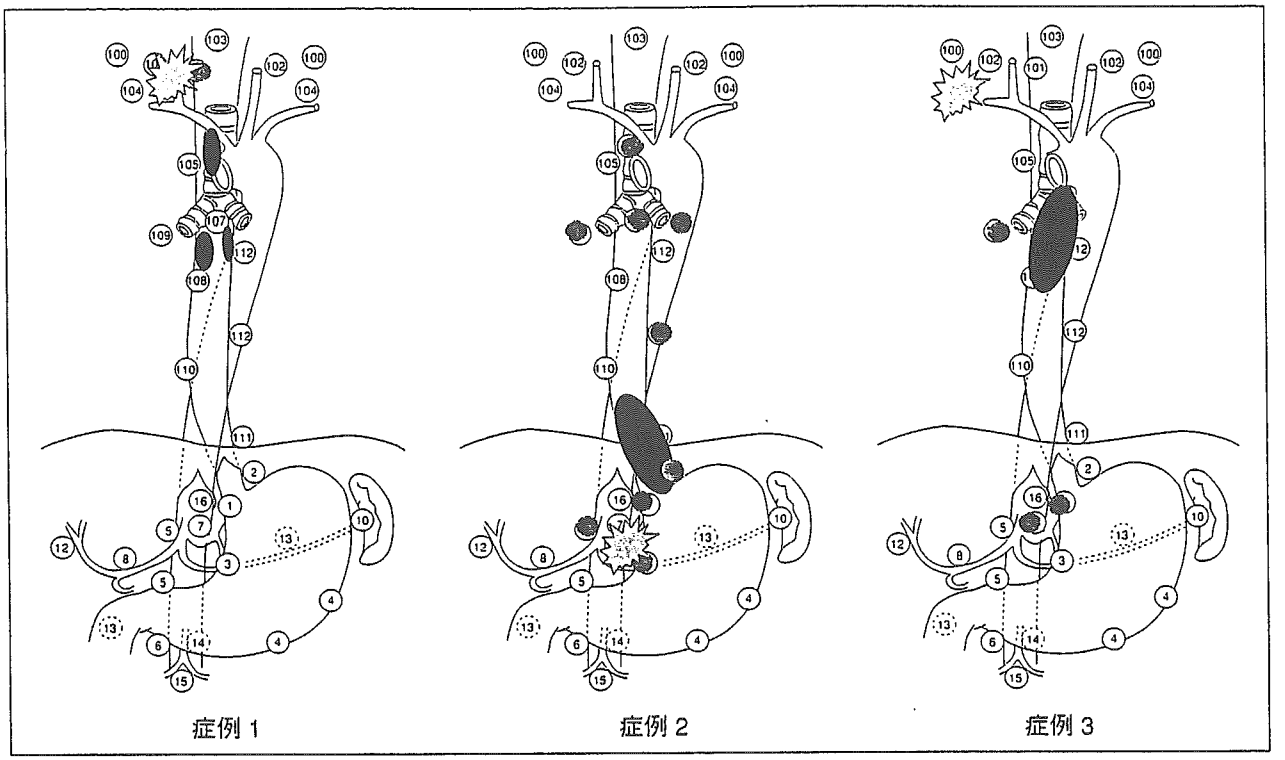

図2 ●：手術時の原発巣 ●：リンパ節転移 ：初再発部位

い時期に腹部リンパ節転移再発が疑われた症例で，初診時広汎なリンパ節転移を有していたにもかかわらず積極的に対応したことが良好な経過に寄与したと考えられた。

〔症例3〕73歳，男性（表2　死亡症例No.5）

進行食道癌（Mt，8.5cm，3型，T4N1-3M0，Stage IVa）で，左主気管支に浸潤を認めたため1998年11月に術前放射線化学療法を開始し，full dose照射後に3領域郭清を伴う手術が行われた。照射野は，上縁が胸部気管リンパ節（#106）を含み，下縁は胸部下部食道（Lt）が十分に含まれる範囲を設定した。放射線治療はField within a field（F-f法）を用い，原発巣（f）に対しては多分割・線量漸増法で総線量69Gy照射した。術後病理組織学的所見では原発巣の治療効果はGrade 2，リンパ節転移はpN2（3/125；#109R，1，7）であった。9カ月後に右鎖骨上リンパ節（#104）転移が認められ，術前照射野につなげる形で両側鎖骨上部に対して放射線化学療法を施行した。主癌巣部には67.2Gy照射し，局所は制御されていたが，他部位の再発で2002年4月に死亡した。術前照射から3年4カ月，再発で放射線治療後2年7カ月の経過であった。本例は初診時すでに手術不能の進行癌であり，リンパ節転移再発時も切除不能であったが，積極的な放射線化学療法が局所制御ひいては延命に寄与したと考えられた。

4）有害事象

化学療法が施行された27例中25例までがlow dose FPとして，13～33回（中央値26回）併用された。主な急性反応は血液毒性で，grade 1以下：6例，grade 2：8例，grade 3：1例，grade 4：2例であった。なお，放射線治療休止例はなかった。一方，化学療法非併用例では21例中17例がGrade 1以下で，grade 3以上の血液毒性をきたした症例はなかった。非血液毒性に関しては化学療法併用の有無にかかわらず，処置を要する身体所見を生じた症例は認めていない。

遅発性反応は診療録の記載に基づいて評価したが，肺，脊髄，心臓，胃・腸，皮膚などで処置を要した異常所見の記載はなく，現時点ではgrade 0～1の範囲にとどまっていると推測された。

4. 考　察

放射線治療で進行食道癌患者を1人治癒させるに要するエネルギーは多大であるが，治癒が得

られた患者の喜びに接する時，つねに与えられる心の平安は何にも代え難いものである[10]。虎の門病院では食道癌の手術に3領域郭清術を採用して20年になる[11]。従来の2領域郭清と比較し，3領域郭清で治療成績の明らかな改善が認められている[5]。上縦隔・頸部郭清が徹底されるようになった結果と考えられる。さらに3領域郭清術の成果として，腫瘍の占拠部位，壁進達度とリンパ節転移の関係が明らかとなり，内視鏡的治療（EMR）のみならず根治的放射線治療の照射野を検討するうえでも有益なデータが提供されることになった。こうして外科腫瘍医のみならず放射線腫瘍医，内科腫瘍医とも食道癌を治療の甲斐ある疾患と認識しうるようになってきた[1-5]。しかし，表在癌と比較するとT2以上の進行癌や再発癌では今なおその予後は明らかに不良である[1) 2) 6) 7) 12)]。

インターネットで国立がんセンターのホームページ[13]にアクセスすると，「医療従事者向けがん情報」のみならず「一般向けがん情報」として誰でも容易に各種がんの詳しい解説を読むことができる。そこで食道癌の項をみると，“他の臓器にがんが広がっている方，多くのリンパ節にがん転移を認める方に限定すると，外科療法でも放射線療法と化学療法の同時併用療法でも治癒は困難です。したがって，早期発見が治療成果を向上させる鍵です。どのがんでもそうですが，特に食道がんはいったん進行すると急に治癒率が下がります。再発した場合には，どのような治療をしても治る可能性は非常に少ないと考えねばなりません。およそ半年くらいの余命と考えられます。手術をすることはほとんどありません。放射線や抗がん剤の治療で1年以上生きられることもありますが，がんの進行が早ければ3カ月以内のこともあります。”と記載されている。

図らずも不利な情報を得た進行（末期）癌患者の心理的内面は想像困難であり，抑鬱を伴う適応障害や認知機能障害をきたす場合も少なくないと思われる。ここにインフォームドコンセントの難しさがあり，臨床腫瘍学clinical oncologyと精神腫瘍学psycho-oncologyが癌の臨床で相補的役割を果たしうる環境が整備されることを願ってやまない[14]。

このように予後が悲観的な食道癌の術後再発症例では，その治療方針として積極的治療と対症的治療のいずれを選択するかに関して意見の分かれる所と思われる。当院では腫瘍の再発部位，再発が限局性か多発性か，切除可能か否か等をふまえて症例ごとに治療方針が検討されてきた。今回，放射線治療の自験例を検討した結果，食道癌の術後再発でも少なからず延命する症例や治癒する症例が認められ，生存期間は平均12.2カ月（中央値6.5カ月）で，5%の5年生存率が得られた。これらの症例では，化学療法としてlow dose FPを主として併用したが，有害事象は許容しうる範囲と考えられた。

