

科の協力を得て行う必要があり、今回当院でも両科の協力を得たうえで施行した。AEFの予見に関しては、当院におけるCRT症例の合併症を検討した結果、術前の上部消化管造影にて潰瘍底形成が深いものやSpur-formationを形成する症例でリスクが高く、とくにCRTの照射線量が35Gyを超えるとAEFが発症しやすいという結果が得られている。AEFの予兆としてはsentinel bleedingという持続する少量の吐血が特徴であり<sup>7)</sup>、当院の過去のAEF症例にも高頻度に認められた。

以上の理由から、当院ではCRT症例は30Gyを超えたところで胸部CTを用いて治療の効果判定を行い、大動脈浸潤症例のAEFが予見される場合はASGを留置する方針としている。このような所見に従い、2005年から現在まで4例にASGを留置した。3例は予定手術、1例は緊急手術でASGを留置した。ASGを留置するようになってからAEFによる急死例は認められなくなった。ASG留置後の合併症としては高熱や胸痛、出血、ステント逸脱などが報告されており、当症例でも持続する高熱は認められたがそれ以外の合併症は経験していない。治療上の問題点としては、AEFの診断がついてから治療開始するまでに人員と時間が必要なこと、ステントおよびグラフトの手配と準備に時間がかかること、保険適応ではないため30万円程度の自己負担が必要なことがある。しかし、発症すれば死に直結する合併症であることには間違いなく、AEFが予見される症例に対してCRTを安全に施行するためには有用な治療手段のひとつであると考えられる。

## おわりに

高度進行食道癌に対するCRTの致死的な合併症のAEFに対しASGを留置することでAEFを回避し得た症例を経験した。CRTにおいて少量の喀血などAEFを予見させる所見が認められた場合、AEFを予想して治療を進め

る必要がある。放射線科や循環器外科の協力を得なければ成立しない治療であること、緊急の場合の人員確保の難しさ、費用などの諸問題はあるものの、大動脈浸潤のある食道癌に対する予防的ASG留置はCRTを安全に勧めるうえで有用な手段であると考えられる。

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## 特集

## 食道癌に対する集学的治療

## 食道癌における初期治療としての根治的化学放射線療法

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Recently, definitive chemoradiotherapy has been developed as a radical treatment for esophageal cancer. Although it could make cure for stage I (T1N0) disease, considerable rate of the patients with advanced cancer had residual or recurrent tumors. Salvage esophagectomy has been performed for these tumors, but mortality and morbidity were relatively high. Survival of the patients with stage II/III diseases who received chemoradiotherapy was comparable to that of those underwent esophagectomy. Definitive chemoradiotherapy might be useful as an initial treatment for esophageal cancer, but considerable rate of the patients with advanced stage had local recurrence.

**Key words:** Esophageal squamous cell carcinoma, Salvage esophagectomy, Radiochemotherapy, Neoadjuvant chemoradiotherapy

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## はじめに

近年、食道癌に対する初期治療として化学放射線療法が腫瘍内科でさかんに行われるようになってきている<sup>1)</sup>。そして、食道癌治療の中心である Stage II/III においても外科手術と生存率に差がないとしている<sup>2)</sup>。一方、化学放射線療法後の遺残や再発に対しての手術（サルベージ手術）が行われるようになった。将来的に食道癌の初期治療は化学放射線療法となり、外科的治療はサルベージ手術に限定されることとなる可能性がある。しかし、化学放射線療法後の長期生存例に晩期障害が出現すること<sup>3)</sup>や食道癌が5年以上経ても再発することやサルベージ手術の困難なこと<sup>4)</sup>がわか

ってきている。そのため、化学放射線療法は初期治療としていまだ確立されていない。

今回、初期治療として根治的化学放射線療法を行った食道癌症例について Retrospective に検討した。その効果とともに遺残・再発に対する治療など遠隔成績について詳述する。

## 1. 初期治療として根治的化学放射線療法を行う食道癌症例

根治的化学放射線療法は臨床病期 (TNM 分類) で T4, N0/1, M0 に対して絶対的適応として行っている。食道癌の他臓器浸潤 (T4) の診断は CT や MRI でも困難なことも多く、手術で完全に切除できないと判断される場合で放射線診断では T4 となる。手術を前提に照射線量を 40 Gy とする術前化学放射線療法は現在でも希望する患者に行われている。T1N0M0 においては JCOG で第

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II相試験(JCOG9807)が行われて手術と同等の成績であったこと<sup>2)</sup>で、ランダム化比較試験(JCOG0502)が現在開始されようとしている。その中間のStage II, IIIでは手術が標準治療であることを説明し、頸部食道癌症例や化学放射線療法希望者つまり手術を拒否した症例に行っている。切除不能のリンパ節転移・臓器転移で根治切除不能のStage IV症例が化学放射線療法の適応である。臨床病期は超音波内視鏡やマルチスライスのCT scan, PET/CTなどの精密検査を施行しているが病理診断とは約70%の一致率であるとされている。

