径3 cm以上，神経叢浸潤（+），リンパ節転移（+），PV/SMV両側性浸潤（+），Borderline resectable膵癌，術後補助療法なし，が予後と有意な相関を示した。これらの因子で多変量解析を行った結果，神経叢浸潤（+），リンパ節転移（+），術後補助療法（−），が独立した予後不良因子であった。Borderline resectable膵癌はPV/SMV両側性浸潤と内容が重複することから多変量解析より省いた。

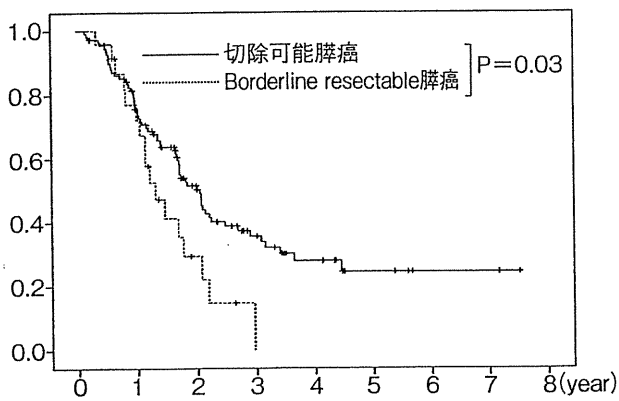

図1 切除可能性による生存曲線

4．再発部位の検討

初回再発が認められた臓器・部位を検討すると（表3），Borderline resectable膵癌では局所再発（42%）が最も頻度が高く，以下，腹膜再発，肝再発であった。切除可能膵癌と比べ有意に局所再発の割合が高かった（$p<0.05$）。

5．術後補助療法の効果

全切除例の検討の結果，術後補助療法有りは予後良好な規定因子であった。しかし，切除可能膵癌，Borderline resectable膵癌のそれぞれで術後補助療法施行の有無と予後の相関を検討したところ，Borderline resectable膵癌では術後補助療法施行の有無で予後に差を認めず（図2），補助化学療法施行患者においても3年以上の生存例を認めなかった。一方，切除可能膵癌では術後補助療法が予後良好な規定因子であった（$p=0.005$）（図3）。Borderline resectable膵癌の手術は侵襲が大きいため術後補助療法に対する忍容性が低いことも予想される。そのため薬剤強度，治療完遂率を切除可能膵癌，Borderline resectable膵癌の補助療法施行例で比較したが有意な差を認めなかった。

表2 患者・腫瘍・治療因子と予後との相関・全切除例

		生存期間（月）	単変量解析 P値	多変量解析 P値
年齢	<70 ≥70	22.1 20.8	0.97	
腫瘍径	≥3 cm <3 cm	20.6 25.5	0.03	0.23
CA 19-9	≥200 U/ml <200 U/ml	20.8 25.0	0.89	
pPV	(+) (−)	21.6 22.1	0.196	
pPL	(+) (−)	16.4 30.1	<0.01	<0.01
LN転移	(+) (−)	20.5 34.7	0.03	0.03
PV/SMV両側性浸潤	(+) (−)	12.8 25.0	0.02	0.15
SMA/CE/CHAへの腫瘍近接	(+) (−)	17.8 22.1	0.62	
切除可能性	Borderline resectable 切除可能	16.0 25.0	0.03	—
癌遺残度	R0 R1	22.4 21.6	0.09	
術後補助療法	有 無	— 20.8	<0.01	0.02

表3　術後再発部位の比較・切除可能膵癌/ Borderline Resectable 膵癌

再発部位	再発割合（%） 切除可能膵癌	Borderline Resectable 膵癌	P 値
局所	31	48	＜0.05
肝臓	45	33	NS
腹膜	28	43	NS
その他の臓器	30	33	NS

