特集

食道癌根治的化学放射線療法における salvage 手術の意義

予後よりみた食道癌に対する化学放射線療法後 salvage 手術の適応

中村　努[*1]　太田正穂[*1]　成宮孝祐[*1]　佐藤拓也[*1]
大木岳志[*1]　林　和彦[*1]　山本雅一[*1]

Indication of Salvage Surgery for Esophageal Cancer after Definitive Chemoradiotherapy: Nakamura T[*1], Ota M[*1], Narumiya K[*1], Sato T[*1], Ohki T[*1], Hayashi K[*1] and Yamamoto M[*1] ([*1]Department of Surgery, Institute of Gastroenterology, Tokyo Women's Medical University)

Although salvage esophagectomy after chemoradiotherapy is a highly invasive operation, surgeons have to treat the patients who had residual or recurrent tumors. We analyzed the data of 46 patients who underwent salvage esophageactomy and 8 patients who did lymphadenectomy. Two patients died of salvage esophagectomy before 1997, but no mortality thereafter, and the total mortality rate has been decreased to 4.4%. Almost all of the patients with lymph node metastasis died after salvage esophageactomy. The indication of salvage esophagectomy might be limited to local recurrence without metastasis. Lymph nodes metastasis should be dissected by salvage lymphadenectomy.

Key words: Esophageal squamous cell carcinoma, Radiochemotherapy, Salvage esophagectomy, Salvage lymphadenectomy

Jpn J Cancer Clin **53**(10): 619～623, 2007

はじめに

食道癌に対する根治的化学放射線療法がさかんに行われるようになり，その遺残・再発例に対する手術を salvage 食道切除術と名付けられた[1])．そして，われわれが以前に報告したように salvage 手術の危険性が高く，術式の低侵襲化が図られてきた[2])．また，手術適応も癌の進展と全身状態を考慮してしぼられるべきである．しかし，もともと根治的化学放射線療法後の遺残や再発が対象であり，手術以外に有効な治療がない症例である．そこで，手術での死亡を避け1年以上生存できれば手術をうける意味があると考えられる．しかし，腫瘍内科や放射線科，最終的に外科でこの条件を満たす症例を選択することは容易ではない．一方，salvage 手術は各種学会で取り上げられ食道癌治療における比重の大きくなっている[3])．今回，最近の治療成績と臨床病理学的所見を検討して，salvage 手術の適応を決める際に重要な因子について詳述する．

1. salvage 食道切除術の成績

食道癌に対して根治的化学放射線療法が行われるようになったが，食道を温存すること自体に再発の危険があり salvage 食道切除術の意味はあると考えられる[4])．当院において salvage 食道切除術は早くから導入し2006年までに46例を数えている（表1）．10年前の1996年までに18例行われ，2例死亡しており約11%の死亡率であっ

*1 東京女子医科大学消化器外科

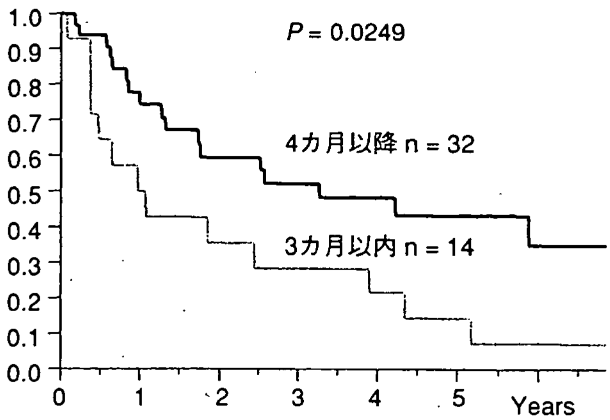

図1 化学放射線療法終了から salvage 食道切除術までの期間と術後生存曲線

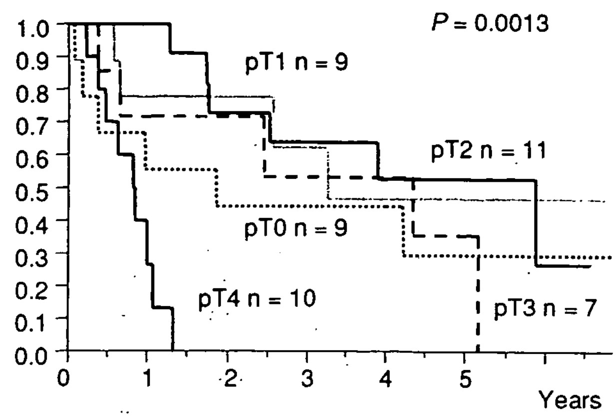

図2 salvage 食道切除術を施行した症例の組織学的深達度と術後生存曲線

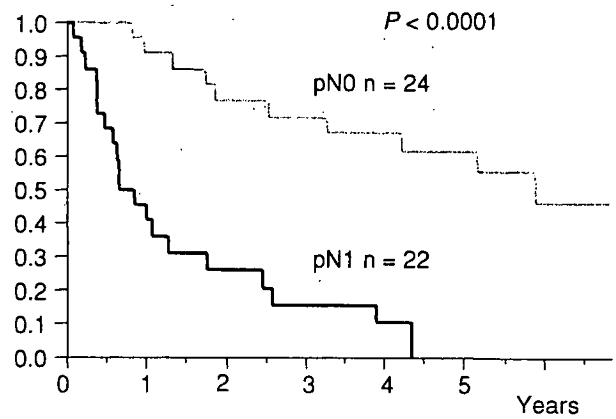

図3 salvage 食道切除術を施行した症例の組織学的リンパ節転移と術後生存曲線

方が salvage 手術後生存率は有意に低下していた（図1）．やはり，癌遺残が治療終了後3カ月以内に多く，化学放射線療法で CR となった症例よりも予後不良であると考えられる．当院では9例（20%）が他院で化学放射線療法が行われ，salvage 手術を目的に紹介された症例である．再発の診断は生検組織で癌が検出されている場合がほとんどである．深達度の診断は EUS などを用いても困難なことが多い．また，PET/CT で明らかな再発と診断された症例は進行した症例であった．

通常の食道癌手術後の予後因子として癌の遺残（R）・深達度（pT）とリンパ節転移（pN）がある．通常の手術では癌が遺残すること（R1, 2）は少なくなったが，他に有効な治療のない salvage 手術では少なくない．また，術前診断が化学放射線療法後で困難なことも R1, 2 が多い要因である．R1, 2 となった症例の術後生存率が低いのは通常手術と同様である．深達度は pT4 の症例が R1, 2 と同様に予後不良であり有意差はあるが，癌がなかった pT0 から外膜まで浸潤した pT3 まで差はなかった（図2）．再発病巣が照射野外の場合はほとんどないが，他医で照射されている症例で境界部から照射野外に発育しているものがあった．また，主病巣の肉眼型は治療後のためさまざまではあるが，粘膜下腫瘍様の壁内転移を思わせる病巣の予後は不良である．リンパ節転移は大きな予後因子であり，リンパ節転移のあった pN1 は全例死亡していた（図3）．しかし，4年前後で死亡した2例はいずれも他病死であり，salvage 食道切除術でリンパ節転移があると予後不良であるが，全例死亡するとはいえない．その原因をみるため転移のあったリンパ節の部位をみると，近位にはなく離れた部位に多いことがわかった．リンパ節転移のあった胸部食道癌症例21例を調べると，縦隔では気管分岐部（No. 107）が4例と多く，腹部では右左噴門リンパ節（No. 1, 2）よりも小彎リンパ節（No. 3）や左胃動脈幹リンパ節（No. 7）に転移している症例が多い結果であった．根治的化学放射線療法で主病巣と近位のリンパ節は照射野に入っているが，照射野外のリンパ節が再燃・再発したのでないかと考えられる．したがって，食道癌取扱い規約では pN1 がわずかに2例で，pN2 が8例と多く以下 pN3：3例，pN4：8例であった．

表2 salvage リンパ節郭清術の内訳

占居部位		治療前 Stage	期間*	転移部位	予 後
1.	Mt	T3N1M1	9月	No. 104R	4年3月死亡
2.	Ut	T4N1M0	11月	No. 104L	3年4月生存
3.	Ce	T2N1M0	5月	No. 102L	4年4月生存
4.	Mt	T3N1M0	6月	No. 104L	1年死亡
5.	Mt	T4N1M0	6月	No. 104R	1年8月死亡
6.	Mt	T1N1M0	1年1月	No. 2	3年8月生存
7.	Mt	T4N1M0	1年1月	No. 104R	10月生存
8.	Mt	T1N0M0	3年1月	No. 104L	1年6月生存

