値60 Gy）を受けた21例（B群）に分け，術式や術後合併症，遠隔成績を検討した．なお非切除症例（バイパス例含む），同時性重複癌症例，UICC stage Ⅳb症例は今回の検討から除外した．

教室における治療方針としては図2のような時代変遷があり，現在教室では周術期の合併症軽減を目的に，照射量46 Gyの時点で切除可能かどうか一度画像評価を行い，手術適応を決めることとしている．化学放射線療法については，現在は原則としてJCOG 0303 A群ないしB群に準拠したレジメンを用いており，46 Gyの時点で画像評価を行っている．患者背景と化学放射線療法のプロトコールについては表1, 2に示したが，患者背景においてA, B群間に有意差を認めなかった．

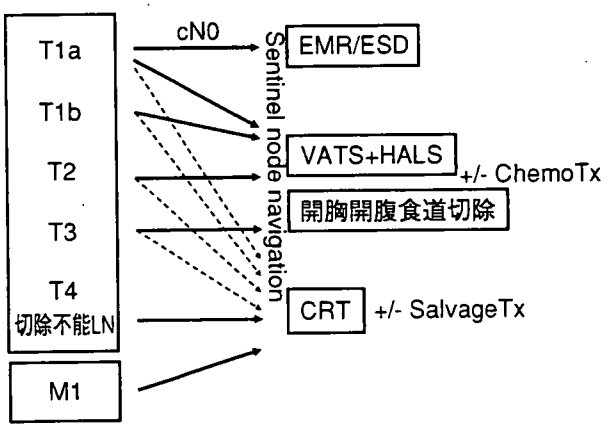


図1　胸部食道癌に対する治療方針(慶應義塾大学外科)

2. 結　果

1) 術式の検討

化学放射線療法の治療効果について表3に示した．化学放射線療法終了後から，手術までの期間は，A群で中央値40日，B群腫瘍遺残例で46日，B群再発例は300日であった．

A, B群間の切除術式について表4に示した．A群の1例を除きほぼ全例で，右開胸開腹胸部食道切除術が施行され，胸腔鏡・腹腔鏡併用の食道切除術は手技の安全性の面から選択されなかった．頸部郭清は56例中17例（30%），胸管合併切除は14例（25%）にのみ施行されたが，A, B群間に差はみられず，両群とも可及的に頸部郭清の省略，胸管の温存が図られていることが明らかとなった．郭清度，R（癌遺残度），手術根治度に関してもA, B群間に有意な差を認めず，R0，手術根治度Aの手術が大半を占めた．

再建術式に関してもA, B群間で有意な差を認めなかった（表5）．安全性を重視し，ほぼ全例で胸壁前経路による胃管再建術が選択された．また空腸瘻も1例を除き造設され，術後の経管栄養に使用された．二期分割手術はB群のハイリスク例（3例）に施行された．

切除標本の病理組織学的結果は，表6に示した．

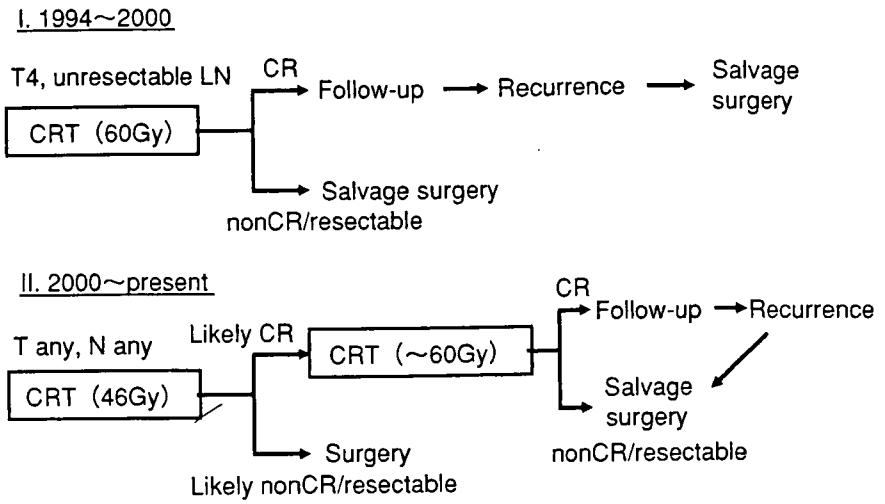


図2　慶應義塾大学外科学教室における化学放射線療法のstrategy

表1　患者背景

	A群 n=35	B群 n=21	Total n=56
性別：M/F	32/3	21/0	53/3
年齢（M±SD）	59±7	61±9	60±8
占居部位：Ut/Mt/Lt	4/26/5	6/13/2	10/39/7
cT factor：T1/T2/T3/T4	1/0/3/31 89%	2/1/2/16 76%	3/1/5/47 84%
cN factor：N0/N1	10/25 71%	7/14 67%	17/39 70%
Stage：Ⅰ/Ⅱ/Ⅲ/Ⅳa	0/2/11/22 94%	2/1/6/12 86%	2/3/17/34 91%

表2　化学放射線療法プロトコールの内訳

	A群(%) n=35	B群(%) n=21	Total(%) n=56
Chemotherapy			
Standard FP	0(0)	6(29)	6(11)
Low dose FP	30(86)	8(38)	38(68)
FP (others)	5(14)	6(29)	11(20)
Docetaxel	0(0)	1(5)	1(2)
Radiotherapy (Gy)			
Median (range)	46(30–48)	60(50–60)	46(30–60)