北村ら[7]は術後再発食道癌26例について放射線治療を主体に治療した結果，平均生存期間は10.8カ月で3年生存率3.8%と報告している。単純に比較はできないが，再発食道癌の成績も集学的治療の進歩で少なからず向上しつつあるように思われる。そこで，再発腫瘍が限局している場合は，治癒可能性を考慮した放射線治療計画を立てるのがよく，安易に対症療法を選択すべきではないと考えられた。特に初再発が上縦隔から頸部-鎖骨上リンパ節領域では，1年以上生存症例が多く認められており，食道癌の特性からもよい適応と考えられた[15]。

一方，腹部リンパ節再発でも1例が長期生存中であり，限局している場合には積極的治療の適応があることを今回の検討は教えてくれた。さらに1年以上生存した13例中4例で経験したように，リンパ節転移では郭清術後の放射線治療に意義があると考えられた。しかし，再発腫瘍はたとえ限局性でも往々にして周囲組織に浸潤している場合が少なくないといわれている。郭清可能な時点でリンパ節転移を発見することの困難さが指摘されている[15]。今後の課題であるが，^{18}FDG-PETがその役割を果たしうるかもしれない[16]。再発腫瘍といえども早期に発見されれば切除可能性は高く，また放射線治療でも局所制御が容易となり，二次的転移の防止，ひいては予後の向上が期待される。

進行食道癌の治療成績が向上した主要因は，3領域郭清術が定型術式として認知され，上縦隔・頸部郭清が徹底されたことによる[5,11,15]。しかし，郭清リンパ節領域に再発をみることも少なくない。術後再発の治療は術後再発の防止と無関係ではない。術中所見と術後病理組織学的所見に基づき，術後照射の適応例/選択基準を明確にできないであろうか。この場合，照射野は外科医の指摘する部位で小範囲にとどめるのが望ましいと考えられる。

現在，外科腫瘍医は放射線治療（放射線化学療法）に期待と信頼を寄せている。放射線腫瘍医も手術や内科的治療に理解を示し，外科医・内科医と協調して集学的治療，臨床研究を推進する必要がある。そのためにも根治的放射線治療で食道癌原発巣を制御させうる有効な分割照射法の確立が急務である[2]が，術後再発腫瘍の制御ひいてはQOLの向上・延命にも寄与する重要な研究課題である。

ま と め

放射線治療を施行した食道癌術後再発48例を分析し，以下の結果を得た。

1）放射線治療後の生存期間は平均12.2カ月（中央値6.5カ月），累積生存率は1年25%，2年19%，3年8%，4年5%，5年5%であった。

2）食道癌の術後再発でも，1年以上生存者が48例中13例（27%）認められており，放射線化学療法で長期生存・治癒を期待できる症例は少なくない。しかも両者併用による有害事象は許容範囲であった。

3）特にリンパ節転移が限局性の場合（鎖骨上部—頸部—上縦隔＞腹部）は，局所制御を念頭に積極的治療を行うことが長期生存を期待しうる必要条件と考えられた。

4）リンパ節転移が切除可能な場合，郭清術後の放射線治療は根治性を高める上で意義がある。

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Summary

Role of radiotherapy for recurrence after curative surgery in patients with esophageal cancer

We evaluated 48cases of radiotherapy with or without chemotherapy for postoperative recurrence in esophageal cancer patients. Following results were obtained. 1) The mean survival time of post-radiotherapy group was 12.2 months and the cumulative 1-, 2-, 3-, 4-and 5-year survival rates were 25%, 19%, 8%, 5% and 5%, respectively. 2) Survivors more than one year were 13 cases (27%) and radiochemotherapy was thought to contribute local tumor control with limited toxicity, resulting in prolonged survival or cure especially in case of localized lymph nodes metastases. 3) Early detection of lymph nodes metastases is important in the improvement of curability, which enable lymph nodes dissection followed by radiotherapy.

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Esophagectomy: Is It Necessary after Chemoradiotherapy for a Locally Advanced T4 Esophageal Cancer? Prospective Nonrandomized Trial Comparing Chemoradiotherapy with Surgery versus without Surgery

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Abstract. The need for surgery after chemoradiotherapy for a T4N0-1M0 squamous cell carcinoma in the thoracic esophagus was evaluated. A series of 53 patients were enrolled in this prospective nonrandomized trial from among 124 patients with an esophageal cancer assessed as T4 in Kurume University Hospital from 1994 to 2002. After the first chemoradiotherapy cycle, which consisted of radiotherapy in a total dosage of 36 Gy and chemotherapy using cisplatin (CDDP) and 5-fluorouracil (5FU), the patients each decided, after being informed of the efficacy of the chemoradiotherapy, whether to undergo surgery. All patients, including those who had undergone surgery and those who had not, later underwent a second chemoradiotherapy cycle consisting of radiotherapy in a total dosage of 24 Gy and chemotherapy using CDDP and 5FU, as far as practicable. Among the responders to the first chemoradiotherapy cycle, there was no significant difference in the long-term (5-year) survival rate between the 18 patients who underwent esophageal surgery and the 13 patients who did not (23% vs. 23%). Among the nonresponders, the 11 patients who underwent surgery showed a tendency toward longer survival than the five patients who had had no surgery. The nonresponders had 1- and 2-year survival rates of 64% and 33%, respectively. The corresponding rates for the 5 nonsurgical patients who completed the two chemoradiotherapy cycle were 20% ands 20%, respectively. For a T4N0-1M0 squamous cell carcinoma in the thoracic esophagus, full-dosage chemoradiotherapy (definitive chemoradiotherapy) is preferred for responders to a half-dose of chemoradiotherapy as much as esophagectomy, whereas esophagectomy may be preferred for nonresponders.

The prognosis after surgery alone for patients who have a locally advanced esophageal cancer, in particular a T4 tumor involving the trachea, bronchus, or aorta, has remained dismal. Combined resection of a neighboring organ(s) together with esophagectomy has offered no benefit to the survival rate for such patients despite the high incidence of mortality and morbidity [1]. Palliative (R1 or R2) esophagectomy followed by radiotherapy with or without chemotherapy has also essentially offered no survival benefit compared with nonsurgical treatment [2].

Many surgeons have considered that chemoradiotherapy followed by surgery (whenever possible) is standard treatment for patients with a locally advanced esophageal cancer (i.e., T3/T4, N-any, M0 clinical stage tumors), whereas chemoradiotherapy alone should be given for nonresectable esophageal cancer or to patients who are medically unfit for surgery [3-5]. These surgeons have believed that only complete (R0) resection of the tumor following chemoradiotherapy can provide a survival benefit for patients with a locally advanced esophageal cancer, and that the volume of chemoradiation should be the minimum required to decrease the otherwise substantial associated postoperative morbidity and mortality (neoadjuvant chemoradiotherapy).

However, the relatively high rate of clinical and pathologic complete response with combined chemoradiotherapy has raised the question of whether surgical resection is necessary after chemoradiotherapy [6]. Radiologists and oncologists have also thought that chemoradiotherapy can offer a survival benefit even for such a tumor, when a complete response is achieved by high-volume chemoradiation (definitive chemoradiotherapy) [7]. They have thought that esophagectomy was necessary, rather, for persistent or recurrent disease after definitive chemoradiotherapy (salvage surgery) [8].

In the prospective nonrandomized trials reported here, long-term results were compared between definitive chemoradiotherapy with and without surgery to evaluate the need for surgery in the multimodal treatment for a T4 esophageal cancer.

Patients and Methods

Population

Among 482 patients with a cancer in the thoracic esophagus referred to the Kurume University Hospital between 1994 and 2002,

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the tumor in 124 patients was defined as T4 according to the TNM classification of the International Union Against Cancer (UICC) [9] during the preoperative staging. The criteria for inclusion in this prospective trial were as follows: (1) biopsy-confirmed squamous cell carcinoma in the thoracic esophagus; (2) locally advanced stage clinically defined as a T4 tumor [tumors defined according to the latest UICC classification as M1-Lym because of celiac or supraclavicular nodal involvement were also included in this trial (regional disease), excluding any patient with distant metastasis (M1-Org)]; (3) no previous treatment; (4) WHO performance status 0 to 2; (5) adequate hematologic, hepatic, renal, cardiac, and pulmonary function; the patient must also have a general condition adequate to tolerate esophagectomy or definitive chemoradiotherapy; (6) =75 years of age; (7) no active double primary cancer; (8) no contraindication to 5-fluorouracil (5FU), cisplatin (CDDP), or extensive irradiation; and (9) the patient must give a written informed consent.