TNM Stage, * 期間：化学放射線療法終了から手術までの期間

3. salvage リンパ節郭清術

根治的化学放射線療法後，主病巣はCRを維持しリンパ節だけ再発した症例が対象となる[7]．当院では頸部の鎖骨上リンパ節（No. 104）が多く，1例のみ左噴門リンパ節（No. 2）であった（表2）．その約半数は治療前にリンパ節転移は診断されておらず，照射野に入ってなかった症例である．したがって，郭清後追加して化学放射線療法も可能で，このような症例の予後は良好であった．しかし，治療前からリンパ節転移と診断されていて再燃したため郭清した症例もある．全例術後合併症もなく約1週間で退院しており，なによりも侵襲が少なく簡便に行えることが利点である．手術後は放射線療法が追加可能なら化学放射線療法を行い，少なくとも化学療法の追加をしている．予後はもともとそこに転移がないと診断され照射野にも入っていなかった部位に転移した症例は良好であり長期生存が得られている．同様に，川西ら[8]は腹腔内リンパ節を郭清しNo. 7とNo. 8aに転移がみられ長期生存した症例を経験している．この術式は適応となる症例が限られていることや術後すぐに他のリンパ節に転移を認めることもあり，その有用性の評価は未だ一定していない．

4. salvage 手術の適応について

食道癌の根治的化学放射線療法後の遺残・再発症例に対する治療であり，できるだけ侵襲の小さな治療が望まれる．すなわち，主病巣に対しては内視鏡的治療であり，リンパ節に対してはリンパ節郭清術となる．治療後の一定期間CRを持続していた症例が主病巣とリンパ節の両方に同時に再発してきた場合，壁内転移やリンパ管侵襲（節外転移）が存在することが多くsalvage食道切除術は再考すべきである．しかし，当院でもFDG-PETやマルチスライスのCTなど新たな画像診断を導入しているがこれらの診断は難しい．術中に気管前や後腹膜などの郭清できないリンパ節転移を認めたり，術後すぐに全身転移してしまうことが多い．そして，Docetaxelなどを含むSecond-lineの化学療法を考慮すべきである．一方，主病巣のみの再発の場合は食道切除術で完全切除（R0）できれば長期生存が可能となる．もし，他臓器浸潤（T4）でR1に終わってもリンパ節転移がなければ約1年の生存は得られ，なによりも食事摂取が可能になり手術の意義は大きい．

まとめ

salvage食道切除術が行われ始めて約10年が経過しようとしている．当院では手術による死亡は少なくなってきたが，合併症（晩期障害）は多くQOLの低下が問題である．根治的化学放射線療法後の再発の診断は適格になってきたが，まだsalvage食道切除術後すぐに再発がみられ半年以内に死亡してしまう例が存在している．とくにCRとなり化学療法を追加した後しばらくして，それまでなかった局所再発と複数のリンパ節転移が同時にみられた場合は全身病（Systemic disease）となっている可能性が高い．放射線療法の追加はもちろん適応外であり，salvage食道切除術で拡大リンパ節郭清をして取りきれても(R0)，すぐに再発してしまう．しかし，有効なSecond-lineの化学療法や抗体療法などがない現状では，手術を希望されかつ画像診断で認められる病巣が手術で取りきれる場合断ることはできない．

表1　salvage 食道切除術の成績と合併症

	前　期 (1992～1996)	後　期 (1997～2006)
手術数	18例	28例
手術死亡	1(5.6%)	
在院死亡	1(5.6%)	
気管壊死	1	
肺炎	4	5
縫合不全（再手術）	6(3)	5(3)
膿胸/創化膿	1	2
胸水	1	7

た．しかし，1997年以降の28例においては手術・在院死亡は経験していない．そして，全例46例（1993～1996年）では10%以上あった死亡率は5%を切って4.4%となった．salvage 食道切除術をさかんに行っている国内の主要施設でも10%前後の手術死亡率を報告している[5]．

合併症は急性呼吸障害（ARDS）などの重篤な症例は減少してきているが，これはMRSA肺炎が終息してきているのも一因と思われる．気管・気管支・肺の合併切除などはしなくなり，反回神経麻痺や気管・気管支の壊死は少なくなった．しかし，現在でも必要な症例には気管・気管支周囲のリンパ節郭清や3領域郭清も行っている．また，胸水貯留は salvage 食道切除術後に頻繁におこる合併症である．通常術後3～5日後に胸水の量が100 ml/日以下を目安に胸腔ドレーンを抜去しているが，salvage 食道切除術後では100 ml/日以下となるのが遅く，またその後に再び胸水が貯留することがあり，また退院後に貯留することもある．胸腔ドレーンを抜去する際にOK-432（ピシバニール）とミノマイシンのカクテルを注入している．縫合不全は再建経路を胸壁前にしなくなり減少してきた．しかし，食思不振などもあり必ず胃瘻など栄養チューブを手術時に挿入している．

術前の全身状態は根治的化学放射線療法後長期間経過していても晩期毒性があり注意が必要である．また，化学療法が追加されている場合もあり，骨髄抑制により白血球数とくにリンパ球数の減少や血小板の減少がみられる．栄養状態つまりアルブミンの低下や腎機能クレアチニンの上昇もみられることがある[2,6]．肺機能は換気量や1秒率が正常でも拡散能（PaO_2）の低下がみられることが多い．また，胸水や心嚢液の貯留をきたしていることがあり，心嚢液貯留に対しては開胸操作中に心嚢を開放するようにしている．いずれにせよ術前未治療の場合より厳格に心肺腎肝機能が保たれていることを確認する必要がある．

手術術式は以前3領域郭清を基本としていたが，右開胸でも2領域とし高位胸腔内吻合など侵襲の軽減を図っている．これは噴門部に放射線の照射が及んだ場合でも胃の血流のよい部分で吻合できるためである．また，大網で気管・気管支側を被うこともでき，胸腔内吻合の利点は少なくない．以前は胸壁前経路を使用してきたが，長い胃管が必要で縫合不全が多く入院期間が延長するため最近では遊離空腸移植が必要など特殊例以外は胸壁前としていない．腹腔鏡で用手下（Hand-assist）による腹部操作は行っているが，胸腔鏡補助下の食道切除は salvage においては施行していない．縦隔のリンパ節郭清は通常のように行っているが，症例により胸膜が肥厚して気管と癒着し不可能な場合がある．当院では通常の手術と同様に右気管支動脈の温存はしていないし，胸管を全例中下縦隔で結紮している．

2.　salvage 食道切除術の予後

salvage 食道切除例と通常の食道癌切除例で臨床病理学的因子のうち予後因子となるものは基本的に差がないと考えられる．しかし，salvage に特有の因子があり反対に問題にならない因子もある．まず，通常の食道癌切除例では女性の予後が男性より良好であるが，salvage 食道切除術でもその傾向がみられたが有意な差はなかった．年齢では75歳以上の症例が6例あったが，予後に差はなかった．占居部位は頸部を含め部位による salvage 食道切除術後の生存率の差はみられなかった．

salvage 手術時に化学放射線療法後の癌遺残と再発は明確に区別できないため，治療終了後3カ月以内と4カ月以降に分けると3カ月以内の

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Editorial

Salvage Surgery for Esophageal Carcinoma after Definitive Chemoradiation Therapy

Hisahiro Matsubara, MD, PhD

Introduction

The salvage operation for esophageal cancer is one of the most interesting topics today among Japanese doctors treating this form of malignant tumor. This topic has been selected as the focus of symposia and panel discussions at many annual meetings of surgical-, esophageal-, or digestive-disease–related societies in Japan. In parallel, definitive chemoradiation therapy has recently shown progress as a treatment modality for resectable esophageal cancer.[1–3] Many patients have chosen to undergo definitive chemoradiation therapy to preserve the upper digestive tract. However, definitive chemoradiation is not yet recognized as a standard therapy for resectable esophageal cancer, since no study has demonstrated better results than surgery. Late adverse events after definitive chemoradiation have been reported, and in failure cases of definitive chemoradiation, additional treatments, including salvage surgery, are often difficult.[4,5] Nevertheless, salvage treatment is needed to improve the overall treatment results in chemoradiation therapy.[3] The benefits and risks of salvage surgery are now a major theme of discussion.

Definitive Chemoradiation for Resectable Esophageal Cancer

Definitive chemoradiation therapy has recently been accepted as one of the important treatment modalities for resectable esophageal cancer. As a nonsurgical treatment, it yields superior results in comparison to radiation alone, based on a randomized controlled study performed by the Radiation Therapy Oncology Group. In the RTOG 85-01 trial, the 5- and 8-year survival rate of the chemoradiotherapy group was 27% and 22%, respectively.[1]

From Department of Frontier Surgery, Graduate School of Medicine, Chiba University, Chiba, Japan

Address reprint requests to Hisahiro Matsubara, MD, PhD: Department of Frontier Surgery, Graduate School of Medicine, Chiba University, 1–8–1 Inohana, Chuo-ku, Chiba 260–8670, Japan.