表3　化学放射線療法の治療効果

	A群(%) n=35	B群(%) n=21	Total(%) n=56
治療効果			
CR	0(0)	5(24) CR後再発例	5(7)
PR	29(83)	16(76)	45(80)
NC	5(14)	0(0)	5(9)
PD	1(2)	0(0)	1(2)
化学放射線療法終了から手術までの期間（中央値）	40日 (27–104)	遺残例 46日(11–69) 再発例 300日(234–347)	43日 (11–347)

表4　切除術式の検討

	A群(%) n=35	B群(%) n=21	Total(%) n=56
到達経路			
右開胸開腹胸部食道切除	34(97)	21(100)	55(98)
非開胸食道抜去	1(3)	0(0)	1(2)
リンパ節郭清			
2領域	24(69)	15(71)	39(70)
3領域	11(31)	6(29)	17(30)
D0/D1/D2/D3	1/1/20/13 94%	0/0/14/7 100%	1/1/34/20 96%
胸管合併切除：Y/N	9/26 74%	5/16 76%	14/42 75%
R0/R1/R2	26/1/8 74%	16/4/1 76%	42/5/9 75%
手術根治度：A/B/C	22/6/7 63%	13/7/1 62%	35/13/8 63%

表5　再建術式の検討

	A群(%) n=35	B群(%) n=21	Total(%) n=56
二期分割手術：Y/N	0/35	3/18 14%	3/53
再建経路（胸前/胸後/後縦）	31/4/0 89%	20/0/1 95%	51/4/1 91%
再建臓器（胃/結腸）	34/1	20/1	54/2
吻合部（頸部/高位胸腔内）	35/0	20/1	55/1
空腸瘻造設：Y/N	35/0	20/1	55/1
手術時間（min）	489±127	472±143	483±133
出血量（m*l*）	533±347	566±374	546±355

表6　切除標本の病理組織学的効果

	A群(%) n=35	B群(%) n=21	Total(%) n=56
原発巣 pCR (Grade 3)	5(14)	7(33)	12(21)
原発巣 non pCR	30(86)	14(67)	44(79)
pN0	14(40)	10(48)	24(43)
pN1	21(60)	11(52)	32(57)

2）術後合併症

各群における術後合併症の頻度については表7に示した．縫合不全，循環不全の頻度はA，B群間に差を認めなかったが，呼吸器合併症（肺炎）の頻度は，A群で35例中9例（26%）だったのに対して，B群では21例中11例（52%）と有意に高かった．また，気管切開を要した重症肺炎例もB群では5例（24%）と高頻度であり，50 Gy以上の根治的照射を受けた患者におけるsalvage手術では，とくに術後肺炎対策が重要であることが示唆された．なお教室では，気管・気管支膜様部壊死は1例も経験していない．

術後30日以内の手術死亡例はA群で1例に認め，全体では56例中1例（1.8%）であった．ま

た，手術死亡例を含む在院死亡は両群ともに2例ずつ認めたため，A群では5.7%，B群で9.5%，全体では56例中4例（7.1%）であった．この在院死亡4例の主たる原因は，術後肺炎によるものが2例，胃管壊死・縫合不全から敗血症を生じたものが1例（手術死亡例）で，もう1例は術中アナフィラキシーショックからARDS，DICを発症し，多臓器不全となった症例であった．

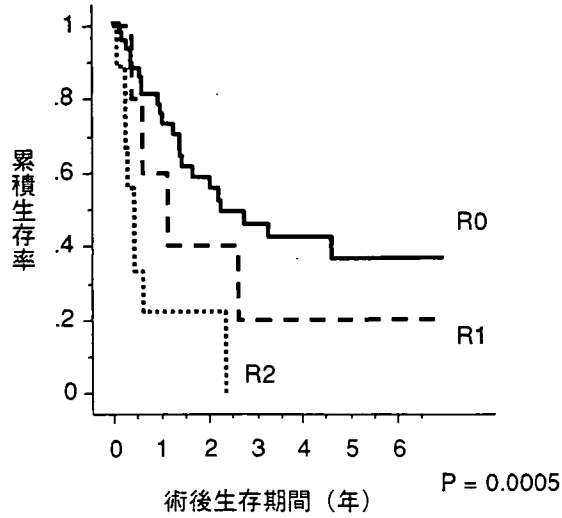
3）術後生存率の検討

今回検討された56例全体での術後生存率は，1年生存率67%，5年生存率29%で，生存期間中央値は759日であったが（図3a）．A, B群間では生存率に差を認めなかった（図3b）．癌遺残度，手術根治度の検討では，R0，手術根治度Aでそれぞれ有意に予後が良好であった（図4a, b）．原発巣とリンパ節転移巣の病理組織学的な検討では，原発巣pCR（Grade 3）症例はnon pCR症例に比べ有意差はなかったものの，予後良好であった（図5）．術後合併症の有無による生存率の比較検討では，とくにB群のsalvage例において呼吸器合併症，縫合不全，循環不全ともに有意な予後不良因子となった．