## 2. 治療方法

当院における根治的化学放射線療法は日本臨床腫瘍研究グループ(JCOG)の食道がんグループのレジメンに沿って行われている。化学療法はCisplatin+5-FUで1992年より特定研究19(特19)が行われ、これは化学療法を放射線療法の1週間前より開始するレジメンであった。1995年よりJCOG9516が開始され<sup>5)</sup>、化学療法と放射線療法を同時に施行するレジメンである。現在もほぼ同様に行われているが、放射線療法の中断はしないようになり、第5週に化学療法の2コース目が行われている。そのほかCisplatinのかわりにNedaplatin(アクブラ)を使用するレジメンが行われている<sup>6)</sup>。近年、低用量CDDP+5FUのレジメンが行われるようになってきている。白血球が減少してきた場合化学療法を中止できる利便性があるが、効果は標準量との間に差があるか不明であるためJCOGで検証中である(JCOG0303)。また、放射線療法はまず前後対向2門にて1日2Gyで20回(40Gy)の時点で斜入にして20~30Gy追加し、合計60~70Gyであった。近年、INT0123(Radiation Therapy Oncology Group 94-05)では2Gy 30回(60Gy)と1.8Gy 28回(50.4Gy)で生存率に差がなかった<sup>7)</sup>。わが国でもRTOGレジメンとして行われ始めている。頸部と全縦隔の長いT字照射を行う場合は1.8Gyで50.4Gyとし、化学療法をやや多く投与するこのレジメンをすでに導入して

いる。一方、T1の場合は治療前に内視鏡でクリッピングをして病巣の上下5cmに限定している。根治的化学放射線療法後の補助化学療法は以前原則として施行していなかったが、2005年より進行癌に対しては行っている。内視鏡検査で局所再発を治療終了後と以後3カ月おきに行っている。CT scan, FDG-PETなどで遠隔再発は4カ月おきに検査している。そして、再発が切除可能ならSalvageの食道切除手術やリンパ節郭清術を優先している。多発リンパ節や臓器転移に対してはCisplatin+5FUは化学放射線療法で使用しており、Docetaxel(タキソテール)を中心としたSecond Lineの化学療法を行っている。

## 3. 治療成績

当センターにおける根治的化学放射線療法の治療成績を臨床診断のStage別に手術成績または術前化学放射線療法施行例と比較した。しかし、これはあくまで参考であって多施設共同のランダム化比較試験が必要であることはいうまでもない。

### 1) 表在癌 Stage I

Stage I (T1N0M0)で根治的化学放射線療法が施行された症例は18例であり、CRは17例(94%)で遺残(nonCRnonPD)が1例あり内視鏡的粘膜切除およびアルゴンプラズマ凝固焼灼を行い治療している。局所再発に対してサルベージ食道切除を4例に施行している。多発食道癌に対して内視鏡的粘膜切除およびアルゴンプラズマ凝固焼灼を行っている症例が2例ある。予後は癌死が1例のみで、頸部リンパ節に再発し照射野外であったため再度化学放射線療法を行ったが再発し死亡している。手術でpT1(sm), pN0, pM0であった症例87例との比較では生存率の差はなかった(図1)。また、この検討からは除外したが内視鏡的粘膜切除(EMR)を先行させて粘膜下層まで浸潤していた9例に対して化学放射線療法をしている。1例がリンパ節再発し死亡しておりほぼ同等の治療成績であった。

現在、JCOGでこのStage I食道癌に対する手術と化学放射線療法のランダム化比較試験

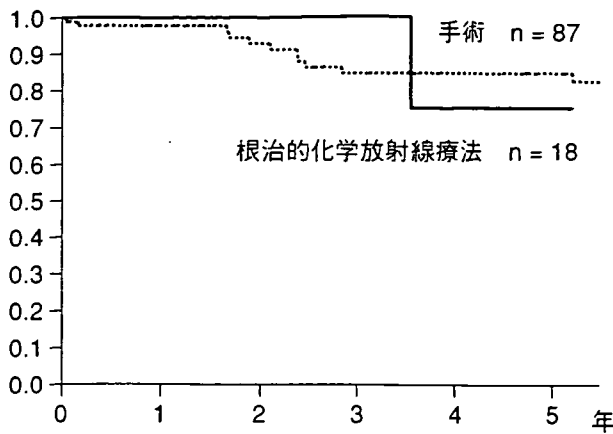


図1 Stage I (T1N0M0) 症例での根治的化学放射線療法例と手術例の生存曲線

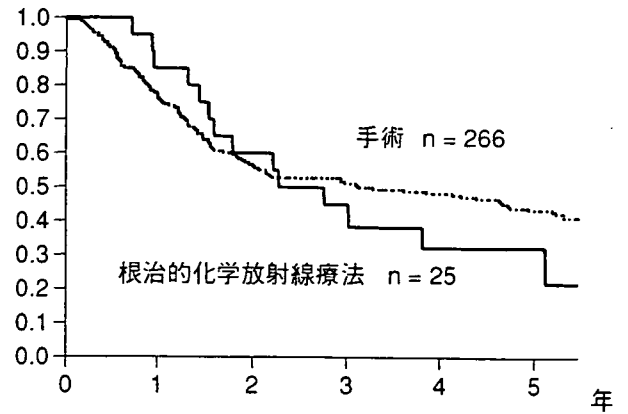


図2 Stage II/III症例での根治的化学放射線療法例と手術例の生存曲線

(JCOG0502) が開始されている。全く異なった治療方法を比較する試験として画期的であると思われる。遠隔成績まで出るには数年を要するが、晩期障害や Quality of Life まで調査し本当に化学放射線療法でよいのか検討すべきと考えられる。

### 2) 切除可能症例 Stage II/III

現在でも Stage II/III 食道癌 (T1/2/3, N0/1, M0) は手術が標準的治療とされている。しかし、腫瘍内科からの報告では根治的化学放射線療法と外科手術と差がなかったとしている<sup>2)</sup>。当センターでは根治的化学放射線療法が施行された症例は 25 例あり、そのほとんどが手術拒否例である。しかし、喉頭合併切除となる頸部症例が 5 例とやや多いなど手術先行例との間に背景因子の差が多少みられる。しかし、全身状態などに大きな差はなく、結果的に 10 例 (40%) でサルベージ手術を受けている。治療効果は CR11 例 (44%) で、PR で終わった症例は早期に再発している。生存曲線は手術先行例と差はなかったが、治療開始から 3 年以降は手術例より低下する傾向にあった (図 2)。しかし、このような Retrospective な検討はバイアスが多く、ランダム化試験を行わなければ結論は出ない。再発形式では局所再発が多く、サルベージ食道切除術の適応となっている。頸部や腹部のリンパ節転移に対しては郭清するサルベージ手術を行っているが、多発で広汎に転移していることが多く手術の適応になる症例は少ない。化学放射線療法の晩期障害や多発