The pretreatment staging evaluation consisted of: (1) a general physical examination; (2) chest and abdominal radiography; (3) contrast esophagography; (4) esophagoscopy; (5) cervical and upper abdominal ultrasonography (US); (6) computed tomography (CT) of the neck, chest, and upper abdomen; (7) magnetic resonance of imaging of the neck and chest; and (8) bone scintigraphy; with (9) bronchoscopy performed only for a cancer in the upper or middle thoracic esophagus.

Among the 124 patients with a T4 esophageal cancer referred to our department during the study period, only 53 were included in this trial. The excluded patients were as follows: 2 with adenocarcinoma or small-cell carcinoma; 16 with distant organ metastases; 9 with previous chemotherapy, radiotherapy, or both; 17 with a low performance status index or a contraindication to surgery or chemotherapy; 7 were >75 years old; 1 had an active double primary cancer; and 19 did not give informed consent for this trial. Among the last group, 11 patients chose preceding surgery (palliative esophagectomy), and the other 8 patients chose chemoradiotherapy alone from the beginning.

Treatment

This study was a nonrandomized prospective trial based on the informed decision that patients chose whether to undergo surgery between the first and second chemoradiotherapy cycles (Fig. 1). The first cycle consisted of (1) CDDP 24 mg/m^2 on days 1 and 8 and 10 mg/day from days 2 to 5 and from days 9 to 12 as a drip intravenous infusion for 2 hours; (2) 5FU 500 mg/day as a continuous intravenous infusion for 24 hours from days 1 to 5 and from days 8 to 12; and (3) radiotherapy delivered in hyperfractions of 1.2 Gy twice a day from days 1 to 5, days 8 to 12 and days 15 to 19, to a total dose of 36 Gy.

The first chemoradiotherapy cycle was evaluated 2 weeks after the end of radiotherapy and consisted of a physical examination, contrast esophagography, esophagoscopy, and CT scan. Patients them each decided whether to undergo surgery after being fully informed of the efficacy of the chemoradiotherapy (informed decision). When patients elected to have surgery, they were subjected to esophagectomy or a bypass operation. On the other hand, when patients elected not to have surgery, they underwent only the second cycle of chemoradiotherapy, which consisted of the same chemotherapy protocol as the first cycle and radiotherapy in a total dose of 24 Gy. Patients who did have surgery also underwent a second chemoradiotherapy cycle the same as described above 1 month after surgery.

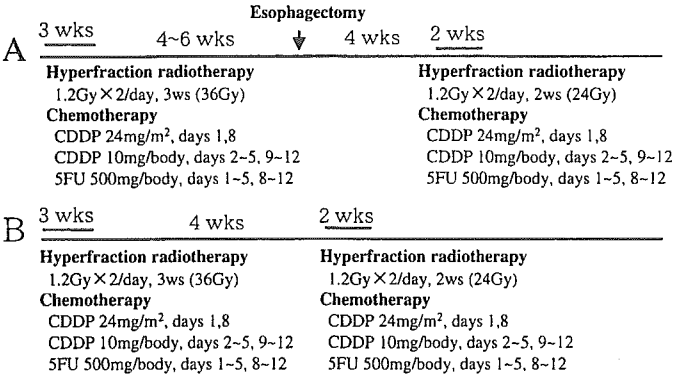

Fig. 1. Our treatment protocol for a locally advanced (T4) esophageal cancer. Arm A: Chemoradiotherapy with surgery. Arm B: Chemoradiotherapy alone. CDDP: cisplatin; 5FU: 5-fluorouracil.

Radiotherapy was administered using an 10-MV linear accelerator. The visible tumor volume also included 2 cm longitudinal margins and 2 cm lateral margins. In cases of definitive chemoradiotherapy, the radiation fields of the second chemoradiotherapy cycle were the same as those of the first cycle. In the patients with surgery, boost fields, with an oblique field, covered the primary tumor with at least 2 cm margins.

Surgery was scheduled for 1 month after the preoperative treatment. Esophagectomy with systemic lymphadenectomy, including thoracoabdominal two fields or cervicothoracoabdominal three fields, was performed through a right thoracotomy with cervical esophagogastrostomy depending on the tumor location and the macroscopic findings of residual tumor (R classification [9]). For patients who underwent curative (R0) resection of a cancer in the upper or middle thoracic esophagus, three-field dissection was performed, whereas for those who underwent curative (R0) resection of a cancer in the lower thoracic esophagus, two-field dissection (total mediastinal lymphadenectomy) was performed [10]. For patients who underwent macroscopic incomplete (R2) resection of an esophageal cancer in any location, selective lymphadenectomy was performed. When, in the opinion of the surgeon, esophagectomy could not be satisfactorily achieved, a bypass operation was done. In all cases, the stomach was used for the reconstruction.

Criteria for Response and Statistical Analyses

After the first chemoradiotherapy cycle, patients were reevaluated using contrast esophagography, endoscopy, and CT scanning. The response was considered complete (CR) when no radiographic evidence of disease was seen, no residual tumor was found during esophagoscopy, and the biopsy was negative. Otherwise, the response was classified as partial (PR): >50% regression in the tumor size in square measure on the contrast esophagograms or >30% regression in the tumor size in its maximal diameter on the CT scan. The final categories were either stable disease (no change, or NC) or progression (progressive disease, or PD) [11, 12]. After resection, a complete histologic response was defined as the absence of residual tumor in the esophagus and in nodal tissue. Toxicity was graded using

the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) [13].

Follow-up using a general physical examination, tumor markers including SCC antigen and carcinoembryonic antigen (CEA), and chest radiographs were performed every month for the first 2 years, every 2 months for 2 to 3 years after treatment, every 3 months for 3 to 5 years after treatment, and every 6 months thereafter. Endoscopy, US of the neck and abdomen, CT scan, and bone scintigraphy were routinely scheduled every year and repeated when any new clinical symptoms appeared or if any of the tumor markers increased to an abnormal level.

The overall survival was estimated according to the Kaplan-Meier method and compared using the generalized Wilcoxon test. The survival rates were calculated as being from the first day of chemoradiotherapy.

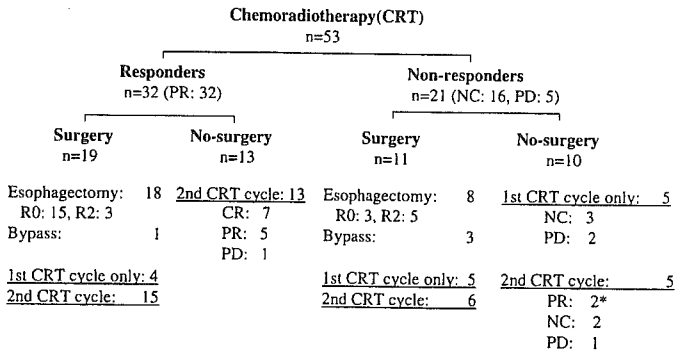

Fig. 2. Response to chemoradiotherapy and treatment modalities. After being informed of the response to the first chemoradiotherapy cycle, each patient decides whether to undergo surgery (informed decision). PR: partial response; NC: no change; PD: progressive disease; R0: no residual tumor (complete resection); R2: macroscopic residual tumor (incomplete resection).

Results

Response to Chemoradiotherapy

Fifty-three patients were enrolled in this trial. All patients received the complete dose of the first chemoradiotherapy cycle planned. After the first cycle, there were 32 (60%) patients with a partial response, 16 (30%) patients with no change or stable disease, and 5 (9%) patients with progressive disease. None of the patients had a complete response. Accordingly, the response rate to the first chemoradiotherapy cycle was 60% (32/53). Among the 23 patients who elected not to surgery, the second chemoradiotherapy cycle was completely administered to 18 patients; among them 7 (39%) patients had a complete response, 7 (39%) had a partial response, and 4 (22%) had no change or progressive disease. The other five patients did not undergo the second chemoradiotherapy cycle due to fistulas, tumor progression, or poor general condition. On the other hand, among the 30 patients who elected to undergo surgery, the second chemoradiotherapy cycle was completely administered to 21 patients but not in the other 9 patients due to postoperative complications or the patient's refusal (Fig. 2).