Ishikura et al. have reported that the 5-year survival rate of definitive chemoradiotherapy for resectable cases was 49%. Chemoradiation, being a nonsurgical treatment, is a standard therapy for esophageal cancer based on the guidelines for esophageal cancer diagnosis and treatment in Japan. However, adverse events, especially those with a late onset, have been reported, including acute myocardial infarction, pericarditis, heart failure, pleural effusion, and radiation pneumonia. Furthermore, there have been some reports of the possibility of ischemic heart diseases being induced by radiation therapy.[6] These late adverse events have caused treatment-related deaths, even in complete response (CR) patients. These papers have concluded that definitive chemoradiation is effective, but that it comes with substantial toxicities. A comparison of the effects of high-dose (64.8 Gy) versus standard-dose (50.4 Gy) radiation therapy on the local control and toxicity revealed that a higher radiation dose did not increase the survival or local control.[2] Based on the results of a Phase III trial, the recommended radiation dose with concurrent 5-FU and cisplatin chemotherapy is 50.4 Gy. An additional investigation on minimizing normal tissue toxicities is warranted. There are still no data from randomized trials comparing definitive chemoradiation and surgery alone for the treatment of resectable esophageal cancer. These different modalities should be examined using a randomized control study, or, if impossible, a prospective clinical trial.

Chemoradiation Followed by Surgery

Surgery is the standard therapy for resectable esophageal cancer. In Japan, three-field lymph node dissection is available for squamous cell carcinoma of the thoracic esophagus. The outcome of the surgical treatment has been improved, but is not sufficient in all patients. Local recurrences after surgery are seen in R0 resection, and R2 resection cannot always be avoided in spite of improvement in preoperative diagnosis. From these points of view, preoperative treatment for resectable cancer has been investigated in many clinical studies. The theoretical benefits of preoperative treatment include improved resection rates, pathological downstaging, and a reduction in recurrence. The efficacy of neoadjuvant chemotherapy has been examined in two large-scale randomized control studies.[7,8] The results of these two studies were different. Therefore the usefulness of preoperative chemotherapy is still controversial. A meta-analysis of randomized controlled trials comparing neoadjuvant chemotherapy and surgery to surgery alone did not demonstrate a survival benefit for the combination of neoadjuvant chemotherapy and surgery.[9]

Preoperative chemoradiation is common, and it is also a widely used modality to improve the results of surgery. Many Phase III trials comparing chemoradiation followed by surgery and surgery alone did not show a benefit for preoperative chemoradiation.[10] Only Walsh et al. reported the efficacy of preoperative chemoradiation in improving the survival.[11] However, a meta-analysis of these trials revealed that chemoradiotherapy followed by surgery significantly reduced the 3-year mortality in comparison to surgery alone.[12] On the other hand, postoperative mortality was significantly increased by preoperative chemoradiation. One of the causes of these controversial results is that the mortality rate in the preoperative group was higher than that of the surgery-alone group. In our nonrandomized study, a three-field lymph node resection with preoperative chemoradiotherapy increased the morbidity rate, but did not increase operative death and in-hospital death in comparison to surgery alone.[13] We therefore need the results of a new large randomized control study with a low perioperative mortality.

In the comparative data between definitive chemoradiotherapy and chemoradiotherapy followed by surgery, chemoradiotherapy resulted in an equivalent survival rate in comparison to chemoradiation followed by surgery.[14] However, surgery significantly increased local control, and patients who underwent surgery had less chance of death from cancer. Moreover, the survival curves for overall survival seem to be different after 3 years. These conflicting findings should therefore be clarified in a large clinical trial.

Salvage Surgery after Definitive Chemoradiation

Definitive chemoradiation for resectable esophageal cancer is the standard therapy for nonresectable treatment as mentioned above. However, CR rates are about 70% in non-T4 disease. Local failure or local persistence has been observed with a higher rate in definitive chemoradiotherapy. Adams et al. have reported that patients who had chemoradiation had double the rate of local recurrence in comparison to those receiving surgery alone.[15] Ohtsu, an authority in chemoradiation for esophageal cancer in Japan, has mentioned that local failure has remained a major issue affecting 45% of patients in the chemoradiotherapy group.[3] Salvage surgery for unsuccessful curative chemoradiation improved the outcome of definitive chemoradiation treatment. However, these patients presented some difficulties during salvage surgery because they often had distant metastases or were in poor physical condition as a result of high-dose radiotherapy.

Salvage surgery is now considered to be an effective alternative surgical method. Neoadjuvant chemoradiotherapy has been shown to increase the morbidity and mortality associated with esophagectomy in many clinical trials, as mentioned above. Definitive chemoradiation has the possibility of further increasing the risks for esophagectomy.[16] A salvage esophagectomy is a high-risk surgical procedure because the patients are in poor physical condition. There are fibrous changes in the mediastinum after radiation, and there are difficulties of anastomosis as a result of the irradiated gastric tube. Respiratory failure and septic conditions resulting from a leakage of anastomosis are the major fatal complications. Urschel and Sellke reported acute respiratory distress syndrome and pneumonia causing respiratory failure after salvage esophagectomy.[17] An underlying radiation pneumonitis is probably the first insult to the lungs, and cytokine release during surgery is the second insult. Mechanical ventilation can cause lung injury, and pulmonary lymphatic obstructions also contribute to acute lung injury. Esophagogastric anastomotic leaks are caused by poor gastric tissue perfusion. Radiation of the proximal stomach can obliterate some of the rich plexus of submucosal vessels, and gastric tube necrosis, airway necrosis, and tracheogastric fistulae are also considered to be important complications. Swisher et al. mentioned that mechanical ventilation, intensive care unit stay, hospital stay, and the leakage of anastomosis are increased in patients undergoing salvage surgery after definitive chemoradiotherapy in comparison to those undergoing planned chemoradiation followed by surgery.[18] The operative mortality also increased in the salvage esophagectomy group. To reduce the complications of salvage esophagectomy, severe eligible criteria are needed. Nakamura et al. reported that there was no difference between the salvage group and the neoadjuvant chemoradiotherapy group in hospital mortality, mechanical ventilation, intensive care unit stay, and hospital stay.[19] In our department, we have experienced no instances of 30-day hospital death, and salvage surgery is therefore not more morbid than a planned esophagectomy after chemoradiation. Most patients survived and were discharged, and they were also able to tolerate an oral diet. We have undergone esophagectomy with three-field lymph node dissection for salvage surgery. However, these patients were carefully selected because of the high operative risk, so this procedure has not been determined as a safe operation. The extent of lymph node dissection is still controversial.

Meunier et al. reported that the factors to predict prolonged survival times in cases of salvage surgery consist of the general health status, the type of initially resected tumor, and a certain recurrence-free delay.[20] Swisher et al. described the merits of salvage surgery in patients with early pathological stage, prolonged time to progression, and R0 resection.[18] A salvage operation remains a therapeutic option for carefully selected patients at experienced esophageal referral centers.

Salvage surgery for recurrent tumors after definitive chemoradiation is still being improved as an operative method. Issues on lymph node dissection, the criteria of patients' eligibility, and the period from recurrence to operation must be addressed. In the future we will attempt to determine whether salvage surgery or a planned esopohagectomy after chemoradiation is the better option.

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Have Surgical Outcomes of Pathologic T4 Esophageal Squamous Cell Carcinoma Really Improved? Analysis of 268 Cases During 45 Years of Experience

Hideaki Shimada, MD, FACS, Tooru Shiratori, MD, Shinichi Okazumi, MD, Hisahiro Matsubara, MD, Yoshihiro Nabeya, MD, Kiyohiko Shuto, MD, Yasunori Akutsu, MD, Hideki Hayashi, MD, Kaichi Isono, MD, FACS, Takenori Ochiai, MD, FACS

BACKGROUND: Because invasion to an adjacent organ (T4) indicates highly advanced disease, and most surgeons avoid esophagectomy, the prognostic impact of clinicopathologic factors for survival of these patients after esophagectomy has rarely been analyzed.

STUDY DESIGN: From 1960 to 2005, a total of 268 patients with esophageal squamous cell carcinoma underwent esophagectomy for pathologic T4 disease (pT4). The impact of clinicopathologic factors on survival was evaluated by univariate and multivariate analysis. Changes in surgical outcomes and longterm survival between the earlier period (1960 to 1989) and the later period (1990 to 2005) were analyzed.