食道癌を含めた局所再発の危険性がある。

### 3) 局所進行癌 T4N0/1M0

10 年以上前までは手術療法が絶対であり、局所進行癌で腫瘍が切除できなかった症例を少なからず経験していた。近年、このような症例には化学放射線療法が必ず行われるようになった。そして、根治的な化学放射線療法を行うか術前 (ネオアジュバント) 化学放射線療法を行うかで方針が分かれるところである。欧米では腺癌が多いこともあり、ネオアジュバント化学放射線療法+手術が主流である<sup>8)</sup>。この場合照射線量は 30~50 Gy で化学療法は 1~2 コースとなり、治療終了後約 3~5 週で手術を行っている。効果のあったつまり Down-staging した症例が手術されており長期生存している。切除標本の病理学的所見で癌を認めない Grade3 (pathological CR) 症例は逆に手術が不要であった可能性がある。根治的化学放射線療法を行い、遺残・再発した場合にサルベージ手術を行った 19 例を含めた生存曲線に有意差は認めていない (図 3)。以上より、当院では根治的化学放射線療法を行い厳重な follow-up を行うようになった。しかし、根治的化学放射線療法で CR となり再発しないで 5 年以上の長期生存した症例が少ないこととサルベージ手術となった場合は死亡率が高くリスクが大きいことなどの不利な要因がある。

文献的にはわが国で 36 Gy の時点で患者に手術するか化学放射線療法を継続するかを決めてもらう非ランダム化試験が行われている<sup>9)</sup>。その結

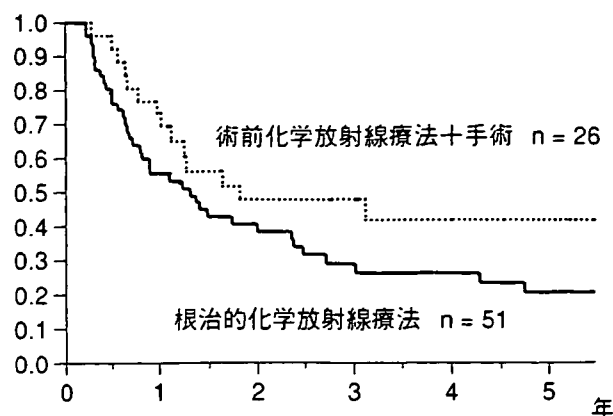


図3 局所進行食道癌 (T4, N0/1, M0) 症例での根治的  
化学放射線療法例とネオアジュバント化学放  
射線療法+手術例の生存曲線

果、化学放射線療法の奏効例が非奏効例よりも有意に生存率が高いことのほか、手術した場合非奏効例の生存期間が延長したとしている。欧米<sup>10)</sup>では化学療法3コースの後、化学放射線療法40 Gyを行い手術する(A)群と50~60 Gy根治的  
化学放射線療法をして手術しない(B)群に振り分ける臨床試験を行った結果、手術は局所コントロールを向上させるが生存率に有意差はなかったとしている。この試験もA群の34%が手術拒否していたり手術在院死が11.3%であったりバイアスが多く問題である。進行食道癌では遠隔のリンパ節や臓器転移で再発死亡することが多く、この場合生存率に差は生じない。むしろ、生存率が高くなった場合、局所コントロールが問題となると考えられる。

#### 4) 遠隔転移例 TxNxM1 (Stage IV)

遠隔転移のある(M1)症例では化学療法の効果が予後に関与することになる。化学放射線療法の前または後に必ず化学療法を行っている。食道癌局所が進行して食事が食べられない場合は局所効果の高い化学放射線療法を優先することになる。遠隔リンパ節転移の症例は放射線の照射野が入れば、化学放射線療法を行う。つまり頸部と腹部の両方のリンパ節に転移がある場合は化学療法が優先される。頸部に大きな(Bulky)転移リンパ節のある症例で化学放射線療法が奏効し長期生存している症例もみられる。T2, 3M1症例において、生存曲線では手術先行例と結果的に差は認

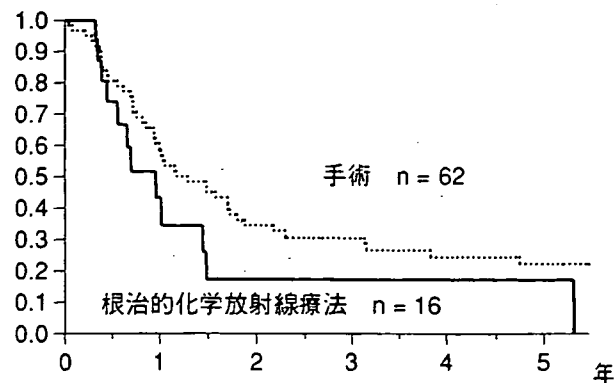


図4 遠隔転移のある食道癌 (T2/3, N0/1, M1) 症例  
での根治的化学放射線療法例と手術例の生存曲  
線

められていない(図4)。

臓器転移では肺転移症例は化学療法が奏効し長期生存例がみられる。最近、化学放射線療法で局所(T2)がCRとなり、外来で多発肺転移に対してCisplatin+TS-1を不定期に繰り返し行っている症例が3年以上経過した。一方、肝転移症例は化学療法の奏効率も低く、より効果的とされるNedaplatinやDoxetaxelを使用しても生存期間の中央値は約半年で、ほとんどの症例が1年以内に死亡してしまう<sup>6)</sup>。通常、化学放射線療法で局所に効果がない場合は転移巣にも効果がない。一方、奏効例に対しては化学療法を外来で繰り返し行っているが、いずれ効かなくなることが多い。