表7　術後合併症の検討

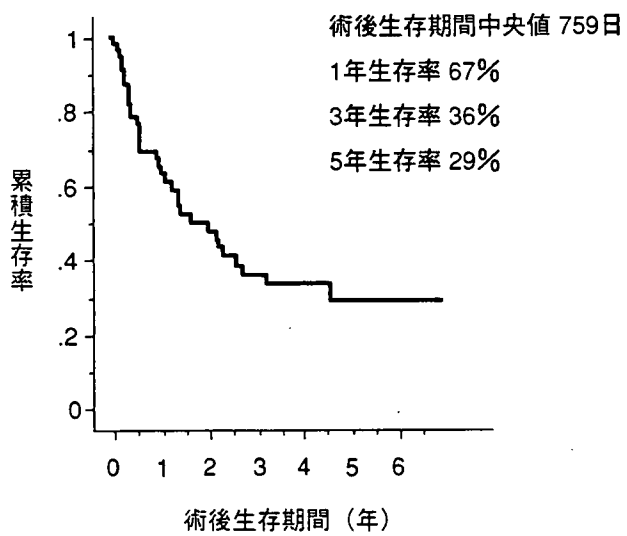
	A群(%) n=35	B群(%) n=21	Total(%) n=56
呼吸器合併症（肺炎）	9(26)*	11(52)*	20(36)
気管切開例	5(14)	5(24)	10(18)
縫合不全(胃管壊死含む)	9(26)	5(24)	14(25)
循環不全	4(11)	5(24)	9(16)
手術直接死亡	1(2.8)	0(0)	1(1.8)
在院死亡(手術死亡含む)	2(5.7)	2(9.5)	4(7.1)