RESULTS: Overall survival rates of all patients were 25% at 1 year, 10% at 3 years, and 5% at 5 years. The survival curve of the later group was significantly better than that of the earlier group ($p < 0.01$). Multivariate analysis indicated that venous invasion (hazards ratio, 1.76; 95% CI, 1.33 to 2.33, $p < 0.01$) and presence of a postoperative complication (hazards ratio, 2.62; 95% CI, 1.96 to 3.51, $p < 0.01$) were independent risk factors for poor overall survival. Presence of residual cancer was also an independent risk factor for poor cause-specific survival (hazards ratio, 2.40; 95% CI, 1.23 to 4.69, $p = 0.01$). Venous invasion and intramural metastasis were risk factors for residual cancer. A total of 38 (14%) patients, 15 in the early period and 23 in the later period, underwent complete resection (R0). Although overall survival after R0 resection in the later period improved slightly, cancer-related survival rates were similar in both periods.

CONCLUSIONS: Although overall survival of patients with pT4 improved after 1990, this improvement might be mainly dependent on curability of the resection. (J Am Coll Surg 2008;206:48–56. © 2008 by the American College of Surgeons)

Extensive radical lymphadenectomy, such as upper mediastinal lymph node dissection or three-field lymph node dissection, was introduced to improve longterm survival after surgery for patients with esophageal carcinoma.[1-3] Despite improvement of surgical outcomes in patients with T1 to T3 disease, early recurrence and death have still been observed in patients with tumor invasion to adjacent organs (T4).[3-5] Because direct tumor invasion to an adjacent organ is evidence of highly advanced disease, most surgeons rarely consider esophagectomy to be indicated at this stage. On the other hand, several reports showed benefits of esophagectomy in certain groups with T4 disease after neoadjuvant treatment.[6-10] Most of these studies included not only patients with pathologic T4 but also those with presumably T4 disease clinically defined during preoperative staging. So we focused on pathologic T4 disease (pT4) at the time of operation in this retrospective study.

After 1990, neoadjuvant chemotherapy, including that with 5-fluorouracil and cisplatin, radiation therapy, or both, became available for patients with clinical T4 tumors.[6-10] Patients with residual or recurrent disease were

Competing Interests Declared: None.

This work was supported in part by a grant-in-aid from the Ministry of Education, Science and Culture of Japan (21st Century Center of Excellence Program).

Received March 25, 2007; Revised May 19, 2007; Accepted June 4, 2007.

From the Department of Frontier Surgery and the Research Center for Frontier Medical Engineering, Chiba University Graduate School of Medicine, Chiba, Japan.

Correspondence address: Hideaki Shimada, MD, FACS, Department of Frontier Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuou-ku, Chiba 260-8677, Japan.

ISSN 1072-7515/08/$34.00
doi:10.1016/j.jamcollsurg.2007.06.013

Table 1. Principal Sites of Tumor Invasion and Curability

Organ invaded	n	%	R0	R1	R2
Aorta	110	42	9	1	100
Major airway	60	22	11	1	48
Lung	32	12	8	0	24
Diaphragm	10	4	4	0	6
Pulmonary vein	9	3	2	0	7
Pericardium	9	3	2	0	7
Others*	38	14	2	2	34
Total	268	100	38	4	226

*Others included pleural organ invasion.

the log-rank test. The influence of each clinicopathologic variable on survival was assessed with Cox's proportional hazards model. The influence of each clinicopathologic variable on the risk of residual cancer was assessed with logistic regression analysis. All statistical analyses were carried out using StatView 5.0 for Windows (SAS Institute). All p values were considered statistically significant if $p < 0.05$.

RESULTS

Surgical records and postoperative course

Table 1 shows the principal sites of tumor invasion and the operation's ability to cure: R0, 38 patients (14%); R1, 4 patients (1.5%); and R2, 226 patients (84%). The most common sites of tumor invasion were the aorta ($n = 110$), airway tract ($n = 60$), and lung ($n = 32$). Although invaded organs and esophagus were resected in combination in 71 patients, resection was incomplete in 33 patients (46%). R0 resection rates varied among invaded organs, ranging from only 8% (9 of 110 patients) for the aorta to 40% (4 of 10 patients) for the diaphragm. Among all 268 patients, the 30-day mortality, overall hospital mortality, and morbidity rates were 6%, 11%, and 51%, respectively. Five-year survival curves according to each time period of surgery are shown in Figure 1. Because the 3 survival curves representing each decade from 1960 to 1989 were similar, there were no significant improvements in longterm survival between 1960 and 1989. But both overall and cause-specific survivals significantly improved in patients treated after 1990. The survival curve of 1990 to 2005 was significantly better than the 3 survival curves from 1960 to 1989 ($p < 0.01$).

Clinicopathologic characteristics and time period of surgery

Clinicopathologic factors were compared between patients treated in the 2 time periods under study (Table 2). Among clinicopathologic variables, patients in the later period were more elderly, had a greater number of metastatic lymph nodes and dissected nodes, had more poorly differentiated tumor types, and underwent more extensive lymphadenectomy than those in the early period. Also, patients in the later period had smaller tumors, less blood vessel invasion, and less residual cancer, and they received neoadjuvant radiation less frequently than did those in the early period.

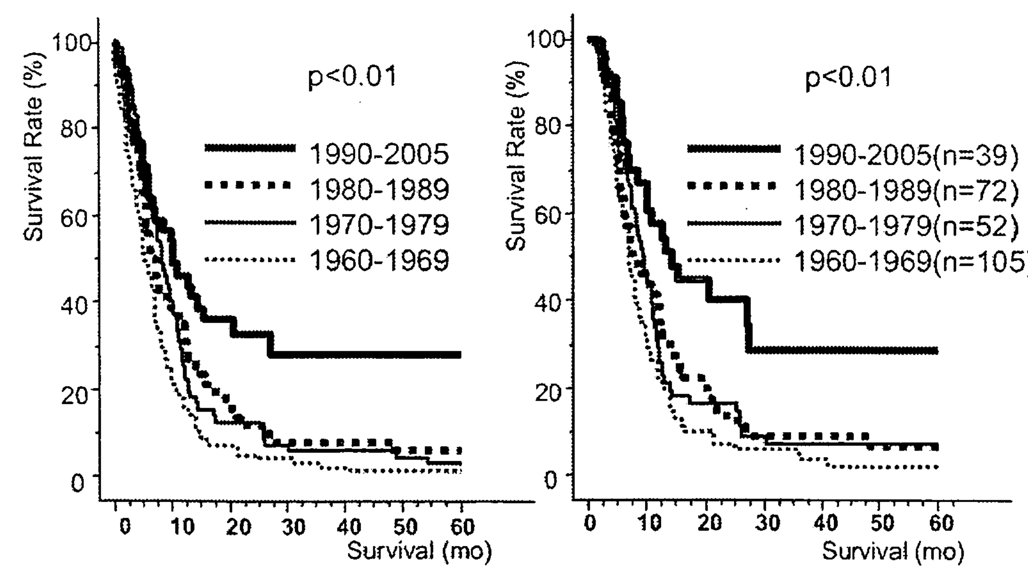

Figure 1. (A) Overall and (B) cause-specific survival curves of patients according to each time period of surgery. Survival curves according to four time periods were compared. Survival curves of each time period were displayed as thick line (1990 to 2005), thick dotted line (1980 to 1989), thin line (1970 to 1979), and thin dotted line (1960 to 1969).

Table 2. Relationship Between Clinicopathologic Characteristics and Years of Operations

Variables	1960–1989, n (n = 229)	1990–2005, n (n = 39)	p Value*
Gender, men /women	200/29	31/8	0.21
Age, ≥ 60 y/< 60 y	106/123	35/4	< 0.01
Tumor location, upper/lower	58/171	9/30	0.84
Tumor diameter (esophagography), >.100 mm/< 100 mm	119/110	10/29	< 0.01
Tumor diameter (surgical specimen), ≥ 50 mm/< 50 mm	106/123	24/15	0.09
N factor, N1/N0	149/80	30/9	0.20
M factor, M1/M0	87/142	15/24	> 0.99
No. of nodes, ≥ 3/0–2	72/157	20/19	0.02
Histology, differentiated/poorly differentiated	134/95	14/25	0.01
Intramural metastasis (+)/(−)	44/185	6/33	0.66
Venous invasion (+)/(−)	129/100	27/12	0.16
T4 organ, artery or vein/others	108/121	11/28	0.04
Residual cancer (+)/(−)	214/15	16/23	< 0.01
1 or 2 FLD/3 FLD	197/32	15/24	< 0.01
No. of dissected nodes, < 15/≥ 15	168/61	3/36	< 0.01
Neoadjuvant radiation (−)/(+)	67/162	23/16	< 0.01
Neoadjuvant chemotherapy (−)/(+)	177/52	26/13	0.16
Postoperative complication (+)/(−)	119/110	19/20	0.73
30-d mortality, n	15	2	> 0.99
Hospital mortality, n	27	3	0.59

*Fisher's exact test.
FLD, field of lymphadenectomy.