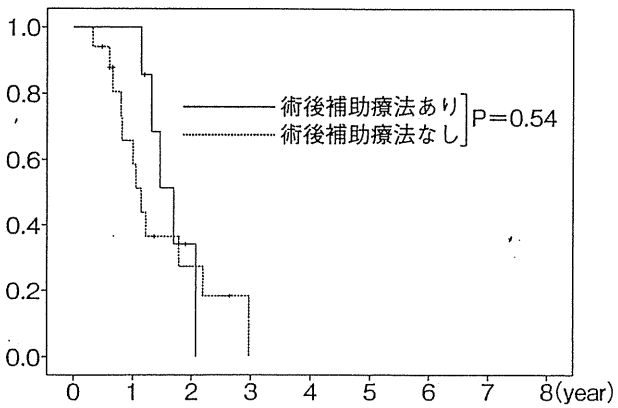

図2　術後補助療法の有無による生存曲線 Borderline resectable 膵癌

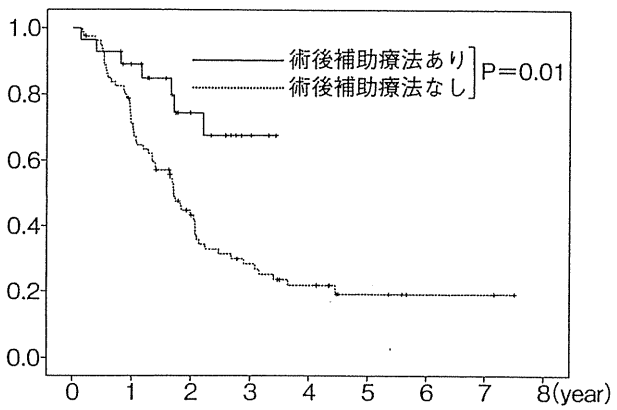

図3　術後補助療法の有無による生存曲線 切除可能膵癌

V．考　察

膵癌は今まで術前画像により切除可能膵癌，局所進行膵癌，遠隔転移を有する膵癌のいずれかに分類され，各カテゴリーに適合する治療，治療開発が行われてきた。しかし最近，切除可能膵癌と局所進行膵癌の間に，R0 切除が不確かな腫瘍群—Borderline resectable 膵癌が新しく定義・分類され[1]，集学的治療のターゲットとして，個別の治療戦略が提起されている[2,3]。局所に癌が遺残する可能性が高い Borderline resectable 膵癌には局所効果の強い術前放射線化学療法の有効性が期待されており，報告はまだ少ないが，術前放射線化学療法施行例で R0 切除 37%，術後生存期間中央値 40ヵ月と良好な成績が報告されている[5]。また，2011 ASCO GI では Borderline resectable 膵癌を対象とした臨床試験が報告され今後の治療開発が期待されている[6]。Borderline resectable 膵癌は膵癌治療成績向上の糸口となる可能性がある。

一方で，Borderline resectable 膵癌を集学的治療の対象として個別に治療するべきか，切除可能膵癌と同じカテゴリーに含むべきか，根拠となる Borderline resectable 膵癌の予後，局所癌遺残度，再発部位の状況は今まで十分に明らかにされていなかった。

今回，自験例の検討で Borderline resectable 膵癌は切除可能膵癌と比べて予後が不良であり，局所再発が多いことが示された。Borderline resectable 膵癌術後の再発は，局所再発，腹膜再発，肝再発の順に多く，肝再発が最も多い切除可能膵癌とは再発形式が異なっていた。特に，局所再発は Borderline resectable 膵癌で有意に高率であり予後不良の一因となっていた。Borderline resectable 膵癌の R1 切除率（29%）は切除可能膵癌の R1 切除率（19%）と比べ高い傾向を示し局所再発の要因と考えられた。ただし，組織学的断端陽性率は標本の取り扱いや評価方法によって施設間差が大きく，再発形式や予後への影響に関する評価は定まっていない[7,8]。組織学的断端評価法の標準化を行い組織学的断端陽性の意義を再評価する必要がある。

局所増悪傾向が強いことに加え，Borderline resectable 膵癌では，予後不良因子である神経叢浸潤，リンパ節転移の他，門脈浸潤，腫瘍径，CA19-9 値などの所見が切除可能膵癌よりも高度な傾向を示し，より進行した腫瘍状況が，予後に影響していると考えられた。

現在の切除可能膵癌に対する標準治療は，CONKO-001 study[9]，ESPAC-1[10]，ESPAC-3[11]の結果より切除＋GEM（もしくは 5-FU/LV）による 6ヵ月間の術後補助療法である。Borderline resectable 膵癌における上記術後補助療法の有効性を検討した報告は今までない。今回の検討で，切除可能膵癌で GEM もしくは S-1 による術後補助療法が予後良好な規定因子であっ