The pathologic response was assessed according to the Guidelines for Clinical and Pathological Studies on Carcinoma of the Esophagus of the Japanese Society for Esophageal Diseases [11] in the 27 resected specimens: 26 specimens after the first chemoradiotherapy cycle and 1 after the second chemoradiotherapy cycle. A complete pathologic response (pCR)-no cancer was seen in the resected specimen of the esophagus-was found in four (15%) patients. Of these four patients, however, two had metastases in their lymph nodes. Accordingly, only 2 (7%) of 26 patients who underwent esophagectomy after the first chemoradiotherapy cycle in our regimen were cancer-free.

Toxicity

Concurrent chemoradiotherapy was generally well tolerated. The major toxicity was hematologic, with 30% of the patients experiencing grade 3 or 4 leukopenia, 13% with grade 3 or 4 anemia, and 9% with grade 3 or 4 thrombocytopenia during or after the first chemoradiotherapy cycle. Altogether, 2 (6%) of 34 patients experienced grade 3 or 4 leukopenia, and 6% of those experienced grade 3 or 4 anemia during or after the second chemoradiotherapy cycle [13]. There were no death due to hematologic toxicity. Among those with nonhematologic toxicity, fistula formation was the most common and serious toxic response, with 6% of the patients developing esophagopulmonary fistula, 6% esophagobronchial fistula, and 2% aortoesophageal fistula during or after the first chemoradiotherapy cycle; 3% of the patients developed an aortoesophageal fistula and 3% an aortobronchial fistula during or after the second chemoradiotherapy cycle. Among the nine patients with fistula formation, five (56%) died of the fistula during hospitalization (Table 1). The overall hospital mortality rate due to chemoradiotherapy associated toxicity was 9% (5/53).

Surgical Results

Chemoradiotherapy followed by esophagectomy resulted in two (8%) hospital mortalities: one 3 days after surgery caused by pulmonary infarction and the other 7 months after surgery caused by a brain abscess. The most common postoperative complications in patients who underwent chemoradiotherapy followed by esophagectomy were recurrent nerve paralysis and aspiration pneumonia, which were the same as those in the patients who underwent surgery alone in our hospital [10]. The most common postoperative complications after chemoradiotherapy followed by bypass operation were anastomotic leak and aspiration pneumonia. The morbidity rates after esophagectomy and after the bypass operation were 85% and 100%, respectively (Table 2).

Survival Outcomes

The median follow-up for the surviving population was 51 months. No patient was lost to follow-up. Altogether, 37 patients died of progressive or recurrent disease: 19 after surgery and 18 after no surgery. Other causes of death were a postoperative complication in one patient (pulmonary embolism), pneumonia without recurrence in one, myocardial infarction in one, and another primary cancer in two (cholangiocellular carcinoma, prostate cancer). For one patient, the precise cause of death and the disease status at the time of death were unknown.

The median survival time for the whole population was 29 months, with 1-, 3-, and 5- year overall survival rates of 60%, 21%, and 16%, respectively. The 1-, 3-, and 5-year survival rates for the 30 patients who elected to undergo surgery (esophagectomy in 26, and bypass in 4) were 73%, 28%, and 17%, respectively. The

Table 1. Toxicity of grade 3 or higher according to the NCI-CTC

First CRTx cycle (n = 53)	
Leukopenia	16 (30%)
Anemia	7 (13%)
Thrombocytopenia	5 (9%)
Esophagopulmonary fistula	3[b] (6%)
Esophagobronchial fistula	3[b] (6%)
Sepsis/fever	2 (4%)
Diarrhea	2 (4%)
Pneumonia	2 (4%)
Aortoesophageal fistula	1[b] (2%)
Renal dysfunction	1 (2%)
DIC	1 (2%)
Second CRTx cycle (n = 39)[a]	
Leukopenia	2 (5%)
Anemia	2 (5%)
Aortoesophageal fistula	1[b] (3%)
Aortobronchial fistula	1[b] (3%)
Pneumonitis	1 (3%)

NCI-CTC: National Cancer Institute-Common Toxicity Criteria Version 2.0, January 30, 1998; CRTx: chemoradiotherapy; DIC: disseminated intravascular coagulation:

[a]Surgery group 21, no-surgery group 18.

[b]Hospital death in one cases each.

Table 2. Postoperative complications

Complication	Esophagectomy (n = 26)	Bypass (m = 4)
Recurrent nerve paralysis	13 (50%)	1 (25%)
Aspiration pneumonia	9 (35%)	3 (75%)
Tracheal ischemia (ulcer, erosion)	6 (23%)	0
Pyothorax	6 (23%)	0
Anastomotic leak	5 (19%)	4 (100%)
Ileus	3 (12%)	0
Severe arrhythmia	2 (8%)	0
Pulmonary infarction	1[a] (4%)	0
MRSA enteritis	1 (4%)	0
Brain abscess	1[a] (4%)	0
Morbidity	22 (85%)	4 (100%)
Mortality	2 (8%)	0

MRSA: methicillin-resistant *Staphylococcus aureus*.

[a]Hospital mortality.

corresponding rates for the 23 patients who elected not to undergo surgery (chemoradiotherapy alone in 16, additional esophageal stent in 6, and emergency salvage surgery in 1) were 44%, 13%, and 13%, respectively. There was no significant difference in the survival rate between the surgical patients and the nonsurgical patients (p = 0.08) (Fig. 3).

The 1-, 3-, and 5-year survival rate for the 32 responders to the first chemoradiotherapy cycle were 75%, 31%, and 23%, respectively, and for the 21 nonresponders the 1- and 3-year survival rates were 38% and 6%, respectively, with no patient surviving more than 4 years. There was a statistically significant difference in the survival rates between the responders and the nonresponders to chemoradiotherapy (p = 0.008) (Fig. 4).

To analyze the outcome fairly, it seems preferable to compare the surgical patients to the nonsurgical patients according to response to chemoradiotherapy. For the 19 surgical patients among the 31 responders, the 1-, 3-, and 5-year-survival rates were 79%, 37%, and 23%, respectively; the corresponding rates for the 13 nonsurgical patients were 69%, 23%, and 23%, respectively. Among the responders to chemoradiotherapy, there was no difference in the survival rate between the surgical patients and the nonsurgical patients (Fig. 5).

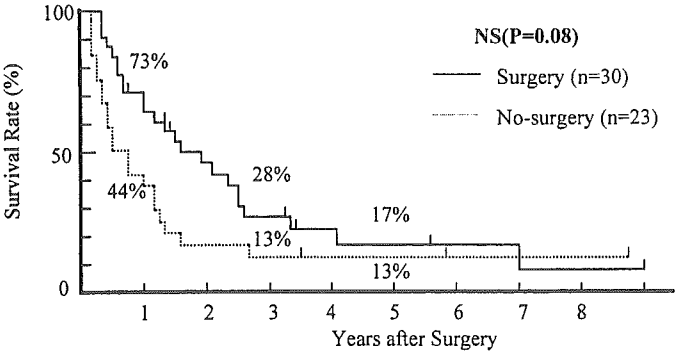

Fig. 3. Survival curves for patients who underwent surgery and those who did not. The survival rate for the surgery group was not different from that for the no-surgery group (p = 0.08).

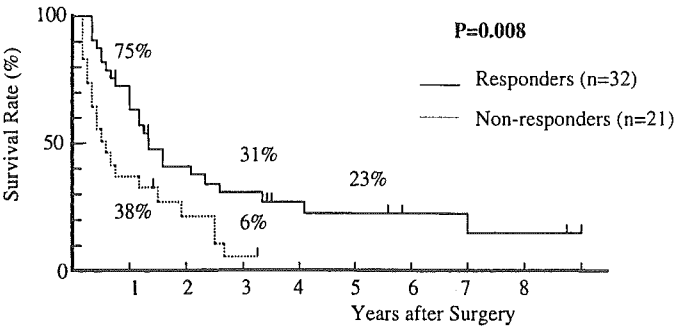

Fig. 4. Survival curves for responders and for nonresponders to chemoradiotherapy. There was a significant difference in the survival rates between the responders and the nonresponders (p = 0.008).