The ratios of patients in stage III to those in stage IV were similar between the 2 periods. In addition, morbidity rates and hospital mortality rates were similar between the two periods.

In the early period, 52% of tumors were larger than 100 mm, 47% of tumors had invaded into an artery or vein, and 93% of tumors were incompletely resected. On the other hand, in the later period, 26% of tumors were larger than 100 mm, 28% had invaded an artery or vein, and 41% of tumors were incompletely resected. The R0 resection rate was significantly better in the later than in the earlier period (59% versus 7%).

Univariate and multivariate analysis for prognostic variables

Overall and cause-specific 5-year survival rates for all 268 patients were 6% and 9%, respectively. Eight patients survived more than 5 years after operation. In these 8 patients, tumor invasion occurred in the aorta (n = 3), airway tract (n = 2), and lung (n = 3). Surgical curability for these 8 patients was R0 (n = 4), R1 (n = 1), and R2 (n = 3). All 4 R0 patients received chemotherapy after operation, and the other 4 patients with residual tumor, R1 or R2, received radiation or chemoradiation postoperatively.

By using univariate analysis, 7 of 19 variables yielded a significant estimate of both overall and cause-specific survival (Table 3; Fig. 2). During the later period, absence of venous invasion, having no residual cancer, undergoing a 3-field lymphadenectomy, having more than 15 dissected nodes, receiving neoadjuvant chemotherapy, and not having postoperative complications were favorable factors for survival. A total of 102 patients with M1 were stage IV. Although stage III patients showed relatively better cause-specific survival than stage IV patients, there was not a statistically significant difference in overall survival (Table 3). To evaluate the impact of these 7 variables on 5-year survival of patients, multivariate analysis using Cox's regression model was performed, as shown in Table 4. Presence of venous invasion, low number of dissected nodes, and postoperative morbidity were identified as independent risk factors to reduced patient survival. Although the presence of residual cancer was not selected as an independent risk factor for overall survival, it was an independent risk factor for reduced cause-specific survival. In addition, the presence of residual cancer had the strongest impact on cause-specific survival (Table 4; Fig. 2).

Univariate and multivariate analysis for presence of residual cancer

Thirty-eight of the 268 patients underwent R0 resection, and the numbers of R0 resection in each decade were 6 in the 1960s, 3 in the 1970s, 6 in the 1980s, and 23 after 1990. The survival curves between those treated in the earlier (n = 15) and later periods (n = 23) were compared

Table 3. Univariate Analysis for Overall and Cause-Specific Survival in Patients with Pathologic Invasion to Adjacent Organ

Variables, n	Overall 5-y survival rates, %	p Value	Cause-specific 5-y survival rate, %	p Value*
Time of surgery, 1960–1989 (n = 229)/1990–2005 (n = 39)	4/28	< 0.01	6/30	< 0.01
Gender, men (n = 231)/women (n = 37)	5/10	0.02	8/12	0.10
Age, ≥ 60 y (n = 141)/< 60 y (n = 127)	4/8	0.45	5/10	0.69
Tumor location, upper (n = 67)/lower (n = 201)	5/5	0.66	8/10	0.94
Tumor diameter (esophagography), ≥ 100 mm (n = 129)/< 100 mm (n = 139)	6/6	0.97	6/10	0.88
Tumor diameter (surgical specimen), ≥ 50 mm (n = 130)/< 50 mm (138)	6/6	0.35	8/8	0.68
N factor, N1 (n = 179)/N0 (n = 89)	4/9	0.32	6/11	0.72
M factor, M1 (n = 102)/M0 (n = 166)	6/6	0.21	5/10	0.07
No. of nodes ≥ 3 (92) versus 0–2 (176)	5/5	0.48	5/11	0.10
Differentiated type (n = 148)/poorly differentiated type (n = 120)	5/5	0.57	10/8	0.35
Intramural metastasis (+) (n = 50)/(−) (n = 218)	5/5	0.84	8/10	0.74
Venous invasion (+) (n = 156)/(−) (n = 112)	1/10	< 0.01	2/13	0.02
T4 organ, artery, or vein (n = 119)/others (n = 149)	6/6	0.96	7/7	0.63
Residual cancer (+) (n = 230)/(−) (n = 38)	4/25	< 0.01	5/37	< 0.01
1 or 2 FLD (n = 212)/3 FLD (n = 56)	4/13	< 0.01	6/25	< 0.01
No. of dissected nodes < 15 (n = 171)/≥15 (n = 97)	2/10	< 0.01	5/11	< 0.01
Neoadjuvant radiation (−) (n = 90)/(+) (n = 178)	2/14	0.15	4/10	0.93
Neoadjuvant chemotherapy (−) (n = 203)/(+) (n = 65)	4/6	< 0.01	5/19	0.03
Postoperative complication (+) (n = 138)/(−) (n = 130)	3/9	< 0.01	5/11	

*Log-rank test.
FLD, field of lymphadenectomy.

(Fig. 3). Although a slight tendency for better survival in the later period was indicated by the overall survival curves, differences between the two periods were not significant. When examining factors according to whether residual cancer was present (n = 230) or absent (n = 38), being in the early period, being male, and having neoadjuvant radiation therapy were significantly associated with presence of residual cancer (Table 5). To evaluate the impact of clinicopathologic variables on the presence of residual cancer, logistic regression analysis was performed, and being in the early period, being male, having intramucosal metastases, and having venous invasion were identified as independent risk factors for residual cancer (Table 6). Although the difference was not statistically significant, aortic invasion had three times more risk than other organ invasion for residual cancer.

Among the 38 patients who underwent R0 resection, 10 patients received chemotherapy after operation. Among these 38 patients, 21 (55%) developed recurrent cancer and 13 patients died of recurrent cancer. The pattern of recurrence was as follows: distant organ, 11 patients; local, 7 patients; lymph node, 2 patients; and dissemination, 2 patients. Because 12 of 38 patients who underwent R0 resection died of other causes, a total of 25 of 38 patients who underwent R0 resection died by the end of this study.

DISCUSSION

Longterm survival of patients with esophageal carcinoma that has invaded adjacent organs remains dismal mainly because there is residual cancer even after esophagectomy. We examined reported data on various multimodal therapies to identify appropriate neoadjuvant treatment that would improve local control and the R0 resection rate.[6-10] Although several reports focused on patients with clinical T4, only a few focused on patients with pathologic T4. Because preoperative assessment of tumor depth has changed during the last few decades, we focused on pT4 patients' survival after esophagectomy.

Preoperative assessment was limited to esophagography, endoscopy, CT, and neck unltrasonography in the earlier period. After 1990, introduction of endoscopic ultrasonography contributed to an accurate diagnosis for T4. A total of 85 patients underwent operation without any preoperative therapy. These patients were operated on with curative intent. But the other 183 patients were operated on with palliative intent and curative intent. We decided the intent just after thoracotomy. Because enhanced CT and endoscopic ultrasonography were very useful to exclude bulky pT4 tumors, the patients in the later period were significantly more likely to have operations with curative intent than were patients in the earlier period. During the

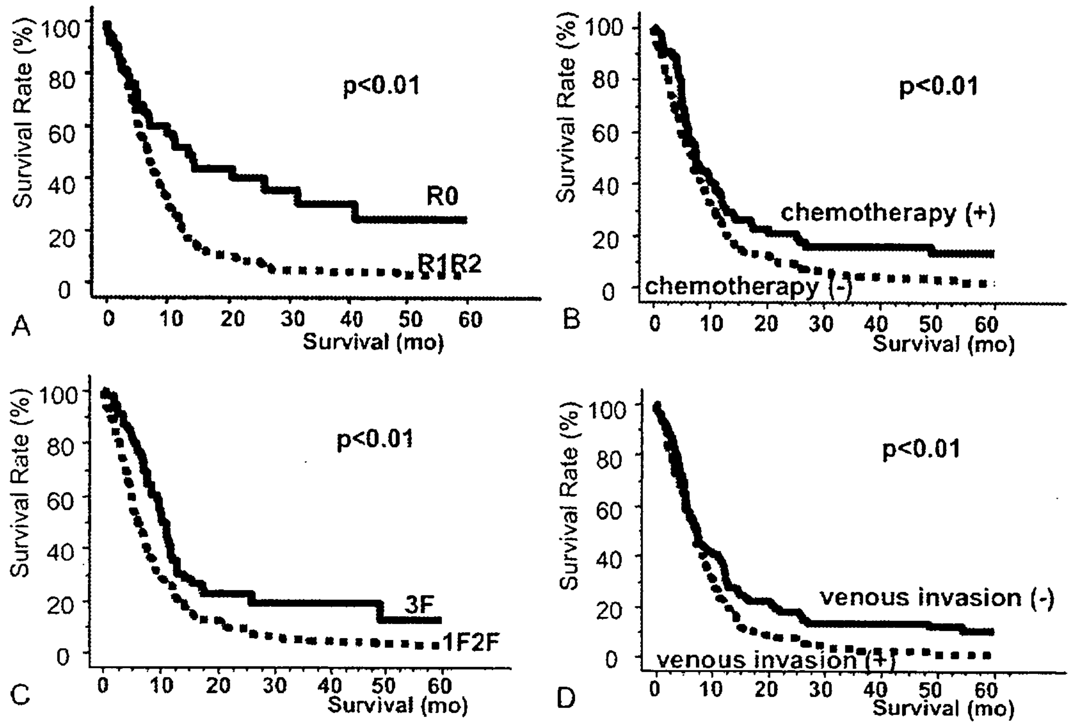

Figure 2. Overall survival curves of patients according to clinicopathologic factors. (A) R0 (no residual tumor) versus R1–R2 (presence of residual tumor). (B) Presence versus absence of preoperative adjuvant chemotherapy. (C) Three-field versus two-field lymphadenectomy. (D) Absence versus presence of venous invasion.