* $P=0.04$

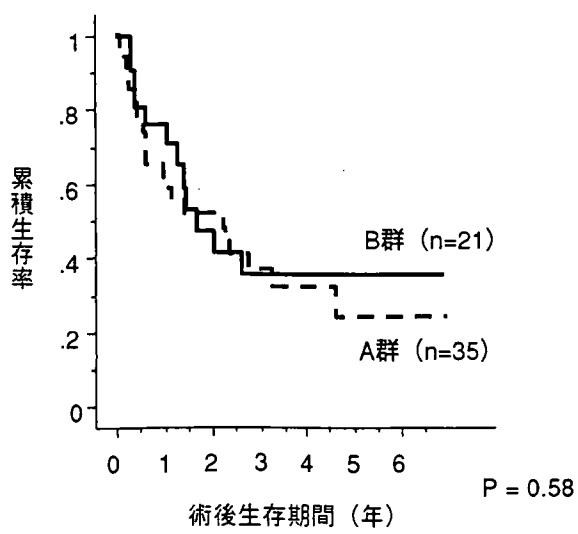


a

図4a　Overall survival（癌遺残度）

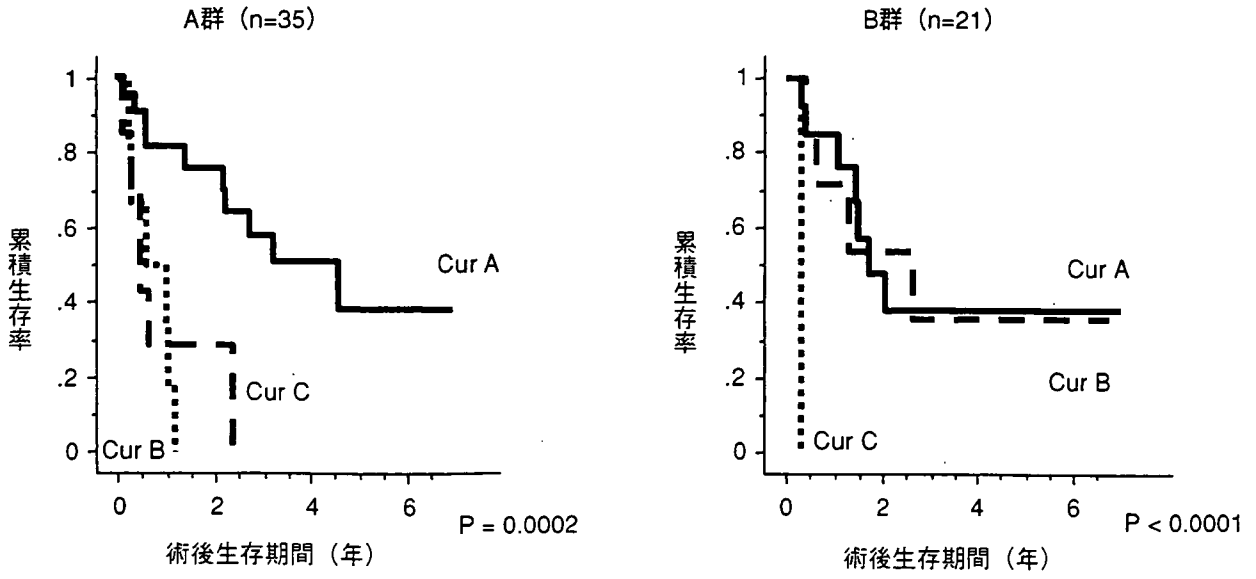


a



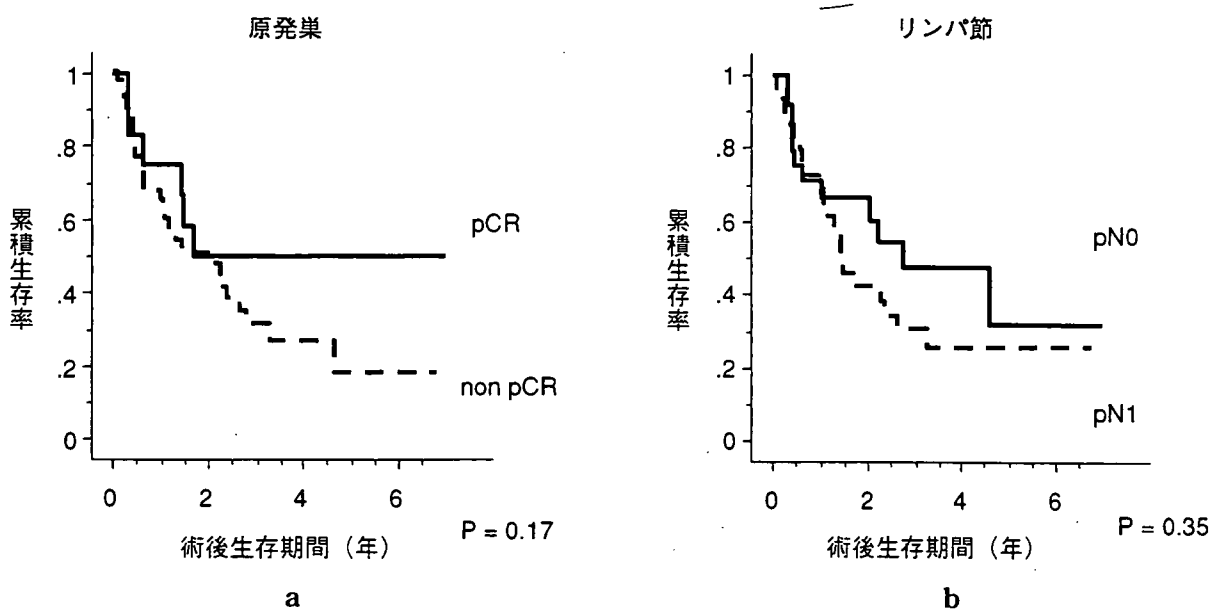
b

図3
a：Overall survival（56例）
b：Overall survival（A, B群間比較）



b

図4b　Overall survival（手術根治度）



a　b

図5　Overall survival（手術根治度）

まとめ

今回の検討から以下のような点が明らかとなった．①A, B群ともほぼ全例で，右開胸開腹胸部食道切除，胸壁前胃管再建術が選択され，安全性を重視した術式の選択がなされていた．②B群（salvage群）はA群に比べ，術後呼吸器合併症の頻度が有意に高かったが，縫合不全，循環不全の頻度は両群間で差を認めなかった．このことよりsalvage手術における術後肺炎対策の重要性が示唆された．③R0，手術根治度Aの手術は有意に予後良好であったことから，治癒切除の重要性が認識された．④B群（salvage群）では術後合併症例は有意に予後不良であった．

以上の結果から，根治的化学放射線療法後のsalvage手術は，安全性と根治性の両立を図ることが要求され，とくに高度な手術手技と緻密な周術期管理が必要であることが認識された．現在教室では，表8に列挙した点に留意したsalvage手

表8　安全性・根治性を重視した胸部食道癌 salvage 手術

Ⅰ．手術
- ●開胸開腹食道切除術(VATS+HALS は用いない)
- ●頸部郭清の省略
- ●胸管の温存
- ●気管支動脈・気管固有鞘の温存
- ●胸壁前経路の選択
- ●血流のよい胃管の作製と大彎側での確実な吻合
- ●空腸瘻の造設
- ●高リスク症例での二期分割手術の選択
- ●R0，根治度 A を目指した手術

Ⅱ．周術期管理
- ●術前画像評価 (CT, PET, EUS, etc)
- ●術後肺炎対策　…気管支鏡，ミニトラック留置，呼吸リハビリ，早期離床
- ●生体反応の制御…シベレスタットナトリウム，ステロイド投与
- ●栄養管理　…術後早期経腸栄養
  術前 Immunonutrition の検討

術を行っており，徐々に成果をあげつつある．また，教室では照射量 46 Gy の時点で一度画像評価を行い，患者への十分な説明のもと 46 Gy で切除をするか，根治照射量まで化学放射線療法を続行するか検討することとしており，周術期の合併症軽減に有効と考えられる．しかしながら 46 Gy の時点で，根治照射量まで続ければ CR となるであろう症例を選別できるかどうかが重要な点であり，現在 PET や血中遊離癌細胞 (Circulating tumor cells) の意義について検討中である．

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胸部食道癌に対する根治目的放射線化学療法後の salvage 手術の意義と適応について

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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

胸部食道癌に対する根治目的放射線化学療法後の salvage 手術の意義と適応について

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The Role and Indication of Salvage Surgery after Definitive Chemoradiotherapy for Thoracic Esophageal Cancer: Sato H[*1], Tsubosa Y[*1], Taku K[*2], Yasui H[*2], Fukutomi A[*2], Yoshino T[*2], Hironaka S[*2], Onozawa Y[*2], Boku N[*2], Zenda S[*3], Hashimoto T[*3] and Nishimura T[*3] ([*1]Department of Esophageal Surgery, [*2]Department of Gastrointestinal Oncology, [*3]Department of Radiation Oncology, Shizuoka Cancer Center)

Salvage surgery may also be the best second-line treatment for local and regional recurrence after definitive chemoradiotherapy, but this has not yet been established. All patients who received salvage surgery had been preoperatively estimated as being "curatively resectable", but non-curative rate was about 20%. The benefits of salvage treatments seem to be limited, since about 30% of patients were recurred within 3 months. Our results suggested the first endoscopic evaluation for the primary site should be performed on 75–90 days from the initiation of treatment, and the next examination as the first response evaluation should be performed about 5 weeks after the initiation of treatment. We need to clarify suitable indications, optimal timing of salvage surgery in the near future.