## まとめ

食道癌治療において根治的化学放射線療法は早期(T1N0M0)と進行期(T4N1/0M0)が適応となっている。早期に対しては化学放射線療法で食道温存がほぼ可能となったが内視鏡的治療の必要な場合があり、照射野外のリンパ節転移再発が少なからず発生するため注意が必要である。一方進行癌症例では根治手術後の遠隔リンパ節・臓器再発が多く予後不良であるため手術でも根治的  
化学放射線療法でも差がでないという一面もある。化学放射線療法の後には追加の化学療法を行いまた内視鏡検査を含めた厳重なfollow-upが重要で、食道温存のために相当な労力が必要である。いず

れにせよ手術一辺倒ではなくなってきたために治療法の選択に苦慮する症例が存在するようになってきた。将来的に遺伝子解析などの科学的な方法によるオーダーメイドの治療法選択が可能になることが期待される。

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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

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

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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 esophagectomy 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 esophagectomy. 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

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## 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<sup>1)</sup>。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<sup>2)</sup>。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<sup>3)</sup>。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<sup>4)</sup>。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

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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<sup>5)</sup>。

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<sup>2,6)</sup>。肺機能は換気量や1秒率が正常でも拡散能(PaO<sub>2</sub>)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子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



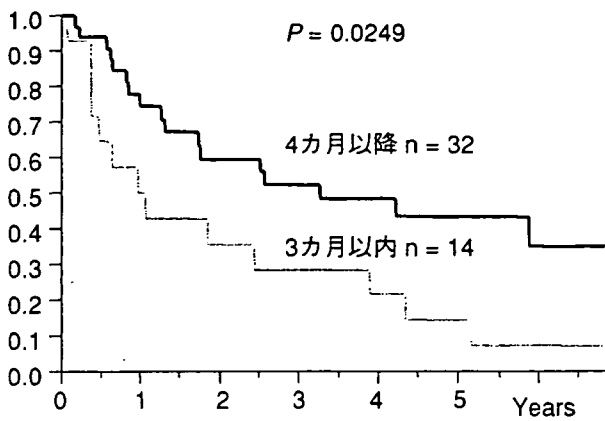


図1 化学放射線療法終了からsalvage食道切除術までの期間と術後生存曲線

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つた。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、リンパ節転移のあつたpN1は全例死亡していた(図3)。しかし、4

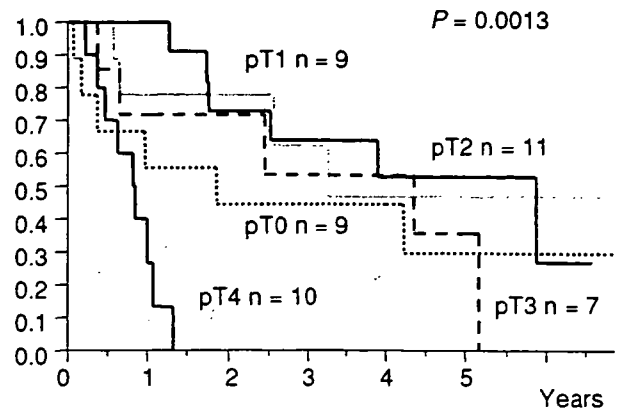


図2 salvage食道切除術を施行した症例の組織学的深達度と術後生存曲線

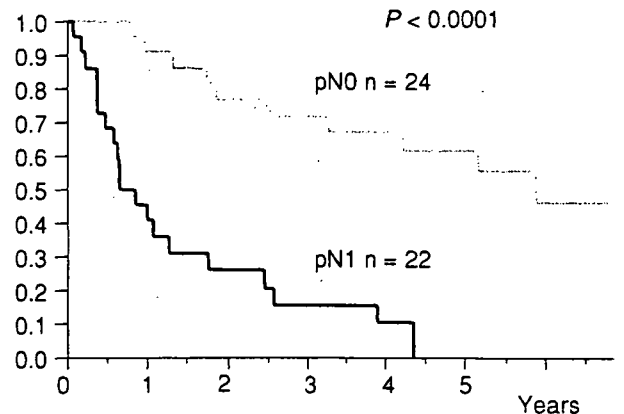


図3 salvage食道切除術を施行した症例の組織学的リンパ節転移と術後生存曲線

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つ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つた。リンパ節転移のあつた胸部食道癌症例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つた。根治的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例であつた。

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<sup>7)</sup>。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、照射野に入ら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<sup>8)</sup>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に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無い現状では、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。

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# 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.<sup>1-3)</sup> 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.<sup>4,5)</sup> Nevertheless, salvage treatment is needed to improve the overall treatment results in chemoradiation therapy.<sup>3)</sup> 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.<sup>1)</sup>

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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.<sup>6)</sup> 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.<sup>2)</sup> 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.<sup>7,8)</sup> 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.<sup>9)</sup>

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.<sup>10)</sup> Only Walsh et al. reported the efficacy of preoperative chemoradiation in improving the survival.<sup>11)</sup> However, a meta-analysis of these trials revealed that chemoradiotherapy followed by surgery significantly reduced the 3-year mortality in comparison to surgery alone.<sup>12)</sup> 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 non-randomized 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.<sup>13)</sup> 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.<sup>14)</sup> 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 chemoradiother-

apy. Adams et al. have reported that patients who had chemoradiation had double the rate of local recurrence in comparison to those receiving surgery alone.<sup>15)</sup> 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.<sup>3)</sup> 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.<sup>16)</sup> 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.<sup>17)</sup> 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.<sup>18)</sup> 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.<sup>19)</sup> 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.<sup>20)</sup> Swisher et al. described the merits of salvage surgery in patients with early pathological stage, prolonged time to progression, and R0 resection.<sup>18)</sup> 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 esophagectomy after chemoradiation is the better option.