most recent time period, after 2000, 10 (71%) of 14 patients received R0 resection. Because bulky invasion into an adjacent organ was less frequent in the later period than in the earlier period, the R0 resection rate was significantly higher in the later period, although slight pathologic invasion was evident.

Examination of R0 resection rates according to the organ invaded showed that rates for the major airway, lung, and diaphragm were higher than for aortic invasion. So to improve the R0 resection rate, preoperative assessment for aortic invasion was the most important in staging for clinical T4. In the largest series of patients who underwent resection for pathologic T4 esophageal carcinoma, Matsubara and colleagues[8] noted that 56 (72%) of 78 patients with pT4 underwent R0 resection. The R0 resection rate according to the organ invaded was 62% for the aorta, 65% for the major airway, and 100% for the lung. These R0 resection rates were similar to those in our series in the later period.

Because accurate diagnosis of tumor invasion remains difficult, it was helpful to identify risk factors for residual cancer. Multivariate analysis showed that being male, having intramural metastasis, and having venous invasion were independent risk factors for residual cancer. In the later

Table 4. Multivariate Analysis for Survival in Patients with Pathologic Invasion to Adjacent Organ

	Overall survival			Cause-specific survival		
Variables	p Value*	Adjusted hazards ratio	(Adjusted 95% CI)	p Value*	Adjusted hazards ratio	(Adjusted 95% CI)
Time of surgery, 1960–1989 versus 1990–2005	0.71	1.11	(0.66–1.86)	0.96	1.01	(0.57–1.80)
Venous invasion, (+) versus (−)	< 0.01	1.76	(1.33–2.33)	< 0.01	1.59	(1.16–2.17)
Residual cancer, (+) versus (−)	0.29	1.34	(0.78–2.29)	0.01	2.40	(1.23–4.69)
1 or 2 FLD versus 3 FLD	0.16	1.39	(0.88–2.17)	0.30	1.30	(0.79–2.13)
Number of dissected nodes, < 15 versus ≥ 15	< 0.01	1.83	(1.23–2.71)	0.06	1.51	(0.98–2.31)
Neoadjuvant chemotherapy, (+) versus (−)	0.08	1.33	(0.97–1.82)	0.21	1.25	(0.88–1.76)
Postoperative complication, (+) versus (−)	< 0.01	2.62	(1.96–3.51)	< 0.01	1.83	(1.31–2.55)

*Cox's proportional hazards model.
FLD, field of lymphadenectomy.

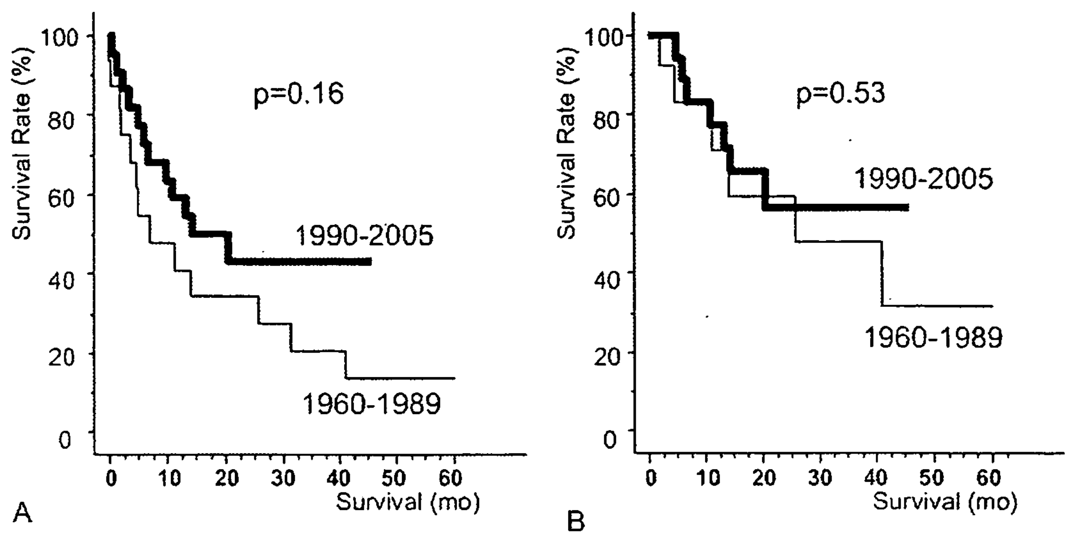

Figure 3. (A) Overall and (B) cause-specific survival of patients after complete resection according to the time period of surgery. Thick lines, 1990 to 2005; thin lines, 1960 to 1989.

period, after 1998, we routinely applied neoadjuvant chemoradiation therapy for tumors with clinical intramural metastasis. This strategy might have improved the R0 resection rate in the later period.

A low number of dissected nodes were identified by multivariate analysis as an independent risk factor for reduced survival. Although most of our patients had residual cancer, the type of lymphadenectomy could slightly contribute to survival. Presence of a postoperative complication was also selected as an independent risk factor for reduced survival, as described previously.[21] From these results, better overall survival of patients with esophageal carcinoma depends on absence of venous invasion, more than 15 dissected nodes, and absence of postoperative morbidity. The patients with all 3 of these factors showed an overall 5-year survival greater than 50%. Although overall survival of patients who underwent R0 resection seemed to improve in the later period, cause-specific survival appeared similar in the 2 time periods. This might mean that improvements in adjuvant treatment after surgery could not overcome the malignant potential of pT4 tumors.

Because this study was retrospective, spanning more than 4 decades, several clinical factors other than the analyzed factors could be associated with improvement of

Table 5. Relationship Between Clinicopathologic Characteristics and Presence of Residual Cancer

Variables	Residual cancer (−), (n = 38)	Residual cancer (+), (n = 230)	p Value*
Time of surgery, 1960–1989/1990–2005	15/23	214/16	< 0.01
Gender, men/women	28/10	203/27	0.02
Age, ≥ 60 y/< 60 y	23/15	128/112	0.48
Tumor location, upper/lower	14/24	53/177	0.10
Tumor diameter (esophagography), ≥ 100 mm/< 100 mm	18/20	121/119	0.86
Tumor diameter (surgical specimen), ≥ 50 mm/< 50 mm	20/18	110/120	0.60
N factor, N1/N0	26/12	153/77	0.86
M factor, M1/M0	12/26	90/140	0.47
No. of nodes ≥ 3/0–2	14/24	78/152	0.72
Differentiated type/poorly differentiated type	21/17	127/103	> 0.99
Intramural metastasis (+)/(−)	8/30	42/188	0.66
Venous invasion (+)/(−)	22/16	134/96	> 0.99
T4 organ, artery, or vein/others	12/26	107/123	0.11
Neoadjuvant radiation (−)/(+)	19/19	71/159	0.03
Neoadjuvant chemotherapy (−)/(+)	28/10	175/55	0.84

*Fisher's exact test.