Key words: Esophageal cancer, Esophageal surgery, Definitive Chemoradiotherapy, Salvage surgery
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はじめに

胸部食道癌に対する根治目的放射線化学療法は，食道温存を可能とした有力な治療選択肢である[1]．しかしながら，腫瘍が遺残したり，一旦，完全寛解（CR）した後に再発することも多く経験する．そのような症例に対する救済（salvage）手術は重要であると考えられているが[2,3]，その意義，適応については議論の多いところである．

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1. 当院における切除可能胸部食道癌症例における基本姿勢

おのおのの専門家が説明し，患者自身による治療法決定を支持する“積極的な患者参加型医療の実践”を心がけている．すなわち消化器内科医師より根治的化学放射線療法の説明，食道外科医師より食道癌手術の説明を施行している．放射線治療に関するより詳細な説明を要する場合，放射線治療医からも説明している．2002年9月から2005年3月までに当院で開胸開腹食道切除再建術が可能と判断され，根治目的の治療が施行された胸部食道癌は94例であった．その治療選択の割合は，手術60例（64%），根治的化学放射線療法34例（36%）であり，おおよそ2/3が手術

を希望した．手術例の1年生存率，2年生存率はそれぞれ86.3%，58.6%，放射線化学療法例では87.6%，66.3%であった．

2. CRのタイミングとsalvage手術について

1) 目　的

胸部食道癌に対する根治目的放射線化学療法後のsalvage手術の意義・適応について，CRのタイミングから明らかにすること．

2) 対象と方法

当院で2002年9月から2005年7月までの胸部食道癌に対しCDDPと5-FUを用いた根治目的放射線化学療法施行例65例を対象とした．症例選択基準は，下記の6つの条件をすべて満たしたものとした．①前治療なし②組織学的に扁平上皮癌③75歳以下④performance status 2以下⑤主要臓器機能が保たれている⑥重篤な合併症がない．放射線化学療法のregimenは，Japan Clinical Oncology Group（JCOG）のJCOG9906に基づき，5-FU 400 mg/m² day1-5, 8-12, 36-39, 43-46, CDDP 40 mg/m² day1, 8, 36, 43，以後，効果により4週ごとに5-FU 800 mg/m² day1-5, CDDP 40 mg/m² day1を追加，放射線総線量は60 Gy（2 Gy/day，予定休止期間2週間）（表1）．遺残・再発した時は，salvage手術を検討した．適応は遺残や再発した癌が，通常の3領域郭清の範囲に限局し，全身状態が耐術可能なものとした．手術の術式は，通常の3領域郭清より郭清の範囲は縮小した．遺残や再発した領域および治療前にリンパ節転移が疑われた領域を重点的に郭清した．

患者背景を表2に示す．StageⅣのM因子はすべて頸部リンパ節転移である．cT4の割合は34例（52%）である．

3) 結　果

Complete Response（CR）と診断された症例は31例（48%），Partial Response（PR）31例（48%），Progressive Disease（PD）3例（4%）．cT4は34例中14例がCR（41%）．CRに入ったタイミングは，2コース終了後11例，3コース9例，4コース8例，5コース以降3例であった．一旦CRと診断された後に14例（45%）が再発した．遺残・再発した症例48例のうち19例（40%）がsalvage切除可能病変と診断．内視鏡を用いたsalvage治療を3例に施行．内視鏡的粘膜下剥離術（ESD）1例，光線力学療法（PDT）1例，ESDを施行後にPDTを施行した1例である．salvage手術は12例に施行．術式は，右開胸食道切除再建9例，胸部下部食道切除・胃全摘1例，頸部郭清2例である．2例（17%）に腫瘍が遺残．そのうちの1例はcT4症例であった．放射線性肺臓炎による術後在院死亡1例．縫合不全2例，細菌性肺炎を1例に認めた．在院死亡した1例を除いた11例中7例（64%）が術後に再発し，3例が3カ月以内であった．5例が郭清範囲内の局所再発である．手術拒

表1　放射線化学療法の治療スケジュール

1〜2コース	1	5	8	12	15	19
CDDP (40 mg/m²)	↓		↓			
5-FU (400 mg/m²)	□		□			
Radiation (2 Gy/day)*	↓↓↓↓↓		↓↓↓↓↓		↓↓↓↓↓	

* 放射線総線量；60 Gy
5週ごとに繰り返す

3コース以降	1	5
CDDP (80 mg/m²)	↓	
5-FU (800 mg/m²)	□	

* 4週ごとに繰り返す

表2　患者背景　n=65

Gender	Location
Male: 56	Ut: 11
Female: 9	Mt: 43
Age　62.4±7.1 y.o.	Lt: 11
cStage	
Ⅰ: 5	
Ⅱ: 2	
Ⅲ: 33	
Ⅳ: 25 (M: Cervical Lymph Node Metastasis)	
*cT4: 34 (52%)	

否例や内視鏡治療例を除くsalvage手術対象12例中，術後無再発生存は4例（33%）．

小　括

（1）cT4食道癌で，CRT後にdown stageにより，根治切除可能であった症例は1例（3%）のみであった．

（2）19例（29%）がsalvage治療の対象となった．

（3）salvage手術は，術前診断に限界があり，結果的に非治癒切除や早期再発となる症例が多い．

（4）salvage手術の意義があったと考えられる症例は33%であった．

（5）3コース以降にCRに入る症例が多いため，早期にsalvage手術を決定すると，CRに入る症例を手術している可能性が高くなる．

（6）CRT後のより早期の段階でCRに入らないと考えられるpopulationを明らかにし，より早期のsalvage手術のタイミングを明らかにすることも必要である（CRに入る症例を手術している可能性は少ないが，非治癒切除にしている可能性はある）．