たのと対照的に，Borderline resectable 膵癌では術後補助療法による生存期間延長効果は示されなかった。Borderline resectable 膵癌は血管合併切除を伴う拡大手術になる場合が多く，術後補助療法の薬剤強度，治療完遂率が低くなることが危惧される。しかし，今回の検討では薬剤強度，治療完遂率ともに両群間で差を認めず術後補助療法の効果が低い原因ではなかった。Borderline resectable 膵癌に対し既存の術後補助療法の効果が不十分である可能性は否定できない。しかし，少数例の検討であるため，Borderline resectable 膵癌における GEM 術後補助療法を否定する確定的な結果ではないことを御留意いただきたい。

R1 膵癌に対する術後補助療法の効果に関して論じた報告が幾つかある。CONKO-001 では，subgroup analyses の結果 R1 膵癌でも R0 膵癌と同様に GEM 術後補助療法が有効であった[9]。しかし ESPAC-1 では R1 膵癌は腫瘍悪性度が高く術後補助療法の効果が低いと報告されており[12]，R1 膵癌に対する術後補助療法の効果に関する評価も定まっていない。Borderline resectable 膵癌に対する術後補助療法の有効性を検討するには，過去の術後補助療法臨床試験登録患者に対して付随研究を行い，術前画像から Borderline resectable 膵癌と切除可能膵癌に分類し，その予後を詳細に検討する必要があると思われる。

今回の結果は，Borderline resectable 膵癌を切除可能膵癌と個別に分類し術前集学的治療の対象とする治療戦略に肯定的な結果であった。組織学的断端陽性の可能性が高く局所増悪傾向の強い Borderline resectable 膵癌に対し局所効果がより強い放射線化学療法を術前に施行し予後改善を目指すことは合目的的であると考えられた。今後，本邦でも Borderline resectable 膵癌を対象とした臨床試験が行われ治療開発が行われることが期待される。

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日本消化器外科学会雑誌. 2011;44(4):428-434

術後7年無再発生存中の胆管癌と膵癌の同時性重複癌の1例

国立がんセンター東病院上腹部外科
同　病理部[1)]

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後藤田直人　　加藤祐一郎　　小嶋　基寛[1)]　　木下　　平

症例は69歳の男性で，右季肋部痛を主訴に近医受診し，下部胆管癌が疑われ当院紹介となった．CT，MRIでは下部胆管壁が全周性に肥厚し，同部には遷延性に造影効果を認めた．さらに，膵頭部に10mm大の遷延性に造影される類円形の腫瘍を認め，同部位はMRIの拡散強調画像においてhigh intensityを示していた．ERCP，MRCPでは下部胆管に20mmにわたる胆管狭窄像を認めたが，膵管には異常所見を認めなかった．以上より，下部胆管癌，リンパ節転移と診断し亜全胃温存膵頭十二指腸切除術を施行した．摘出標本では下部胆管腫瘍とは別に膵頭部に15mm大の白色結節を認め，病理組織診断では下部胆管および膵頭部に中分化型管状腺癌を認めた．両腫瘍は連続性を認めず，組織像が異なることより胆管癌，膵癌の重複癌と考えられた．術後，軽度の膵液瘻を認めたが保存的に軽快し，術後38日目に退院となった．術後7年現在，無再発生存中である．

はじめに

近年，癌に対する診断技術や治療法の進歩，さらに平均寿命の延長に伴い，多くの重複癌症例が報告されるようになった[1)]．しかし，胆管癌と膵癌の重複癌の報告は少なく，さらに切除後長期生存例は極めてまれである．今回，我々は外科的切除により術後7年間，無再発生存中の胆管癌と膵癌の重複癌症例を経験したので，若干の文献的考察を加えて報告する．