On the other hand, for the 11 surgical patients among the 21 nonresponders, the 1- and 2-year-survival rates were 64% and 33%, respectively; the corresponding rates for the 5 nonsurgical patients who completed both the first and second chemoradiotherapy cycles-definitive chemoradiotherapy-were 20% and 20%, respectively. For the nonresponders to chemoradiotherapy, the surgical patients had a tendency toward longer survival than the nonsurgical patients, although there was no significantly difference between them (p = 0.168) (Fig. 6). Among five patients classified as nonsurgical patients, one underwent salvage surgery after definitive chemoradiotherapy and survived 32 months, whereas the other four patients died within 1 year. Accordingly, the 1- and 2-year-survival rates of the patients who underwent surgery were 66% and 39%, respectively, whereas the corresponding rates for the patients who did not were 0% and 0%. The difference between them was statistically significant (p = 0.001).

Discussion

We have presented the results of a prospective comparative trial of 53 patients with T4N0-1M0 squamous cell carcinomas in the thoracic esophagus treated with chemoradiotherapy and with or without surgery. This trial was not randomized. It was difficult for us to perform a randomized control trial comparing surgery versus no surgery in Japan. Patients themselves chose a treatment arm-surgery versus no surgery-(informed decision) based on

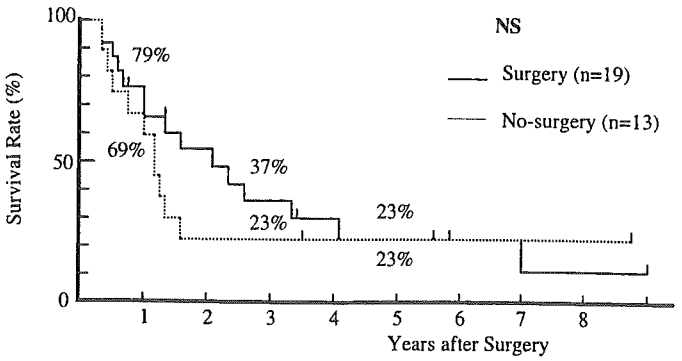

Fig. 5. Survival curves for the responders to chemoradiotherapy. There was no difference in the survival rates between the patients who underwent surgery and those who did not.

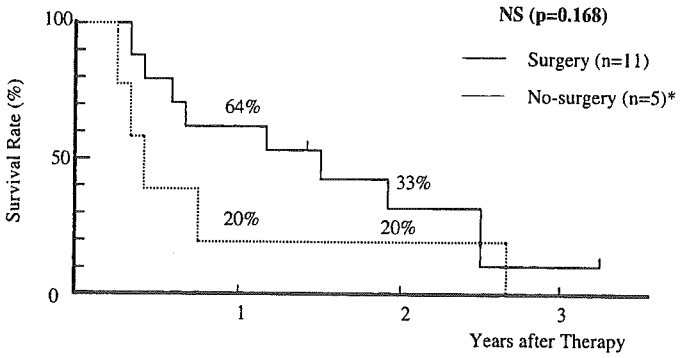

Fig. 6. Survival curves for nonresponders to chemoradiotherapy. *Patients who received both the first and second chemoradiotherapy cycles (i.e., definitive chemoradiotherapy). There was a tendency toward a better survival rate for patients who underwent surgery than for those who did not (p = 0.168).

information from both surgeons and radiologists about their response to the first chemoradiotherapy cycle, the method of the next treatment, expected prognosis, and other factors. Because of such a complicated situation, we obtained informed consent using a certain printed form from almost all patients enrolled, whereas for other patients we used hand-written consent forms

A total of 14 patients did not receive the second chemoradiotherapy cycle because of fistulas, postoperative complications, patient's refusal. Moreover, 5 of the 14 patients underwent neither surgery nor the second chemoradiotherapy cycle mainly due to a fistula or poor general condition (or both). When the survival rates were compared in this study, therefore, we included the patients who underwent surgery, regardless of esophagectomy or bypass and regardless of with or without the second chemoradiotherapy cycle; in contrast, we excluded the patients who did not undergo the second chemoradiotherapy cycle from the nonsurgical patient group.

In this trial, chemotherapy using (1) CDDP 24 mg/m^2 on days 1 and 8, and 10 mg/day on days 2 to 5 and days 9 to 12; (2) 5FU 500 mg/days on days 1 to 5 and days 8 to 12; and (3) hyperfraction radiotherapy of 1.2 Gy twice a day on days 1 to 5, days 8 to 12, and days 15 to 19, to a total dosage of 36 Gy were applied as the first cycle. The clinical effect of the first chemoradiotherapy cycle was evaluated after 2 weeks; then more than 1 to 2 weeks was needed to obtain informed consent. Thus the interval between the first and second cycles of chemoradiotherapy, even in the nonsurgical cases, was about 4 weeks on average. In one-third of patients who underwent chemoradiotherapy according to this regimen, a nadir of grade 3 or higher bone marrow suppression was observed 2 weeks after chemoradiotherapy (Table 1). It was therefore difficult to start the second chemoradiotherapy cycle within 3 weeks after the first chemoradiotherapy cycle. On the other hand, we thought that the first cycle of chemoradiotherapy in our regimen should achieve an effect equal to that of other regimens of neoadjuvant chemoradiotherapy for T4 esophageal cancers [4, 5]. The biologic effect of twice-daily radiotherapy of 2.4 Gy per day, to a total dosage of 36 Gy for 3 weeks, was considered comparable to that of once-daily radiotherapy of 2 Gy per day to a total dosage of 40 Gy for 4 weeks. The area under the curve (AUC) of the CDDP concentration in the blood after administration of CDDP 24 mg/m^2 on days 1 and 8 and 10 mg on day 2 to 5 and day 9 to 12; that is approximately 150 mg/2 weeks in total, was considered comparable to that after every-day administration of CDDP 10 mg for 4 weeks, that is, 200 mg/4 weeks in total.

The 5-year survival rate in this trial was 16% for the whole population, 23% for the responders, and 0% for the nonresponders. The 5-year survival rate was 17% for the surgical patients and 13% for the nonsurgical patients. Surgery did not seem to have improved the survival for responders to the first chemoradiotherapy cycle: Those patients had a 5-year survival rate of 23% with surgery versus 23% without surgery. On the other hand, surgery seemed to have improved the survival for nonresponders to the first chemoradiotherapy cycle: Those patients had 1- and 2-year survival rates of 64% and 33%, respectively, with surgery versus 20% and 20%, respectively, without surgery. When the patient undergoing salvage surgery was included in the surgical patient group, the 1- and 2-year survival rates for the surgical patients were 66% and 39%, respectively, whereas the corresponding rates for the nonsurgical patients were 0% each. It was concluded that in patients with a T4N0-1M0 esophageal cancer definitive chemoradiotherapy offered a survival similar to that achieved by surgery for responders but not for nonresponders.

Many studies using neoadjuvant chemoradiotherapy followed by esophagectomy to treat locally advanced esophageal cancers have been reported. Most of them used CDDP-based chemotherapy with a radiation dosage between 40 and 45 Gy. The complete histologic response rate in the resected specimens ranged from 28% to 33%. This rate for all patients who had undergone neoadjuvant chemoradiotherapy has ranged from 18% to 28%. They reported the superiority of neoadjuvant chemoradiotherapy followed by surgery over chemoradiotherapy alone or surgery, alone [3-5]. However, some investigators have doubted the need for surgical resection after chemoradiotherapy for a locally advanced esophageal cancer [6]. Phase III studies to determine any significant benefit from neoadjuvant chemoradiotherapy followed by surgery for a locally advanced esophageal cancer compared with chemoradiotherapy alone are rare.

Recently, a French randomized controlled trial on locally advanced but resectable (T3-4N0-1M0) esophageal cancers including squamous cell carcinoma and adenocarcinoma compared chemoradiotherapy followed by surgery to chemoradiotherapy alone. It demonstrated similar 2-year survival rates (34% vs. 40%) for the two treatment modalities in the responders to two-thirds doses of definitive chemoradiotherapy [14]. A German randomized controlled trial also demonstrated no difference in 3-year

survival rates (28% vs. 30%) between preoperative chemoradiotherapy followed by surgery versus chemoradiotherapy alone for a T3-4N0-1M0 squamous cell carcinoma [15]. As reported above, some authors have maintained that surgery is not necessary for responders to chemoradiotherapy.