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## A Retrospective Study of Definitive Chemoradiotherapy for Elderly Patients With Esophageal Cancer

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**Objective:** The efficacy and safety of definitive chemoradiotherapy (CRT) for elderly patients with esophageal cancer have not been fully elucidated yet. We conducted a retrospective comparison of the outcomes of CRT between elderly and nonelderly patients with Stage II–III (non-T4) esophageal cancer.

**Methods:** There were 33 elderly (aged over 71) patients and 145 nonelderly (aged under 70) patients who fulfilled the selection criteria. The treatment consisted of the continuous infusion of fluorouracil (5-FU) and the intravenous infusion of cisplatin (CDDP) combined with 60 Gy of radiation.

**Results:** Although the CR rate was almost identical between the 2 groups (63.6% vs. 63.4%, respectively), the recurrence rate after CR was higher in the elderly patients group than in the nonelderly patients group (47.6% vs. 33.7%,  $P = 0.32$ ). The elderly patient group showed a significantly inferior survival in comparison to the nonelderly patient group with a median survival time (14.7 months vs. 35.1 months,  $P = 0.01$ ). Discontinuations at the end of CRT were more frequent in the elderly patient group than in the nonelderly patients (57.6% vs. 17.3%,  $P = 0.01$ ). In addition, over Grade 3 hematologic adverse events were more frequently observed in elderly patients than in nonelderly patients. There were no obvious differences in patients who died of causes other than primary disease.

**Conclusion:** This retrospective analysis revealed a significantly inferior efficacy even in selected elderly patients. Although improving the dose intensity of CRT should be desirable even in elderly patients, it seems to be difficult because of more substantial toxicity in elderly patients.

**Key Words:** definitive chemoradiotherapy, elderly patients, esophageal cancer

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Esophageal cancer is still a virulent disease. In Japan, the cancer incidence of esophageal cancer was 14,830 in 1999. The number of esophageal cancer death was estimated to be 11,172 in 2004. The mortality rate for Japanese patients with esophageal cancer was 3.55% of all deaths due to malignant neoplasms in 2001. About 30% of those arose from elderly patients who were over 71 years of age. The number of esophageal cancers in elderly patients is therefore expected to increase in the near future as the number of elderly individuals increases.

Surgery is still the mainstay treatment of esophageal cancer. A radical surgical resection with so-called three-field nodes dissection has achieved a favorable survival in Japan.<sup>1</sup> The indications for such radical surgery, however, are not well defined particularly for elderly patients. Definitive chemoradiotherapy (CRT) is now considered to be the standard treatment modality for patients who are medically unfit for surgery or who desire to preserve their organ function. There have been many reports regarding the treatment results of definitive CRT by cisplatin (CDDP) and 5-fluorouracil (5-FU).<sup>2–7</sup> However, there have so far been few reports on definitive CRT in elderly patients.

In general, elderly patients have limitations in their ability to tolerate intensive treatments such as CRT in comparison to nonelderly patients because of medical comorbidities and reduced functional reserve of organs. In addition, the dose and schedule of CRT are based on the results from the clinical studies which have usually targeted nonelderly patients. The adequate dose and schedule for elderly patients thus have not yet been clearly determined based on clinical studies. Because elderly patients tend to have more serious adverse events, sometimes resulting in excessive dose reduction, elderly patients may therefore receive treatment which may be an inappropriately reduced dose.<sup>8</sup> However, even elderly patients may be suitable candidates for intensive treatment.

To clarify efficacy and safety for elderly patients, particularly those who are considered to be suitable candidates for definitive CRT by CDDP and 5-FU, we conducted a retrospective comparison of the treatment results between elderly and nonelderly patients groups.

## PATIENTS AND METHODS

### Selection Criteria

The subjects were recruited from the database of patient with newly diagnosed esophageal cancer at the National Cancer Center Hospital East between August 1992 and October 2002. We used an aged over 71 years as the cutoff point for defining elderly patients in this study.

The patients were selected according to the following selection criteria: 1) histologically confirmed squamous cell carcinoma (SCC); 2) Clinical Stage II or III except for T4 disease in UICC-TNM staging; 3) Eastern Cooperative Oncology Group scale performance status (PS) 0 or 1; 4) adequate organ function; and 5) thoracic esophageal cancer. The exclusion criteria were as follows: 1) prior therapy for esophageal cancer, 2) other malignant tumors except for early stage, and 3) uncontrollable serious complications.

There were 725 patients (elderly 150 patients, nonelderly 575 patients) who were newly diagnosed with esophageal cancer. Of these patients, 58 elderly and 198 nonelderly patients were classified as Stage II or III (except for T4). There was 1 colon cancer patient in the elderly patient group and 2 laryngeal and 1 lung cancer in nonelderly patient group, although each clinical stage was unknown. Finally, 33 (56.9%) elderly patients and 145 (73.2%) nonelderly patients fulfilled selection criteria and were included in our analysis.