症　　例

患者：69歳，男性

主訴：右季肋部痛

既往歴：特記すべきことなし．

家族歴：兄，胃癌．

現病歴：右季肋部痛を主訴に近医受診．精査にて下部胆管癌が疑われ，精査加療目的に当院入院となった．

入院時現症：身長163cm，体重68kg，体温36.1℃．眼瞼結膜に貧血なし．眼球結膜に黄疸なし．腹部触診上，異常所見なし．

入院時血液検査所見：肝酵素および胆道系酵素の上昇を認めたが，黄疸は認めなかった（AST：133IU/*l*，ALT：230IU/*l*，ALP：786IU/*l*，γ-GTP：1,363IU/*l*，T-Bil 1.2mg/dl）．腫瘍マーカーの上昇（CEA：6.5ng/ml，CA19-9：228U/ml）を認めた．

腹部CT：遷延性に造影される下部胆管壁の全周性肥厚を認めた．また，膵頭部に遷延性に造影される

＜2010年10月20日受理＞別刷請求先：細川　勇一　〒277-8577　柏市柏の葉6—5—1　国立がんセンター東病院上腹部外科

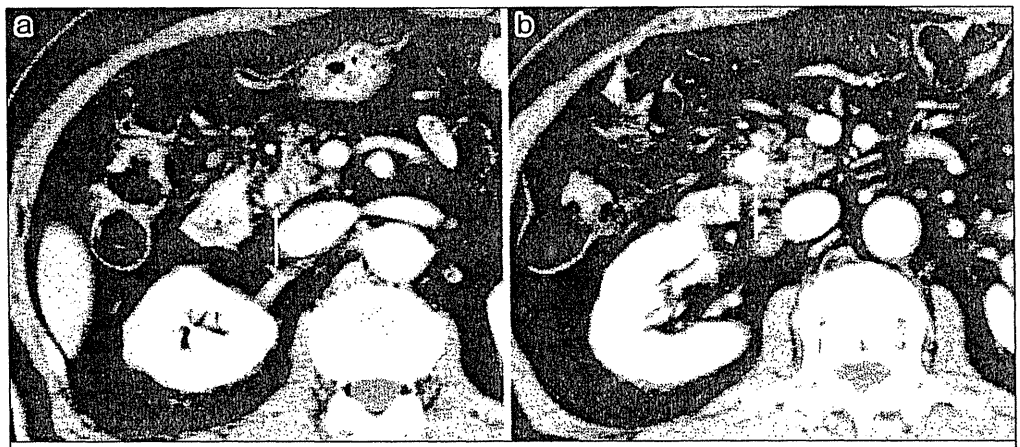

Fig. 1 a: Abdominal CT showed an enhanced thickened inferior bile duct (arrow). b: CT showed an enhanced tumor in pancreas head (arrow).

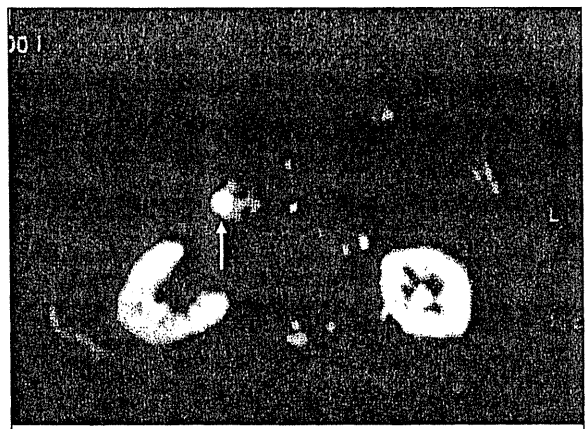

Fig. 2 The tumor presented as a high signal area in diffusion weighted imaging.

1cm 大の類円形腫瘍を認めた（Fig. 1a, b）.

腹部 MRI：下部胆管に狭窄像を認め，同部位は拡散強調画像で拡散低下を認めた．また，CT で指摘された膵頭部の類円形腫瘍は，T1 強調画像で low，T2 強調画像で low，拡散強調画像で拡散低下を示した（Fig. 2）.

ERCP：下部胆管に狭窄像を認めたが，膵管には異常所見を認めず，膵胆管合流異常も認めなかった（Fig. 3）.

以上より，下部胆管癌，リンパ節転移と診断し開腹手術を施行した.

手術所見：上腹部正中切開にて開腹．腹膜播種，肝転移などの明らかな非治癒因子を認めず，亜全胃温存膵頭十二指腸切除術を施行した.