Another approach has been to explore whether surgical resection after chemoradiotherapy can improve the survival results compared to chemoradiotherapy alone. Murakami et al. [16] reported results from a trial comparing chemoradiotherapy alone to chemoradiotherapy followed by esophagectomy for locally advanced (T3 or T4) esophageal cancers. They divided the patients into two groups. In one group, esophagectomy was performed in nonresponders to chemoradiotherapy but was not performed in responders; in the other group, patients underwent esophagectomy alone. The 5-year survival rate was no different between the two groups (31% vs. 30%). They concluded that surgery was not necessary for responders to chemoradiotherapy. Whether esophagectomy is necessary for those who do not respond chemoradiotherapy remains controversial. Murakami et al. suggested, similar to our conclusion, that surgery was necessary only for nonresponders to chemoradiotherapy. There are some reasons to support esophagectomy for nonresponders. First, clinical evaluation of the response to chemoradiotherapy does not always correlate with the pathologic response. Therefore, a complete pathologic response in the resected specimen or complete R0 resection of esophageal cancer can be achieved even in patients who were evaluated as being nonresponders. In this trial, 3 (27%) of the 11 nonresponders to the first chemoradiotherapy cycle underwent R0 resection of esophageal cancer (Fig. 2). Second, esophagectomy for nonresponders to the first cycle of chemoradiotherapy and subsequent chemoradiotherapy (the second cycle of chemoradiotherapy) might be comparable to salvage surgery for partial responders to definitive chemoradiotherapy [17].

A consensus is not always obtained regarding the need for esophagectomy in a multimodol treatment regimen for T4 esophageal cancers. Further evaluation using a large-scale prospective randomized study is needed.

Acknowledgments

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Invited Commentary (DOI: 10.1007/s00268-004-1081-3)

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The authors performed a prospective nonrandomized trial to evaluate the role of surgery secondary to chemoradiotherapy in patients with T4N0-1M0 esophageal cancer. They found significantly better survival in responders to chemoradiotherapy than in nonresponders and a better survival rate in the surgery group than in the nonsurgery group. They analyzed whether responders obtained any additional benefit by undergoing surgical resection compared with responders who did not, probably because per-

formance of surgery after chemoradiotherapy was associated with a high rate of serious postoperative complications. They could not detect any benefit of surgical resection following chemoradiotherapy by comparing the survival curves of these two groups, although the 2- and 3-year survival rates were 55% and 37%, respectively, which were higher than the rates of 23% and 23%, respectively, in the nonsurgery group. The same analysis was done for nonresponders and showed no significant difference in survival between the surgery and nonsurgery groups, but the 1- and 2-year survival rates for the surgery group (64% and 33%, respectively) were considerably better than in the no-surgery group (20% and 20%, respectively).

This is an important study for trying to determine the role of surgery in treating of a T4 stage esophageal cancer, which cannot be cured by surgery alone and might be systemic with micrometastases. From a historical point of view, surgery after radiation therapy has not achieved good results for resectable esophageal cancer because of the difficulty performing anatomically precise resection due to severe postradiation fibrosis and various severe postoperative complications. The survival curves in their Figures 4 and 5 show that the 5-year survival rate for responders was 23% irrespective of surgery, so surgery might provide little if any benefit for T4N0-1M0 cancer in this protocol.

In the discussion, the authors recommended surgery for nonresponders, and not for responders. This might be reasonable because surgery did not lead to better survival in responders and a tendency for a better survival rate with the surgery group was noted only in nonresponders. The survival curves of nonresponders in their Figure 6 shows higher survival rates within 2 years for the surgery group compared with the nonsurgery group. We might say that surgery can be recommended for the nonresponders who would like to have a higher probability of living 1 to 2 years longer. In Figure 5, we see a 50% two-year survival rate for the surgery group of responders, although it is only 23% for the no-surgery group, so surgery might also be recommended for responders who want a higher probability of living at least 2 years.

In conclusion, this is an interesting study that showed meaningful efficacy of chemoradiotherapy for T4N0-1M0 esophageal cancer independent of surgery. We would like to see another prospective randomized study by these investigators using another protocol.

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ORIGINAL ARTICLE

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Salvage surgery after definitive chemoradiotherapy for esophageal cancer

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Abstract
Background. Definitive chemoradiotherapy has been performed as a first-line treatment for esophageal cancer, whereas salvage surgery might be the only reliable treatment for patients with recurrence after definitive chemoradiotherapy.
Methods. We reviewed 38 patients with squamous cell carcinoma who underwent esophagectomy and 6 patients who underwent lymphadenectomy after definitive chemoradiotherapy (≥50 Gy).
Results. The median survival time and 5-year survival rate after salvage esophagectomy were 16 months and 27%, respectively. Three of the 7 patients who had cervical esophageal cancer underwent cervical esophagectomy with laryngeal preservation. Two patients (5.2%) who underwent salvage esophagectomy with three-field lymphadenectomy before 1997 died of postoperative complications, but no patient died of complications thereafter. Although the overall survival after salvage esophagectomy was correlated with residual tumor (R) ($P = 0.0097$), the median survival time of 7 patients with residual tumors (R_2) was 7 months. Overall postoperative survival was closely correlated with the response to chemoradiotherapy ($P < 0.0001$) but was not associated with histologic effects on resected specimens. Survival was significantly correlated with the depth of viable tumor invasion (pT) ($P = 0.0013$) and with lymph node metastasis (pN) ($P < 0.0001$). Long-term survival was achieved in 5 of the 6 patients who underwent salvage lymphadenectomy.
Conclusions. Salvage surgery should be considered for patients with recurrence after definitive chemoradiotherapy. Salvage lymphadenectomy may be useful for recurrence confined to the lymph nodes whereas postoperative complications of salvage esophagectomy should be warranted.

Key words Esophageal cancer · Squamous cell carcinoma · Chemoradiotherapy · Salvage surgery · Salvage lymphadenectomy

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Introduction

Definitive radiotherapy combined with infusion of cisplatin and 5-fluorouracil (5-FU) improves the survival of esophageal cancer patients compared with radiotherapy alone [1,2]. Medical and radiation oncologists have also reported the improved survival of esophageal cancer patients treated by definitive chemoradiotherapy without surgery [3–7]. However, local failure and lymph node metastasis are frequent problems after definitive chemoradiotherapy [8,9]. Further radiotherapy is not indicated because the dose will exceed that treated by the spinal cord and no effective second-line chemotherapy agents for esophageal cancer have been discovered. Thus, surgery is the only useful treatment for recurrence after definitive chemoradiotherapy. The outcome of salvage esophagectomy after definitive chemoradiotherapy is comparable with that of esophagectomy after neoadjuvant chemoradiotherapy [10,11], but the operative risk of salvage esophagectomy might be higher than that of esophagectomy after neoadjuvant chemoradiotherapy [11]. Lymphadenectomy might also be indicated including as part of salvage surgery after definitive chemoradiotherapy.

In this study, we reviewed the profile and prognosis of esophageal cancer patients who underwent salvage esophagectomy or lymphadenectomy after definitive chemoradiotherapy. To search for prognostic valuables after salvage esophagectomy, we examined various clinical and pathological parameters.

Patients and methods

We reviewed the records of 725 patients with esophageal cancer who underwent esophagectomy between 1992 and 2003 at the Institute of Gastroenterology of Tokyo Women's Medical University in Japan. Thirty-eight patients with a clinical diagnosis of esophageal cancer who received definitive chemoradiotherapy (≥50 Gy) before esophagectomy were included in this study, whereas 3 patients who underwent esophagectomy 10 years or more after definitive radiotherapy were excluded. Lymphadenectomy was performed in 6 patients in whom lymph node metastases were detected after definitive chemoradiotherapy. In all patients, chemotherapy consisted of 5-fluorouracil and/or cisplatin/nedaplatin was given concurrently or sequentially with definitive radiotherapy.

Eight patients who received chemoradiotherapy at another hospital were referred to our institute at the diagnosis of recurrence. The other 30 patients received chemoradiotherapy and were followed in our institute. Data on the general condition and clinical stage before treatment were obtained in all patients. A diagnosis of squamous cell carcinoma was histologically confirmed before treatment by endoscopic biopsy in all of the patients. Clinical staging was based on the results of barium swallow, endoscopy, endoscopic ultrasound (EUS), and computed tomography (CT) scanning, and was performed according to the TNM classification (UICC) [12].