3. 内視鏡検査による原発巣のCR判定とそのタイミングの検討

1）背　景

放射線治療後の効果判定は，検査時期により内視鏡所見が異なる．効果判定が早い場合，食道炎や潰瘍残存などの所見により腫瘍残存の判定が困難である．判定時期が遅い場合，原発巣の遺残の判定が遅れ，salvage治療のタイミングが遅れる可能性がある．また現時点で，治療終了後早期の段階で，腫瘍消失もしくは増悪を予測する有効な指標はない．

2）目　的

局所進行食道癌に対する根治的放射線（化学）療法症例の適切な原発巣効果判定時期を明らかにすること．

3）対象と方法

2002年9月から2004年12月まで当院において根治的放射線（化学）療法が施行された局所進行扁平上皮癌症例120例中，前治療がなく，治療終了後に少なくとも2回以上の原発巣効果判定を施行している90例を対象とした．原発巣の内視鏡によるCR判定基準は，①全食道が観察可能②腫瘍の残存なし③潰瘍形成なし④生検で陰性の4つの基準をすべて満たすものとした．salvage治療は，原則として明らかなPDを確認するまで行わない方針とした．

表3　CRと判定された症例　n=55

性別	
男/女	50/5
年齢	
中央値（範囲）	65(47-87)
PS	
0/1/2	20/30/5
部位	
Ce/Ut/Mt/Lt/Ae	6/6/30/12/1
腫瘍径（mm）	
中央値（範囲）	50(15-150)
肉眼型	
Type 0/1/2/3/4	10/5/28/12/0
T Stage	
T1/T2/T3/T4	10/2/22/21
N Stage	
N0/N1	14/41
M Stage	
M0/M1	41/14
治療レジメン	
5-FU+CDDP+RT	24
5-FU+CDGP+RT	9
5-FU+RT	3
RT alone	1

4）検討結果1：原発巣がCRと判定されたグループについて治療開始からCR判定されるまでの期間

CRと判定されたのは55例であった．その患者背景を表3に示す．CRに入るまでの期間に，CRと判定できなかった理由とその判定時期を表4に示す．また内視鏡的効果判定時期と生検結果を表5に示す．原発巣効果判定において，治療開始からCR判定されるまでの中央値は97日であり，CR判定の遅い症例では約7カ月の期間を要した．治療開始後75日以内に効果判定を行った47件中4件が生検にて癌細胞陽性であり，75

表4　CRと判定できなかった理由とその判定時期

	～90日	～120日	～150日	～180日	～210日
のべ検査数	55	46	29	42	27
non-CR判定件数	33	14	4	2	0
CR判定できなかった理由					
生検結果陽性	4	0	0	0	0
狭窄*	10	6	0	0	0
潰瘍	27	10	3	1	0
その他	21	4	2	1	0

* 狭窄所見を認めた場合non-CRと判定し，内視鏡的食道拡張術を施行

表5　内視鏡的効果判定時期と生検結果

内視鏡的効果判定時期（治療開始日より）	検査件数	生検結果		施行せず
		陽性	陰性	
75日以内	47件	4	39	4
75日以降	128件	0	127	1

日以降効果判定を行った128件では全例生検にて癌細胞陰性であった．

5）検討結果2：原発巣がCRと判定されなかったグループについて治療開始からPD判定されるまでの期間

CRと判定されなかったのは35例であった．その患者背景を表6に示す．PDと判定された時期を表7に示す．治療開始90日以内でPDと判定されたのは1例（3%）であり，治療開始後90～150日以内に17例（47%）がPD判定されており，2週間単位で最も多くPD判定された期間は105～120日であった．

両検討の効果判定結果を時系列で表す（表8）．治療開始75日以内で生検陽性でもCRになるcaseがあり，90日以降に生検陽性でCRになるcaseはなく，210日以降にCRになるcaseはなかった．

小　括

局所進行食道癌に対する根治的放射線（化学）療法症例の内視鏡検査は治療開始後75～90日に初回の検査を行い，2週間から1カ月の間隔で2回目の検査を施行するのが適切と考えられた．今後，原発巣CR後の検査間隔の検討とLNについても評価時期と方法の検討が必要である．本検討結果を表1の放射線化学療法のregimenに当てはめると，内視鏡による原発巣の評価からみたsalvage手術の適応は，3コース終了後のPD，4コース終了時でのPDとPR・SDの生検結果陽性例，5コース終了時でのすべてのnonCRである．

表6　CRと判定されなかった症例　n＝35

性別	
男/女	32/3
年齢	
中央値（範囲）	63(49-81)
PS	
0/1/2	11/22/2
部位	
Ce/Ut/Mt/Lt/Ae	1/5/23/2/4
腫瘍径（mm）	
中央値（範囲）	70(25-120)
肉眼型	
Type 0/1/2/3/4	1/3/22/8/1
T Stage	
T1/T2/T3/T4	1/0/10/24
N Stage	
N0/N1	4/31
M Stage	
M0/M1	5/31
治療レジメン	
5-FU+CDDP+RT	26
5-FU+CDGP+RT	5
5-FU+RT	3
RT alone	1

まとめ

salvage手術は，結果的に非治癒切除や早期再発となる症例が多く，根治が得られる症例は限ら

表7　判定時期と判定結果

	～90日	～120日	～150日	～180日	181～日
のべ検査数	46*	32	22	15	18
PD判定件数	1	10	7	2	15

* 35例すべてが90日以内に少なくとも1回の内視鏡検査を受けている
最後に原発巣non-CRと判定されてからPD診断に至るまでの期間　中央値（範囲）　37(11-176)日

表8　両群の効果判定結果と時系列

治療開始～(日)	～75	90	97	105～120	150	201日
A群	生検陽性の可能性	CR判定 50%				全例CR判定
B群	PD判定 6%		PD判定 47%			

初回内視鏡検査　効果判定

2週間～1カ月

れていると考えられる．術式は，通常の郭清範囲より縮小せざるを得ないが，術後の再発形式は局所に多かった．したがってCRT前やsalvage手術前の癌の存在部位を重点的に切除すべきである．Salvage手術の適応は，resectabilityがあり耐術可能な3コース終了以前でのPD，4コース終了時点でのPDとPR・SDの生検結果陽性例，5コース終了時点でのすべてのnonCRと考える．この適応の妥当性は，今後のprospectiveな検討が必要である．

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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

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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

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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.