### Pretreatment Evaluation

Routine pretreatment evaluations included endoscopy of the upper gastrointestinal tract, and computed tomography of the neck, chest, and abdomen. Endoscopic ultrasonography and bronchoscopy were optional. The clinical stages were based on the UICC (International Union Against Cancer tumor-node-metastasis system) TNM classification of malignant tumors, 1997.

### Treatment Schedule

The dose and schedule of the concurrent CRT delivered to the patients have been previously reported in detail by our institution. Briefly, the treatment consisted of the intravenous infusion of CDDP 40 mg/m<sup>2</sup> on days 1 and 8, and the continuous infusion of 5-FU 400 mg/m<sup>2</sup> on day 1 to 5 and 8 to 12. This schedule was repeated twice every 5 weeks. Concurrent radiation therapy was performed up to 60 Gy in 30 fractions during an 8-week period with a 2-week break in the middle. For responders, additional chemotherapy consisted of the intravenous infusion of CDDP 80 mg/m<sup>2</sup> on day 1 and then the continuous infusion of 5-FU 800 mg/m<sup>2</sup> on days 1 to 5 was repeated twice every 4 weeks. Radiation therapy was delivered with megalovoltage equipment using anterior-posterior opposed fields, including the primary tumor and the regional nodes as far as possible.

### Response and Toxicity Evaluations

The objective response was evaluated according to World Health Organization response criteria for measurable lesions.<sup>9</sup> The method for evaluating the response included physical examination, blood test, endoscopy (including bi-

opsy), neck and chest and abdomen CT, and toxicity. A complete response (CR) for the primary tumor was defined as the complete disappearance of all signs of active tumor with a negative biopsy and lasting for 4 weeks or longer.

The method for evaluating the response and toxicity included physical examination, blood test, endoscopy (including biopsy), neck, chest, and abdominal CT. Follow-up examinations after completing CRT were basically conducted every 3 months in the first year and then every 6 months thereafter using esophagoscopy and a CT scan. Toxicity was evaluated by the National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 2.0.<sup>10</sup>

### Statistics

The average dose per 1 week during CRT (8 weeks) was calculated as the dose intensity (DI). The planned DI (PDI) which was calculated beforehand was 20 mg/m<sup>2</sup> week in CDDP, and 1000 mg/m<sup>2</sup> week in 5-FU, respectively. The relative dose intensity (RDI) was calculated in the ratio of actual DI to PDI. The overall survival was measured from the date initiating the treatment to either the date of death or the date of the last patient contact when the patient was still alive. We estimated the survival curves using the Kaplan-Meier method and then compared these 2 groups with the log-rank test. For the categorical data, group comparisons were based on the Mann-Whitney *U* test. Statistical analyses were performed using the StatView version 5.0.1 software program (SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

The patient characteristics are listed in Table 1. There was a tendency that the elderly patient group included more PS1 patients and Stage II patients (33.3% and 54.5%, respectively) than the nonelderly patient group (16.6% and 42.8%, respectively). There were no patients over 80-year-old in the elderly patient group. The elderly patient group tended to have more comorbid diseases at baseline than the nonelderly patient group (39.4% vs. 23.4%, respectively), although those diseases had been mostly controlled with or without drug medication.

### Efficacy

Table 2 shows the efficacy outcomes of both groups. Almost identical CR rates were observed between the 2 groups, namely, 63.6% for the elderly and 63.4% for the nonelderly patients groups. However, a higher recurrence rate after achieving CR was observed in the elderly patient group (47.6%) than in the nonelderly patient group (33.7%), although the difference was not statistically significant. The median follow-up period was 57.0 months for the surviving patients. Figure 1 shows the survival curves of both groups indicated a significantly inferior survival in the elderly group than in the nonelderly group (14.7 months vs. 35.1 months, *P* = 0.01). Table 3 shows the survival results of both groups. The same inferior results in the elderly patients were seen regarding



TABLE 1. Patient Data

	Elderly (71+ years) Patients [no. (%)]	Nonelderly (≤70 years) Patients [no. (%)]
Patients	33 (100)	145 (100)
Gender		
Male	31 (93.9)	130 (89.7)
Female	2 (6.1)	15 (10.3)
Age (yr)		
Median age	74	61
Range	71-79	39-70
Performance status		
0	22 (66.7)	121 (83.4)
1	11 (33.3)	24 (16.6)
Tumor site		
Upper	7 (21.2)	31 (21.3)
Middle	17 (51.5)	75 (51.7)
Lower	9 (27.3)	39 (26.9)
Histologic type of SCC		
Well/moderately differentiated	24 (72.7)	113 (77.9)
Poorly differentiated	9 (27.3)	32 (22.1)
T stage		
1	2 (6.1)	6 (4.1)
2	2 (6.1)	27 (18.6)
3	29 (87.8)	112 (77.2)
N		
0	14 (43.1)	45 (31.0)
1	19 (56.9)	100 (69.0)
Clinical stage		
II	18 (54.5)	62 (42.8)
III (non-T4)	15 (45.5)	83 (57.2)
Comorbid diseases*		
Total	13 (39.4)	34 (23.4)
Hypertension	8 (24.2)	14 (9.7)
Diabetes	2 (9.1)	10 (6.9)
Heart diseases	1 (3.0)	9 (6.2)
Lung diseases	1 (3.0)	2 (1.4)
Others	5 (15.2)	5 (3.4)

\*Including duplication.

the median survival time (MST) as well as the 3- and 5-year survival rates.