The response was assessed at 1 month after chemoradiotherapy according to the criteria for the response assessment of nonsurgical treatment proposed by the Japanese Society for Esophageal Diseases [13]. The primary tumor was reevaluated by review of the barium swallow, endoscopy, and biopsy findings, whereas the metastatic lesions were assessed by using CT scans of the neck, chest, and abdomen as well as the results of EUS. Diagnosis of response to chemoradiotherapy in the patients was evaluated together in the primary tumor and in the metastatic lesions.

On examination of the resected specimens, the depth of tumor invasion (pT) was defined on the basis of the deepest detected layer of viable cancer cells. Lymph node metastasis (pN) or distant metastasis (pM) was defined by the detection of viable cancer cells in lymph nodes or other organs. The tumor response to treatment was also evaluated by examination of the resected specimens according to the histopathologic criteria for assessing the effects of radiation and/or chemotherapy [13]. If no viable cancer cells were detected (grade 3), this was classified as a pathologic complete response (pCR), whereas viable cancer cells comprising less than one-third of the tumor (grade 2) was classified as a partial response. If viable cancer cells comprised one-third or more of the tumor (grade 1) or there was no discernible effect of treatment (grade 0), this was classified as no response.

Differences of quantitative data were assessed by Student's *t* test. Differences of percentages were evaluated by the two-sided chi-square test or Fisher's exact test. Survival was calculated from the day of operation until the last known date of follow-up. All survival data were analyzed with Statview, Version 4 (SAS Institute, Cary, NC, USA). Survival curves were constructed according to the Kaplan–Meier method and were compared using the log-rank test.

Table 1. Characteristics of patients who underwent esophagectomy after definitive chemoradiotherapy

Characteristics	Number of patients (n = 38)
Male : female ratio	28 : 10
Median age, years (range)	63 (36–79)
Tumor location	
Cervical	7 (18%)
Upper	3 (8%)
Middle	21 (55%)
Lower	7 (18%)
Tumor invasion	
T1	6 (16%)
T2	2 (5%)
T3	12 (32%)
T4	18 (47%)
Distant metastasis	
M0	29 (76%)
M1	9 (24%)
Total dosage of irradiation: mean (range)	62.4 (50–78) Gy

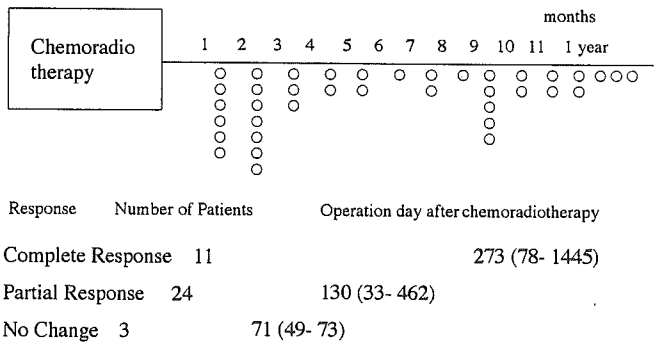

Fig. 1. Interval between the final day of chemoradiotherapy and salvage esophagectomy

Results

The tumor locations and pretreatment clinical stages are shown for the 38 patients who underwent salvage esophagectomy in Table 1. The median interval from the final day of chemoradiotherapy until the operation was 156 (33–1445) days (Fig. 1), and its duration was associated with the response to chemoradiotherapy.

Although three of the seven patients who had cervical esophageal cancer underwent cervical esophagectomy with preservation of the larynx, one patient died of tracheal obstruction caused by local recurrence. The other four patients underwent pharyngolaryngoesophagectomy.

Table 2. Approaches and short outcomes of salvage esophagectomy

Approaches	Early period (n = 15)	Later period (n = 16)	Probability
Right thoracotomy	11	7	
Left thoracotomy	2	6	NS
Transhiatal	2	3	
Lymph node dissection			
Three-field	6	4	
Two-field	5	5	NS
Local and abdominal	4	7	
Outcomes			
Mortality (within 30 days)	1		
Hospital mortality (>30 days)	1		
Leakage (surgery)	6 (3)	3 (2)	
Pneumonia	4	2	
Wound infection	1	1	
Pleural effusion	1	2	
Residual tumors (%)			
R_0	9	10	
$R_{1,2}$	6	6	

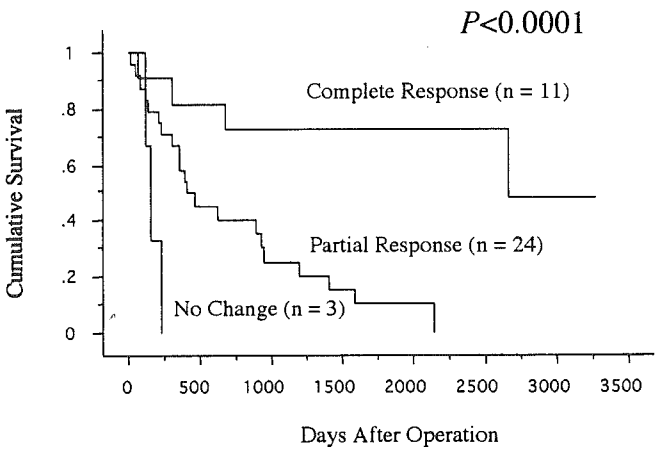

Fig. 2. Survival after salvage esophagectomy was correlated with response to definitive chemoradiotherapy

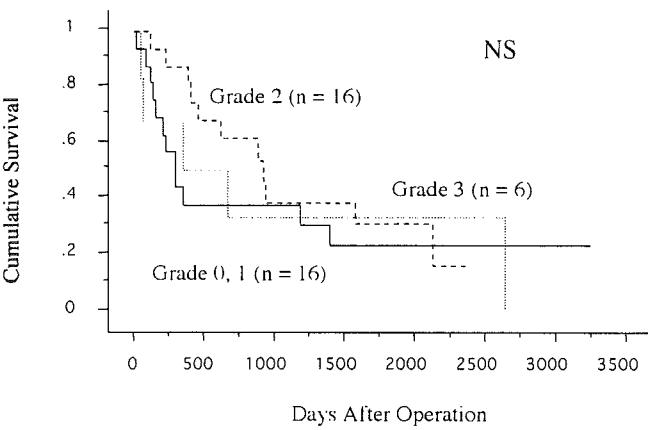

Fig. 3. No differences were shown in overall survival after salvage esophagectomy according to histopathologic effect in the resected specimens

Surgical procedures and postoperative complications of esophagectomy are shown for 31 patients with thoracic esophageal cancer (Table 2). Two patients (5.2%) who underwent extended esophagectomy with three-field lymph node dissection before 1997 died of postoperative complications; less-invasive procedures were adopted thereafter. One patient died of acute respiratory distress syndrome (ARDS) on postoperative day 22, and 1 patient died of anastomotic leakage and pneumonia on postoperative day 62. Both patients underwent extended esophagectomy via right thoracotomy with three-field lymphadectomy during the early period (1992–1996). Then, three-field lymphadenectomy was performed limited to 4 patients with cervical metastasis diagnosed preoperatively. There was no operative mortality and no hospital deaths during the later period (1997–2003). The incidence of postoperative pneumonia also decreased in the later period (from 5 to 2 cases). However, the incidence of anastomotic leakage was high in the both periods (5 versus 4 cases).