Table 6. Multivariate Analysis of Risk Factors for Residual Cancer

Variables	Multivariate p value*	Adjusted hazards ratio	(Adjusted 95% CI)
Time of surgery, 1960–1989 versus 1990–2005	< 0.01	90.90	(15.87–500)
Gender, men versus women	< 0.01	8.26	(2.07–33.33)
Age, ≥ 60 y versus < 60 y	0.19	2.28	(0.66–7.86)
Tumor location, lower versus upper	0.13	2.85	(0.73–11.18)
Tumor diameter (esophagography), ≥ 100 mm versus < 100 mm	0.54	1.47	(0.35–6.84)
N1 versus N0	0.39	1.97	(0.42–9.32)
M1 versus M0	0.56	1.55	(0.35–6.85)
Poorly differentiated type versus differentiated type	0.31	2.00	(0.53–7.55)
Intramural metastasis (+) versus (−)	0.03	5.37	(1.13–25.6)
Venous invasion (+) versus (−)	0.04	4.22	(1.08–16.55)
T4 organ, artery, or vein versus others	0.10	3.12	(0.81–11.90)
Neoadjuvant radiation therapy (+) versus (−)	0.83	0.87	(0.23–3.23)
Neoadjuvant chemotherapy (+) versus (−)	0.31	0.45	(0.10–2.11)

*Logistic regression analysis.

longterm survival. These include adjuvant treatment after recurrence, introduction of cisplatin, quality of postoperative care, and management of noncancerous disease. Other differences that may not have occurred at the earlier time period (eg, better glucose or blood pressure control) may indeed have been responsible for the improved survival in the later period, rather than a technical aspect of surgery. Because the number of patients receiving each regimen of chemotherapy was relatively small, it was difficult to evaluate "the benefit" of each course of chemotherapy. In addition, all 15 patients who received cisplatin + 5-fluorouracil were treated in the later period. Twenty-three patients treated with cisplatin showed better survival than the other patients, but the difference was not statistically significant (data not shown). But those clinical factors might be fairly evaluated by combination analysis with "time period of surgery" in a multivariate analysis.

Not all patients with T4 disease are candidates for esophagectomy, but according to the data presented, there may be some patients who could benefit. Because most patients with advanced disease at initial presentation are currently referred for neoadjuvant therapy, the clinical dilemma for esophageal surgeons and oncologists becomes deciding which patients with persistent T4 disease are candidates for surgery with curative intent. With advancing endoscopic stent technology, there are fewer and fewer patients needing palliative resection.

In conclusion, postoperative complications, venous invasion, and residual cancer were risk factors for dismal survival in patients with pT4 tumors. Intramural metastasis, venous invasion, and aortic invasion were risk factors for residual cancer. Although survival curves of all pT4 patients, shown in Figure 1, significantly improved after 1990, this improvement might be mainly dependent on curability of the resection. From the experience in operating on patients with pT4 disease and the data presented in this article, we concluded that the patients with intramural metastasis, aortic invasion, or both should be excluded from candidates for resection. We also suppose that neoadjuvant chemotherapy and extended lymphadenectomy may be associated with a better prognosis.

Author Contributions

Study conception and design: Shimada
Acquisition of data: Shiratori, Okazumi, Matsubara, Nabeya, Shuto
Analysis and interpretation of data: Akutsu, Hayashi
Drafting of manuscript: Shimada
Critical revision: Isono, Ochiai

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Diseases of the Esophagus (2007) 20, 12–18
DOI: 10.1111/j.1442-2050.2007.00632.x

DISEASES OF THE ESOPHAGUS

Original article

Concurrent chemoradiation for patients with squamous cell carcinoma of the cervical esophagus

T. Uno,[1] K. Isobe,[1] H. Kawakami,[1] N. Ueno,[1] H. Shimada,[2] H. Matsubara,[2] S. Okazumi,[2] Y. Nabeya,[2] T. Shiratori,[2] T. Kawata,[1] T. Ochiai,[2] H. Ito[1]

Departments of [1]Radiology and [2]Frontier Surgery, Graduate School of Medicine, Chiba University, Chuou-ku, Chiba, Japan

SUMMARY. **Little is known concerning the role of concurrent chemoradiation (CCRT) in the management of carcinoma of the cervical esophagus. We retrospectively evaluated our treatment approach for patients with cervical esophageal cancer with special emphasis on CCRT with or without surgery. Medical records of 21 consecutive patients with cervical esophageal carcinoma treated mainly with CCRT (1997–2004) were reviewed, and factors that influenced patient survival were analyzed retrospectively. Nineteen received CCRT with cisplatin/5-fluorouracil and five underwent curative surgery. Two patients who were deemed unfit for CCRT received radiation therapy alone. All had three-dimensional treatment planning (median total dose, 40 Gy with surgery, 64 Gy without surgery). Of the 19 patients who received CCRT, 11 patients including five who underwent curative surgery achieved initial local control. Neither of the two patients who received radiation therapy alone achieved local control. Among 19 patients who underwent CCRT, 9/11 with T1–3 grade tumors achieved initial local control, but only 2/8 patients with T4 tumors ($P = 0.011$, χ^2 test) achieved initial local control. No patient without initial local control survived > 20 months compared with 2-year and 5-year survival rates of 60% and 40% in those who achieved initial local control ($P = 0.038$). No patient with T4 tumors survived > 18 months, whereas 2- and 5-year survival rates were 62% and 41%, respectively, in those with T1-3 tumors ($P = 0.006$). The significant effect of T-classification on survival was maintained when analyzed among 19 patients who received CCRT. CCRT shows promise for cervical esophageal carcinoma. T-classification and initial local control had significant impact on survival.**

KEY WORDS: **cervical esophagus, cisplatin, concurrent chemoradiation, esophageal cancer, radiation therapy.**

INTRODUCTION

Carcinoma of the cervical esophagus is relatively uncommon, representing less than 5% of all cases of esophageal cancer.[1,2] Before the era of chemotherapy as treatment for esophageal cancer, it was treated with radical surgery, radiation therapy, or a combination of both. However, the prognosis for patients remains poor, with fewer than 20% of patients surviving for 5 years.[3] Recent progress with concurrent chemoradiation (CCRT) for patients with locally advanced head and neck or thoracic esophageal cancer has motivated many physicians to treat cervical esophageal cancer with initial CCRT. For many cases, initial radical surgery has mandated simultaneous total laryngectomy.[4,5] Thus, in the present clinical practice, most patients with carcinoma of the cervical esophagus prefer initial CCRT rather than surgery because of possible laryngeal preservation. The purpose of this study is to present the results of treatment and to analyze factors that influence patient prognosis, based on a retrospective review of charts for a series of 21 consecutive patients managed mainly with initial CCRT with or without surgery.

Correspondence: Takashi Uno, MD, Department of Radiology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuou-ku, Chiba 260-8670, Japan.
Email: unotakas@faculty.chiba-u.jp

PATIENTS AND METHODS

From 1997, patients with locally advanced cervical esophageal cancer have mainly been treated with initial CCRT with or without surgery at the Chiba

University Hospital. Patients with less advanced lesions who are not fit for surgery or who have refused surgery have also been treated with CCRT. Eligibility for the present study included the following: (i) histologically confirmed squamous cell carcinoma of the cervical esophagus; (ii) Karnofsky Performance Status (KPS) score of at least 70; (iii) no distinct comorbidity such as severe pulmonary or cardiovascular disease, with assurance by the attending physician that the medical status of the patient allowed curative treatment; and (iv) written informed consent. For some cases with large tumors extending beyond the cervical esophagus, tumor was judged as originating from the cervical esophagus when the main tumor was situated within this region. It was not difficult to judge this because, in such cases, almost the entire cervical esophagus was usually invaded by bulky tumors. Patients with hematogenous visceral metastases were ineligible. However, patients assigned to stage IV disease due to upper mediastinal lymph node involvement were eligible because of the potential for curative treatment. Baseline laboratory requirements included a white blood cell count greater than 3000 cells/mL, an absolute neutrophil count greater than 1500 cells/mL, and a platelet count > 100 000 platelets/mL. Either serum creatinine had to be < 1.5 mg/dL or calculated creatinine clearance had to be > 60 mL/min. During the study period, a total of 25 patients with cervical esophageal cancer were referred for radiation therapy. Of those, two had recurrent disease after surgery, one had simultaneous lung metastases, and one required only symptomatic palliation for a remote advanced lesion. The remaining 21 patients were entered into the present study. The patients' characteristics are shown in Table 1. There were 14 men and seven women. Age ranged from 48–87 years, with a median of 67 years. KPS scores were 70 in one patient, 80 in seven patients, and 90 in 13 patients. Patients were staged according to the 1997 UICC-TNM staging system; results were stage I in one patient, IIA in four, IIB in one, III in eight, and IV in seven patients. Primary lesion length ranged from 2–8.5 cm, with a median of 5 cm. T-classification was determined by endoscopic ultrasound when the tumor was passable. T4 lesions were confirmed by multiple diagnostic modalities, including endoscopic ultrasound, computed tomography (CT), and endoscopic examination of the tracheobronchial tree. Results were T4 in nine patients, T3 in eight, T2 in two, and T1 in two patients. Of the 21 patients, seven had M1 lesions due to lymph node metastasis below the level of the clavicle.