摘出標本所見：摘出標本の割面では，下部胆管に 3cm にわたる壁肥厚を認め，下部胆管狭窄を認めた．また，膵頭部に下部胆管の壁肥厚とは連続性のない 1.5cm 大の白色調の結節性病変を認めた（Fig. 4a, b）.

病理組織学的検査所見：胆管病変は淡明な胞体を有する立方状の異型細胞が不整な管腔を形成しながら増殖しており，膵組織への浸潤像を認めた．組織学的に中分化型管状腺癌であった（Fig. 5a）．膵病変は好酸性な胞体を有する高円柱状の異型細胞が不明瞭な管腔を形成しながら増殖しており，組織学的に

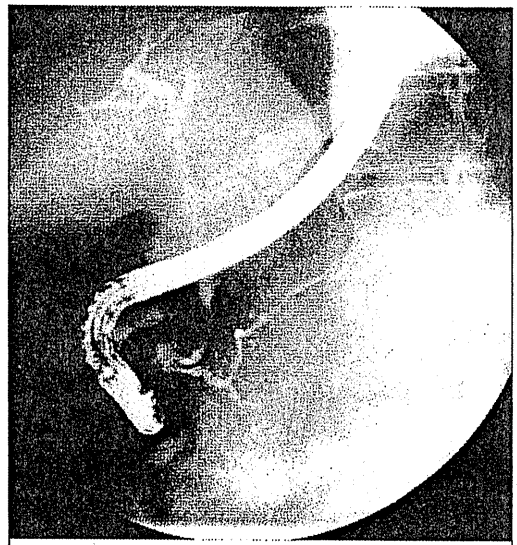

Fig. 3 ERCP showed a stenosis in the common bile duct, but a normal pancreatic duct, and no anomalous arrangement of the pancreaticobiliary ductal system.

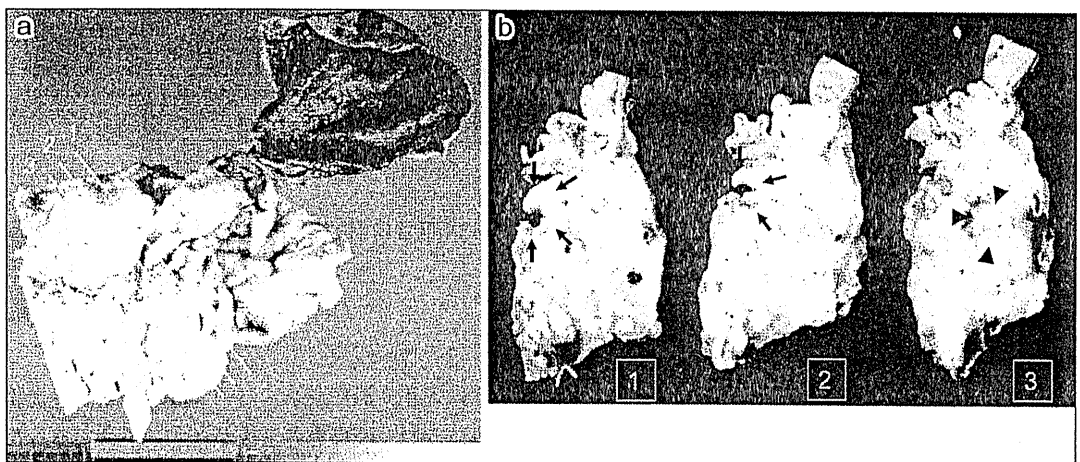

Fig. 4 Macroscopic findings of resected specimen revealed a thickened inferior common bile duct (arrow in Fig. b), a tumor sized 15mm in pancreas head (arrow head in Fig. b).