With a median follow-up period of 61 months, the median survival time and the 5-year survival rate after salvage esophagecotmy were 16 months and 27%, respectively. There were no significant differences of overall postoperative survival in relation to the pretreatment clinical staging. In contrast, the response to chemoradiotherapy had a significant influence on postoperative survival ($P < 0.0001$) (Fig. 2). Postoperative survival was not influenced by the interval between the final day of chemoradiotherapy and the day of surgery. There was also no difference in survival related to the pathologic effect of therapy on the resected specimens (Fig. 3). Four of six patients with a pathologic complete response (grade 3) died of pneumonia or heart failure. The survival of the patients without residual tumor (R_0) was significantly better than that of the R_1 or R_2 patients ($P = 0.0097$) (Fig. 4). However, the median survival time of 7 patients with residual tumors (R_2) was 231 days (133–410 days). The depth of viable tumor invasion (pT) ($P = 0.0013$) (Fig. 5) and lymph node metastasis

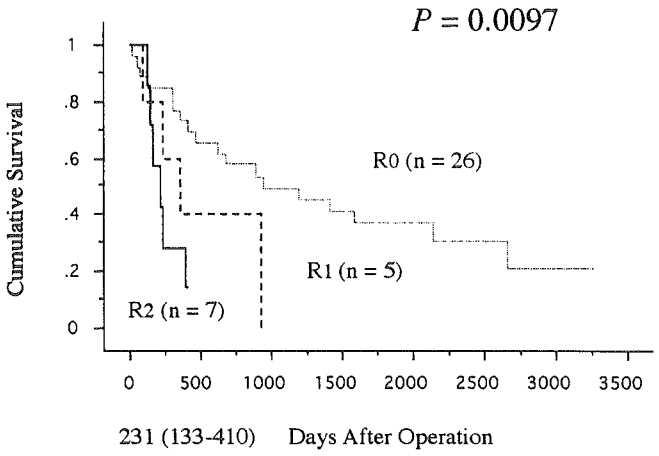

Fig. 4. Survival of patients after salvage esophagectomy without residual tumors (R_0) was significantly better than that of patients with R_1 or R_2

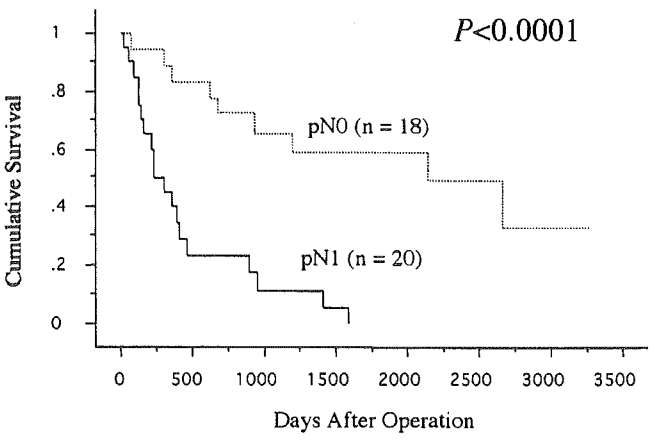

Fig. 6. Survival after salvage esophagectomy was correlated with viable metastasis in the resected lymph nodes (*pN*)

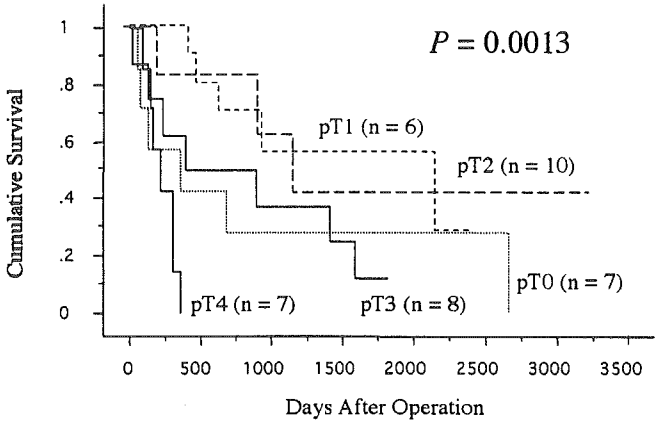

Fig. 5. Survival after salvage esophagectomy was correlated with depth of viable cancer cells in the resected specimens (*pT*)

(pN) (Fig. 6) ($P < 0.0001$) both had a significant influence on survival.

Six patients underwent lymphadenectomy alone for lymph node metastasis after chemoradiotherapy (Table 3). The primary tumors showed a complete response in all six patients. Among them, three patients had metastatic nodes within the radiation field (cases 2, 3, and 4), but the other three had nodes located outside the field and were given further radiation after lymphadenectomy (cases 1, 5, and 6). One patient died of multiple metastases to distant lymph nodes, but the other five patients survived without recurrence.

Discussion

Definitive chemoradiotherapy is performed as a first-line treatment for squamous cell cancer of the esophagus, not only for advanced disease but also for operable tumors. The CR rate is reported to be high, ranging from 33% to 61%, but the long-term survival rate is low [5–7]. A considerable number of patients develop local and/or regional recurrence after definitive chemoradiotherapy. Surgeons are forced to treat these patients because only salvage surgery is an effective treatment for recurrence after definitive chemoradiotherapy. Although we could not compare with the outcome of definitive chemoradiotherapy without surgery, the results of this study indicated that salvage surgery might be regarded as an effective second-line treatment after definitive chemoradiotherapy.

Esophagectomy with three-field lymphadenectomy is the most radical surgery, but it is not suitable for all patients treated by definitive chemoradiotherapy because of the high operative risk. Our previous study showed that the risk of salvage esophagectomy was higher than that of planned esophagectomy after neoadjuvant chemoradiotherapy [11]. Although the interval between chemoradiotherapy and esophagectomy was not short, two patients died of postoperative complications. We could not anticipate these complications because both patients had no obvious indicators on physical examination or laboratory tests. A recent study showed that several cancer-free patients died of chronic heart failure, pneumonia, and myocardial infarction after definitive chemoradiotherapy [14]. These events tended to occur in the postoperative period after salvage esophagectomy, suggesting that salvage surgery should be done by a less invasive approach.

At present, definitive chemoradiotherapy is indicated in patients with cervical esophageal cancer to preserve the larynx. Three of our seven patients with cervical cancer underwent cervical esophagectomy with preservation of the larynx, but one patient developed local recurrence. Both the diagnosis of recurrence and detection of the proximal tumor margin might be difficult because of esophageal stricture. Therefore, salvage cervical esophagectomy with preservation of the larynx might only be indicated for a limited number of patients. Recently, we have used positron emission tomography with 2-[^{18}F]-fluoro-2-deoxy-D-glucose

Table 3. Characteristics of patients who underwent lymphadenectomy after definitive chemoradiotherapy

Patients	Stage	Location	Interval[a]	Lymph node[b]	Prognosis after lymphadenectomy
1. 75 Male	T3N1M1	Middle	9 months	Rt-supraclavicular	56 months alive
2. 54 Male	T4N1M0	Upper	11 months	Lt-supraclavicular	46 months alive
3. 43 Male	T2N1M0	Cervical	5 months	Lt-deep cervical	16 months alive
4. 79 Male	T3N1M0	Middle	6 months	Lt-supraclavicular	12 months dead
5. 67 Male	T1N0M0	Middle	13 months	Lt-cardial	38 months alive
6. 67 Male	T4N1M0	Middle	13 months	Rt-supraclavicular	16 months alive

[a] Interval from the final date of radiotherapy to the operation date
[b] Location of recurrent lymph node: Rt, right; Lt, left

(FDG-PET), but it cannot detect small recurrent tumors [15].

The pretreatment clinical stage was not associated with postoperative survival after salvage esophagectomy, but the clinical response to chemoradiotherapy was closely correlated. Histologic response on the resected specimens was not associated with postoperative survival because recurrent tumors might show viability without degeneration long term after achieving complete response. Therefore, histologic response might be useful for patients who underwent esophagectomy after neoadjuvant chemoradiotherapy but not for salvage esophagectomy, with the exception of pathological complete response (grade 3). Although staging of recurrence after definitive chemoradiotherapy might be difficult by imaging, residual tumor (R), pathologic tumor invasion (pT), and lymph node metastasis (pN) were valuable for prognostic factors after salvage esophagectomy. Even though their tumors were deemed unresectable on imaging, six patients with macroscopic residual tumors (R_2) survived for more than 4 months after salvage esophagectomy. Although we could not compare with results of nonsurgical treatment for these patients, palliative esophagectomy might improve the prognosis unless postoperative complications occur.

Salvage lymphadenectomy is another mode of salvage surgery for lymph node metastasis after chemoradiotherapy. When the local tumor maintains a complete response, esophagectomy may be unnecessary and the risk of lymphadenectomy is lower than that of esophagectomy. This study showed that the outcome of salvage lymphadenectomy was favorable, except in one patient who died of multiple metastases. The results of salvage lymphadenectomy were similar to those of lymphadenectomy for recurrence in the cervical nodes after esophagectomy with two-field lymphadenectomy. To improve the outcome of salvage surgery, patients with recurrence after definitive chemoradiotherapy should probably be immediately referred to experienced surgical institutions by their medical and radiation oncologists.

In conclusion, salvage surgery seems to be useful for recurrence of esophageal cancer after definitive chemoradiotherapy, but less invasive approaches should be adopted for salvage esophagectomy because of the high operative risk. Salvage lymphadenectomy is also useful for patients who have distant nodal metastasis without local recurrence.

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