### Compliance

The treatment compliance in each group is shown on Table 4. Nineteen of the 33 elderly patients (57.6%) did not receive additional chemotherapy after CRT segment, whereas such discontinuations were seen in only 25 patients (17.3%) in the nonelderly group. The reasons for discontinuing chemotherapy in the 19 elderly patients were as follows: 10 due to toxicity from CRT, 3 due to disease progression, 3 due to patient refusal, 1 due to progression of dementia, 1 due to cessation of follow-up, and 1 due to unknown reasons. Patients who required dose reduction during CRT were more frequently seen among the elderly patients (33.3%) than

TABLE 2. Response and Recurrence Results

	Elderly Patients [% (no.)]	Nonelderly Patients [% (no.)]	P
CR rate	% (No.)	% (No.)	
Total	63.6 (21)	63.4 (92)	0.98
Stage II	39.4 (13)	29.7 (43)	0.38
Stage III (non-T4)	24.2 (8)	33.8 (49)	0.39
Recurrence rate after CR			
Total	47.6 (10)	33.7 (31)	0.32
Stage II	23.8 (5)	14.1 (13)	0.49
Stage III (non-T4)	23.8 (5)	19.6 (18)	0.76

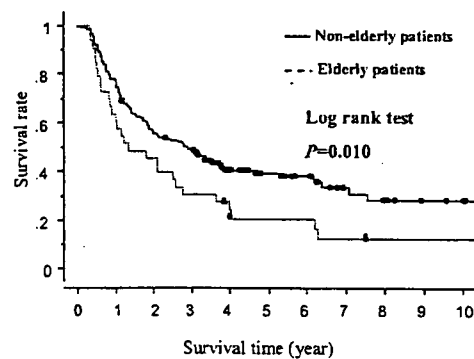


FIGURE 1. The survival curves of both groups indicated a significantly inferior survival in the elderly group than in the nonelderly group (14.7 months vs. 35.1 months,  $P = 0.01$ ).

TABLE 3. Survival Results

	No. of Patients	MST (Mo)	3-Year Survival (%)	5-Year Survival (%)
Elderly patients				
Stage II	18	14.2	33.3	27.8
Stage III (non-T4)	15	19.1	26.7	10.0
Total	33	14.7	29.3	21.4
Nonelderly patients				
Stage II	62	65.3	57.4	50.2
Stage III (non-T4)	83	30.1	42.8	32.3
Total	145	35.1	49.4	39.6

MST indicates median survival time.

among the nonelderly patients (10.3%). These reductions in the chemotherapy doses ranged from 20% to 30%. Only a slight difference in RDI was observed between the 2 groups: RDI for CDDP and 5-FU was 0.92 in the elderly patient group versus 0.96 in the nonelderly patient group.

Planned radiation therapy was completed in 31 of 33 patients (93.9%) in the elderly patient group and in 143 of 145 patients (98.6%) in the nonelderly patient group, respectively.

### Adverse Events

The adverse events over grade 3 are listed in Table 5. Hematologic adverse events were more frequently seen in the

TABLE 4. Compliance

	Elderly Patients	Nonelderly Patients	P
Number of completed chemotherapy courses [% (no.)]			
1 course	3.1 (1)	2.1 (3)	0.74
2 courses	54.5 (18)	15.2 (22)	<0.001
3 courses	9.1 (3)	14.5 (21)	0.41
4 courses	33.3 (11)	68.3 (98)	0.001
Dose reduction during CRT [% (no.)]	33.3 (11)	10.3 (15)	0.04
Radiation therapy completed [% (no.)]	93.9 (31)	98.6 (143)	0.68
Dose intensity during CRT (mg/m <sup>2</sup> per week)			
CDDP	18.5	19.2	
5-FU	924	960	
Relative dose intensity during CRT			
CDDP	0.92	0.96	
5-FU	0.92	0.96	

TABLE 5. Grade 3/4 Adverse Events

	Elderly Patients [% (no.)]	Nonelderly Patients [% (no.)]	P
Leucopenia	70.0 (23)	49.7 (72)	0.042
Anemia	51.5 (15)	17.9 (26)	0.001
Thrombocytopenia	33.3 (11)	18.6 (27)	0.063
Nausea and vomiting	6.1 (2)	2.8 (4)	0.34
Stomatitis	6.1 (2)	2.1 (3)	0.21
Esophagitis	9.1 (3)	6.2 (9)	0.55
Renal dysfunction	0 (0)	6.2 (9)	0.14
Treatment-related death	0 (0)	0.7 (1)	0.63

elderly patients than in the nonelderly patients, although these events were mostly manageable. All other adverse events were under Grade 2 in most cases.

### Causes for Death

There were no obvious differences in patients who died of causes other than primary disease: 6.9% (2 of 27 dead patients) in the elderly patient group and 7.8% (7 of 90 dead patients) in the nonelderly patient group, respectively. Two patients in the elderly patient group died of other causes: 1 patient due to cerebral events and another due to pneumonia. On the other hand, 7 patients in non-elderly patient group died of other causes: 2 due to pneumonia, 1 due to myocardial infarction, 1 due to other cancer, 1 due to suicide, and 2 due to unknown reasons.

### DISCUSSION

A randomized Phase III trial has been conducted in elderly patients with lung cancer.<sup>11</sup> That trial showed single-agent chemotherapy improved survival of elderly patients.