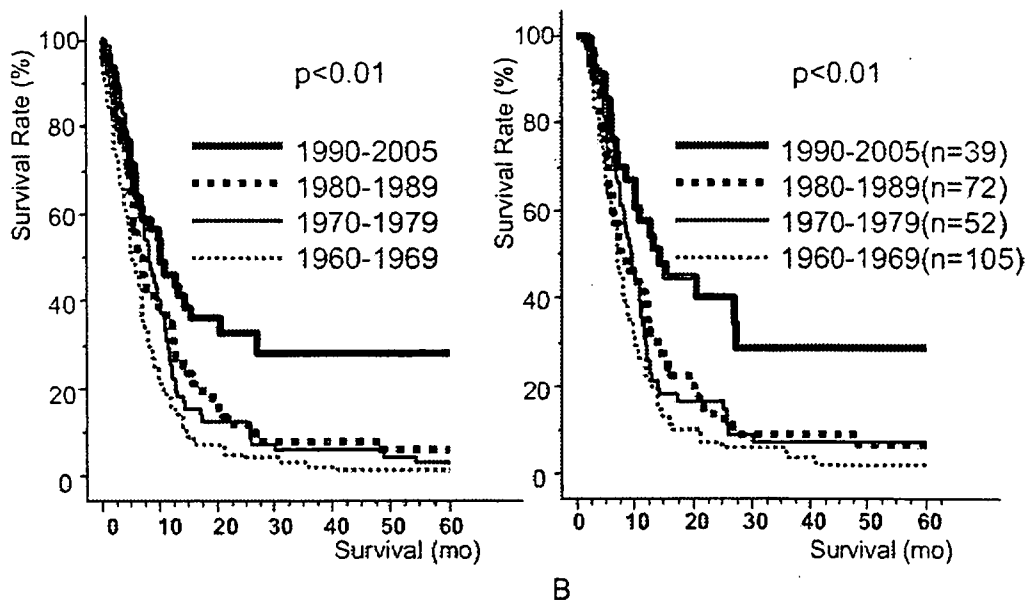

Figure 1. (A) Overall and (B) cause-specific survival curves of patients according to each time period of surgery. Survival curves according to four time periods were compared. Survival curves of each time period were displayed as thick line (1990 to 2005), thick dotted line (1980 to 1989), thin line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

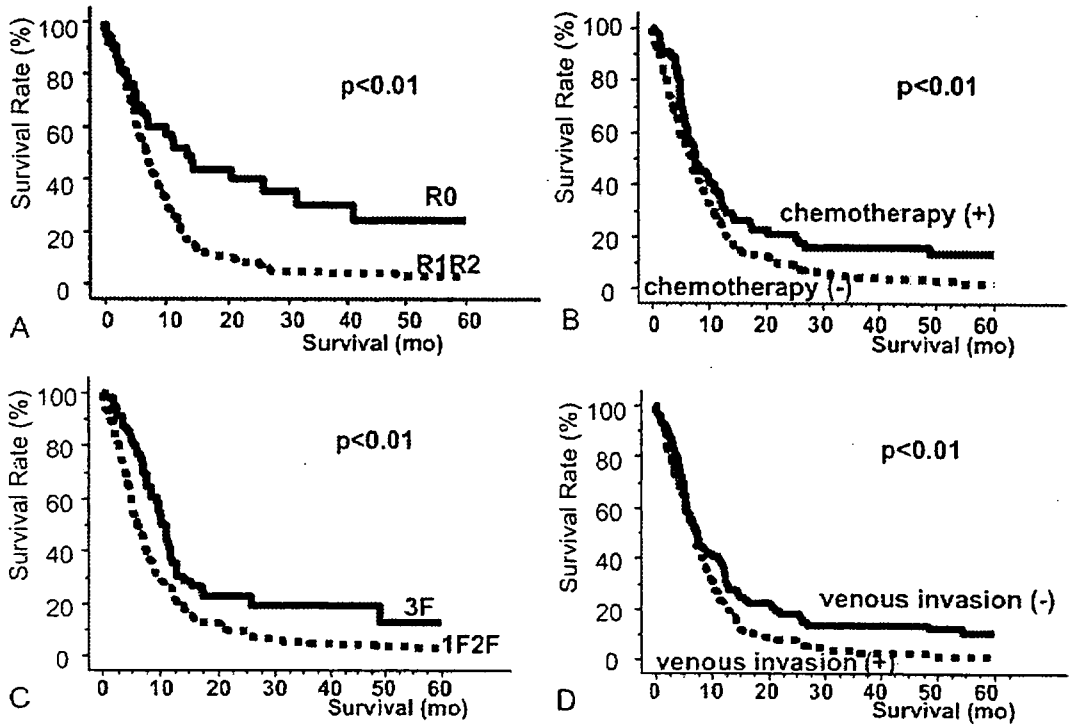

Figure 2. Overall survival curves of patients according to clinicopathologic factors. (A) R0 (no residual tumor) versus R1–R2 (presence of residual tumor). (B) Presence versus absence of preoperative adjuvant chemotherapy. (C) Three-field versus two-field lymphadenectomy. (D) Absence versus presence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