Table 1 Patient characteristics

Age (years)	
Range (median)	48–87 (67)
Gender	
Men : women	14 : 7
Karnofsky performance status (KPS)	
70/80/90	1/7/13
TN-classification	
T1N0	1
T1N1	1
T2N0	2
T3N0	3
T3N1	5
T4N1	9
Stage	
I	1
IIA	4
IIB	1
III	8
IV	7
Tumor length (cm)	
Range (median)	2–8.5 (5)

Radiation therapy

For all patients, treatment planning was performed using a CT simulator (AcQSIM PQ2000S; Philips Medical System, Andover, MA). CT images were acquired using 3-mm slice thickness. Dose distribution was calculated using a 3D treatment planning system (FOCUS; CMS Japan K.K., Tokyo, Japan). All patients were treated with 10-MV photons. For patients with superficial cervical lymph node metastasis, bolus with an adequate thickness was added for the anterior port. For 15 of the 21 patients, initial radiotherapy was delivered using anterior and posterior opposing techniques with a planning target volume (PTV) encompassing the lymph node area extending from the subcarinal region to the upper cervical region; this was done irrespective of clinical nodal status (i.e. a short T-shape field). In order to compensate for dose heterogeneity produced by conventional antero-posterior opposed field irradiation, 5–10% dose was added using the field-within-a-field technique to the area below the clavicle. A similar field, but with a lower border extended to include the lower mediastinal nodes (i.e. a long T-shape field), was used in two patients. The remaining four patients were treated with a simple local field in which the primary tumor plus clinically swollen lymph nodes were included in the PTV with a generous margin using paired anterior oblique wedge fields. A fractional daily dose of 2.0 Gy at the midplane or beam intersection point, up to a total dose of 40 Gy, was prescribed for initial radiotherapy. Off-cord oblique fields were used after a dose of 40 Gy for patients treated without surgery. The total dose for the 15 patients treated without surgery ranged from 60–74 Gy, with a median of 64 Gy. All six patients who underwent surgery received 40 Gy as the total dose.

Chemotherapy

All but two of the 21 patients, an 87-year-old woman and a patient with liver cirrhosis, received CCRT using combination cisplatin and 5-fluorouracil. Fourteen patients received one cycle of systemic cisplatin (15 mg/m^2, 5 consecutive days) and 5-fluorouracil (500 mg/m^2/day as a continuous infusion 5 days/week). Both agents were administered concurrently with radiation therapy starting on day 1. Five patients received a daily intravenous dose of 5 mg cisplatin and 250 mg 5-fluorouracil during the entire radiotherapy course. Prophylactic parenteral nutritional support was initiated for all patients who underwent CCRT. Anti-emetic drugs, such as type 3 serotonin receptor antagonists, were used as needed.

Surgery

At the time 40 Gy had been delivered, surgical resection was recommended for patients whose tumors still had considerable bulk and were considered resectable and who were fit for surgery. Six patients consented to surgery. Of those, one patient underwent simple gastrostomy alone because his tumor (which had invaded the trachea) had insufficient initial shrinkage and was considered unresectable at the time of surgery. The remaining five patients underwent curative surgical resection; four patients were treated by transthoracic esophagectomy performed by a combined right thoracic abdominal and cervical approach with larynx preservation, and one patient received pharyngo-laryngo-esophagectomy resulting in permanent tracheostomy.

Local control, toxicity evaluation and survival

Response Evaluation Criteria in Solid Tumors (RECIST)[6] have become the most commonly used criteria. However, their applicability for esophageal cancer has not been fully validated. Accordingly, in the present study, alternative criteria proposed by Tahara *et al.* were used with slight modification.[7] For patients treated without surgery, response at the primary site was evaluated as complete response (primary-CR) when both of the following were confirmed by endoscopic examination: (i) disappearance of the tumor lesion; and (ii) absence of cancer cells in biopsy specimens. 'Disappearance of ulceration' in this criteria is not applicable because no patient had ulcerative lesions in this study. When these criteria were not satisfied, a non-CR was designated. Because patients who underwent surgery had received only 40 Gy, these criteria by themselves cannot be applicable for them. However, for statistical analyses, patients who achieved primary-CR and those who underwent curative surgical resection were grouped together and defined as an initial local control group. Acute toxicities were graded according to the National Cancer Institute common toxicity criteria version 2.0. Overall survival was estimated using the method of Kaplan-Meier. Log-rank statistics were used to examine differences between groups.

RESULTS

Local control, failure sites and patient status at the last follow-up are summarized in Table 2.

Local control

Of 15 patients treated without surgery, six patients achieved primary-CR, while nine had non-CR. All these six patients who achieved primary-CR underwent CCRT. Thus, among 19 patients who received CCRT, a total of 11 patients including five who underwent curative surgery achieved initial local control. Neither of the two patients who received radiation therapy alone achieved local control. Local control was more frequently observed with T1–3 tumors. When analyzed by T-classification, 9/12 patients with T1–3 tumors achieved initial local control, whereas only 2/9 patients with T4 tumor ($P = 0.014$, χ^2 test) achieved initial local control. Of the latter two patients, one achieved local control after surgery. Among 19 patients who underwent CCRT, 9/11 patients with T1–3 tumors achieved initial local control, whereas only 2/8 patients with T4 tumors ($P = 0.011$, χ^2 test) achieved initial local control. The pathological T-classification (pT) for five patients who underwent curative surgery were pT0 in two, pT1 in one, pT3 in one, and pT4 in one.

Failure pattern

A total of 13 patients developed recurrent disease. According to the UICC staging system, for cervical esophageal cancer, regional lymph nodes refer to lymph nodes above the clavicle only. However, because of close proximity to the primary tumor, upper mediastinal lymph node recurrence was regarded as nodal recurrence, and sites of recurrence were divided into local recurrence, nodal recurrence, and visceral metastases. The most predominant site of recurrence was local. The breakdown by site showed local recurrence alone in four patients, visceral metastases alone in two, local and nodal in two, local and visceral in three, nodal and visceral in one, and local, nodal, and visceral in one patient. No patient developed nodal recurrence alone. The first site of recurrence was local in eight patients, nodal in one, and visceral metastases in four patients. Of the nine patients with T4 tumors, all but one patient who achieved primary-CR without surgery had recurrence. Of those, all had tumor progression in the primary site and three had visceral metastases. The first failure sites in these eight patients were local in six and visceral metastases in two. Of 12 patients with T1–3 tumor, five experienced recurrence, with local recurrence in two, nodal recurrence in two, and visceral metastases in four patients. The first failure sites in these five patients were local in

Table 2 Responses, first failure sites, and follow-up of all patients

#	Age/ gender	TN factor	Length (cm)	Chemotherapy	Radiotherapy		Response at the primary site	Surgery	L c
					Field	Dose (Gy)			
1	61M	T4N1	8	CDDP+5FU	Long T	61	Non-CR	–	N
2	78M	T4N1	8	CDDP+5FU	Local	64	Non-CR	–	N
3	87F	T4N1	5	–	Short T	60	Non-CR	–	N
4	54M	T4N1	8.5	CDDP+5FU	Short T	66	Non-CR	–	N
5	71M	T4N1	3.5	dCDDP+5FU	Local	60	Primary-CR	–	Y
6	63M	T4N1	5	dCDDP+5FU	Local	64	Non-CR	–	N
7	48F	T4N1	3	CDDP+5FU	Short T	40	NA	Esophagectomy	Y
8	69M	T4N1	5	CDDP+5FU	Short T	40	NA	Gastrostomy	N
9	61M	T4N1	5	CDDP+5FU	Short T	74	Non-CR	–	N
10	68M	T3N1	5	CDDP+5FU	Short T	60	Primary-CR	–	Y
11	66F	T3N0	2.5	CDDP+5FU	Short T	60	Non-CR	–	N
12	72M	T3N1	4	CDDP+5FU	Short T	68	Primary-CR	–	Y
13	70F	T3N0	2	dCDDP+5FU	Local	40	NA	Esophagectomy	Y
14	60F	T3N1	7	CDDP+5FU	Short T	40	NA	Esophagectomy	Y
15	74F	T3N0	5	CDDP+5FU	Short T	40	NA	PLE	Y
16	72M	T3N1	6	CDDP+5FU	Short T	40	NA	Esophagectomy	Y
17	55M	T3N1	5	CDDP+5FU	Short T	60	Non-CR	–	N
18	73F	T2N0	5	dCDDP+5FU	Short T	60	Primary-CR	–	Y
19	66M	T2N0	6	–	Long T	66	Non-CR	–	N
20	59M	T1N1	3	CDDP+5FU	Short T	66	Primary-CR	–	Y
21	63M	T1N0	6	dCDDP+5FU	Short T	66	Primary-CR	–	Y

dCDDP+5FU, daily intravenous cisplatin and 5-fluorouracil; NA, not applicable; PLE, pharyngo-laryngo-esophagectomy; DOD, died of disease; ID, i
NED, no evidence of disease; TRD, treatment-related death.