Pignon et al<sup>12</sup> described age has no impact on toxicity of curative thoracic radiotherapy for elderly patients. There are little clinical data about definitive CRT for elderly patients with esophageal cancer. A Phase III trial by Herskovic et al<sup>2</sup> included 28 of 121 patients older than 70 years. While this trial included elderly patients, it did not specifically report toxicity or efficacy in elderly compared with nonelderly patients and did not reach any conclusions about whether CRT should be used in elderly patients. Thus elderly patients (age, >71 years) have historically been excluded from many clinical studies evaluating esophageal cancer treatment. As a result, treatment for elderly patients is poorly defined. The age cutoff to define the elderly patients still remains controversial. Various cutoff points have been used in each study. Over 30% of esophageal cancer arises from patients older than 71 years. In addition, there are very few patients older than 80 years who can tolerate definite CRT with sufficient doses in daily practice. It therefore seemed reasonable to use an age of >71 years as the cutoff point for defining elderly patients in this retrospective study.

There were obvious differences in patients' treatment based on age in this retrospective analysis: 33 of 58 (56.9%) of elderly patients with Stage II or III (non-T4) esophagus cancer received definitive CRT, whereas 145 of 198 (73.2%) of nonelderly patients received definitive CRT. Given this difference in treatment, we consider our analysis to be a comparison of the treatment outcomes between "highly-selected elderly patients and nonelderly patients."

Despite such selection bias, this study demonstrated an inferior survival in the elderly patient group than in the nonelderly group. There might be some reasons that caused such an inferior survival in the elderly group: a lower response, a higher mortality due to complications, and a lower compliance. In the present analysis, the CR rates were almost identical between the elderly patients (63.6%) and nonelderly patients (63.4%), thus supporting the notion that no obvious differences exist in the response to the CRT between the 2 groups. However, there were obvious differences in the treatment compliance between the 2 groups, particularly in the rate of administration of additional chemotherapy (42.4% vs. 82.8%) following completion of CRT. In addition, the elderly group showed a higher recurrence rate (47.6%) after achieving CR than the nonelderly group (33.7%). The lower treatment compliance in the elderly group might therefore have caused a higher recurrence rate, thus resulting in the inferior survival. Contrary to these differences, no significant differences in the mortality due to complications, including to those related to the late toxicity of CRT, were observed between the 2 groups. These results suggest that the lower compliance of the treatment in elderly patients might thus be the major reason for the inferior outcomes. However, toxicities, particularly hematologic toxicity, also tended to be more substantial in elderly patients. Although improving the dose intensity of CRT is still required, it nevertheless seems difficult to achieve when considering the toxicity data.

Our treatment schedule for CRT was different from that of other published schedules.<sup>13,14</sup> Although this difference in the schedule might cause the lower compliance in elderly patients, it seems to be unlikely since the planned dose intensities of the chemotherapeutic agents in this regimen were equivalent to those in the standard ones and this regimen also yielded similar efficacy results to those of the standard regimens.

### CONCLUSION

This retrospective analysis revealed a significantly inferior efficacy in elderly patients than in nonelderly patients. Considering the efficacy results, improving the dose intensity of CRT should thus be highly desirable even in elderly patients in daily practice as well as in future studies. However, it seems to be difficult to achieve this objective, since these data showed more substantial toxicity even in "selected elderly patients." These conflicts remain a dilemma for oncologists to overcome in the treatment of elderly patients, although this study is expected to provide valuable information, which can hopefully lead to the establishment of more appropriate treatments for elderly patients with esophageal cancer.

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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的化学放射線療法後  
salvage 手術の検討

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**Salvage Esophagectomy after Chemoradiation for Patients with Thoracic Esophageal Cancer:** Takauchi H\*1, Saikawa Y\*1, Suda K\*1, Ando T\*1, Hiraiwa K\*1, Irino M\*1, Yoshikawa T\*1, Ozawa S\*2, Ando N\*3, Kitajima M\*1 and Kitagawa Y\*1 (\*1Department of Surgery, Keio University School of Medicine, \*2Department of Surgery, Banbuntane Houtokukai Hospital, Fujita Health University, \*3Department of Surgery, Tokyo Dental College Ichikawa General Hospital)

Recent advances in multimodal treatments for patients with esophageal cancer focus on “salvage” esophagectomy following definitive chemoradiation. However the definitive chemoradiation may result in severe postoperative complications including pneumonia and anastomotic leakage. In this study, we retrospectively analyzed the management and the prognosis of the patients with thoracic esophageal cancer who underwent the esophagectomy after chemoradiation. Long-term survival can be achieved by the “curative and safe” salvage esophagectomy. We concluded that performance of curative resection and the prevention and management of postoperative pneumonia are particularly crucial for ideal salvage esophagectomy after definitive chemoradiation.

**Key words:** Chemoradiotherapy, Esophagectomy, Pneumonia, Esophageal cancer, Salvage

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## はじめに

胸部食道癌に対する化学放射線療法は、慶應義塾大学医学部外科学教室ではこれまでに T4 ないし切除不能リンパ節を有する食道癌、あるいは M1 食道癌に対して施行されてきた (図 1)<sup>1~4)</sup>。しかし最近では T1b-T3 症例においても手術拒否例を中心に化学放射線療法施行例が増加している<sup>5,6)</sup>。またそれに伴い、腫瘍の遺残や CR 後の再発例に対する食道切除術も積極的に行われるよ

うになった<sup>7)</sup>。

今回われわれは、教室における化学放射線療法後に施行された食道切除術の成績を検討し、その問題点を明らかにした。さらに、問題点を解決するために行うべき手術、周術期管理につき考察した。

## 1. 対象と方法

慶應義塾大学医学部外科学教室で 1994 年 1 月から 2005 年 12 月までに化学放射線療法が施行された胸部食道扁平上皮癌 158 例のうち、化学放射線療法後に食道切除術が行われた 56 例を対象とした。照射量 50 Gy 未満 (中央値 46 Gy) の 35 例 (A 群) と 50 Gy 以上の根治的照射 (中央

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