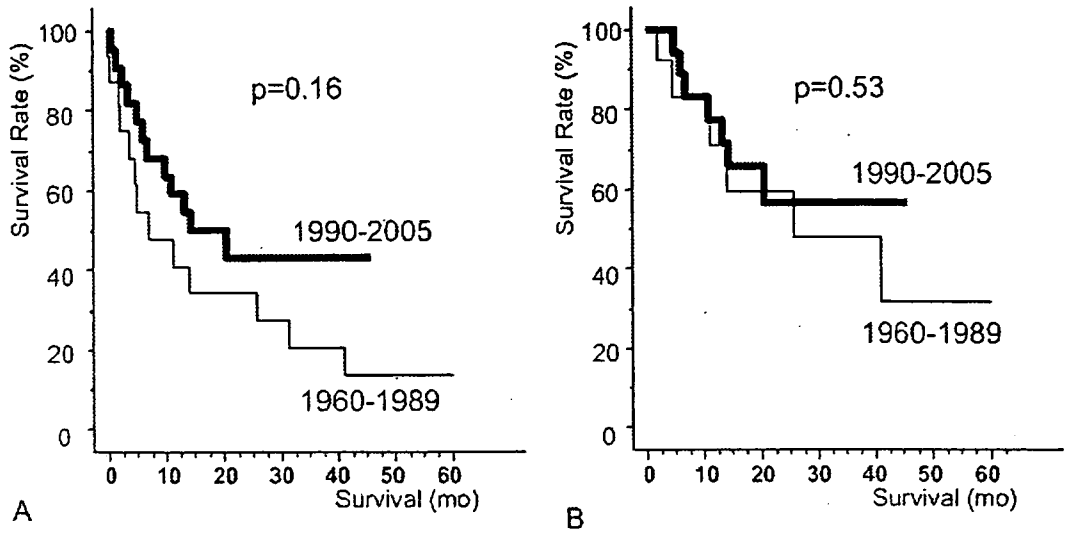

Figure 3. (A) Overall and (B) cause-specific survival of patients after complete resection according to the time period of surgery. Thick lines, 1990 to 2005; thin lines, 1960 to 1989.

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
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Analysis and interpretation of data: Akutsu, Hayashi
Drafting of manuscript: Shimada
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CASE STUDIES

Endoscopic submucosal dissection of recurrent or residual superficial esophageal cancer after chemoradiotherapy

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Background: Treatment of local recurrent or residual superficial esophageal squamous-cell carcinoma (SCC) with conventional EMR often results in a piecemeal resection that requires further intervention.

Objective: The aim of this study was to evaluate the efficacy of endoscopic submucosal dissection (ESD).

Design: A case series.

Patients: Between January 2006 and September 2006, 4 local recurrent or residual superficial esophageal SCCs were treated by ESD.

Interventions: ESD procedures were performed by using a bipolar needle knife and an insulation-tipped knife. After injection of glycerol into the submucosal (sm) layer, a circumferential incision was made, and an sm dissection was performed. All lesions were determined to be intramucosal or sm superficial, without lymph-node metastasis by EUS before treatment.

Main Outcome Measurements: Tumor size, en bloc resection rate, tumor-free lateral margin rates, and complications were recorded.

Results: All 4 ESD cases were successfully resected en bloc, and the tumor-free lateral margin rate was 75% (3/4) by histopathology examination. The mean tumor size of the resected specimens was 35 mm (range, 15-50 mm). There were no complications.

Limitations: The number of ESDs in our series was limited, and there are no long-term follow-up data.

Conclusions: ESD for recurrent or residual superficial esophageal tumors after chemoradiotherapy achieves the goal of an en bloc resection, with a low rate of incomplete treatment without any greater risk than the EMR technique.

Esophageal cancer is one of the most difficult GI cancers to detect at an early stage, even by endoscopy. Recently, a narrow-band imaging endoscope was developed and was shown to be advantageous for the early detection of squamous-cell carcinoma (SCC) in the esophagus and the pharynx, although it still is not widely in use.[1,2]

Some esophageal cancers have been detected as invasive tumors, and surgery has been the standard treatment for such lesions. However, higher mortality rate because of surgery has been reported (range 2.1% to 13.7%), as has poor patient quality-of-life after surgery.[3,4]

There is a current preference to treat esophageal SCC by primary chemoradiotherapy (CRT),[5,6] but 13% of patients treated for esophageal SCC with CRT have a recurrence or a residual tumor. Surgery after CRT is unsatisfactory,[7,8] and endoscopic treatment can be proposed when the tumor is superficial,[9-13] but a strip biopsy is difficult, because fibrosis and piecemeal resection frequently occur even for small lesions. A search of the literature confirmed that en bloc resection by endoscopic submucosal dissection (ESD) provides better results in the stomach.[14-17] ESD was recently reported to be useful in the treatment of superficial esophageal SCC[18-20]; however, the feasibility and safety of ESD for local recurrent or residual tumors is unclear. Previously, we reported on

Abbreviations: B-knife, bipolar needle-knife; CRT, chemoradiotherapy; ESD, endoscopic submucosal dissection; IT-knife, insulation-tipped-knife; NCCH, National Cancer Center Hospital; SCC, squamous-cell carcinoma; sm, submucosal.

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