は中分化型管状腺癌であった(Fig. 5b). また, 背景膵組織内には膵管内上皮にPanIN2〜3相当の異型を認める成分を散在性に認めた. 胆管病変と膵病変は両者とも中分化型管状腺癌であるものの組織像が異なること, 両腫瘍細胞には連続性がみられないこと, 背景膵管内にPanIN2〜3相当の異型上皮を認めることより, 本症例は胆管癌および膵癌の重複癌であると診断した. 最終病理組織学的診断は胆管癌 pat BiAbAp, circ, 浸潤型, 6.2×0.8cm, tub2, int, INFβ, ly1, v1, pn2, s(+), Hinf0, Ginf0, Panc2, Du0, PV0, A0, N0, T4N0M0, pStage IVa, T3N0M0, Stage IIA (UICC), 膵癌 Ph, 結節型, 2.0×1.5cm, tub2, int, INFβ, ly0, v2, ne1, mpd(+), CH(−), Du(−), S(+), RP(+), PV(−), A(−), PL(−), OO(−), N0, T3N0M0, Stage III, T3N0M0, Stage IIA (UICC) であった. 術前に転移リンパ節と考えていた膵頭部の類円形腫瘤は, 術前画像をretrospectiveに読影すると, 膵癌組織の位置と一致していた.

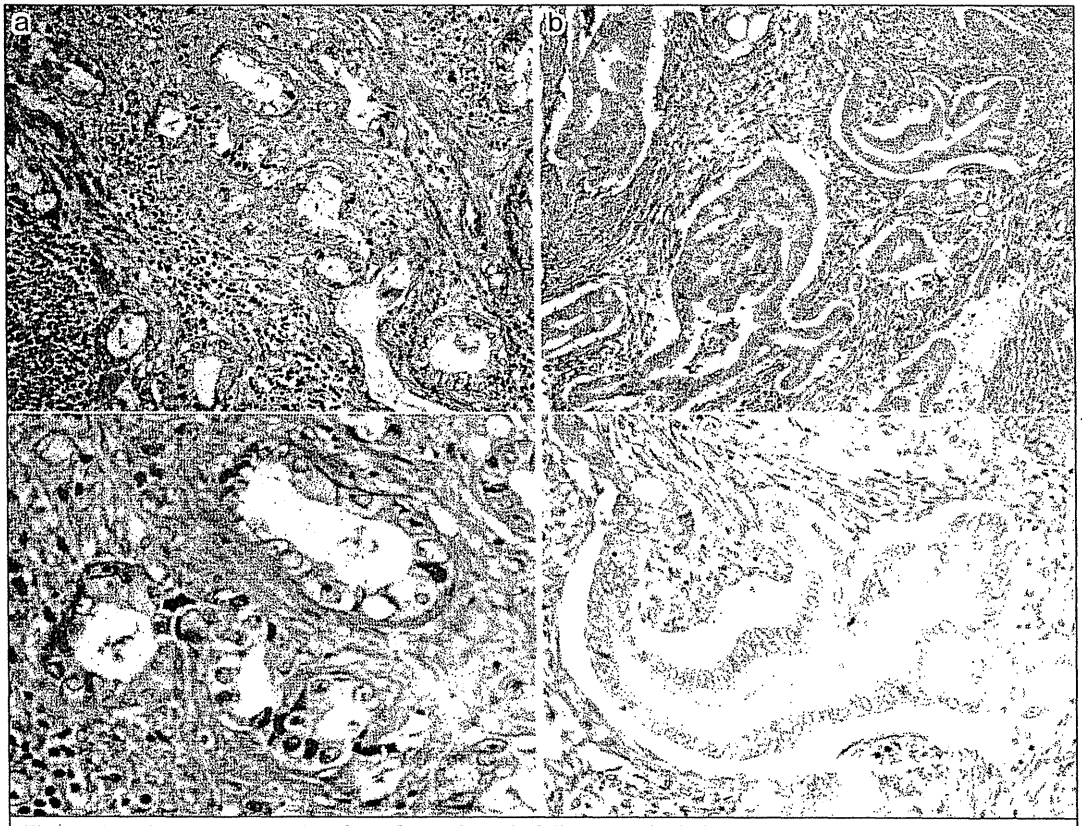

Fig. 5 Microscopic examination showed a moderately differentiated tubular adenocarcinoma of bile duct (Fig. a), and a moderately differentiated tubular adenocarcinoma in pancreas head (Fig. b).

術後経過：軽度の膵液瘻を認めたが保存的に軽快. 術後38日目に自宅退院となった. 術後補助化学療法は施行せず，術後7年経過するも無再発生存中である.

考　察

近年，高齢者の増加や悪性疾患に対する治療の進歩などにより，消化器系においても重複癌の発生頻度は増加傾向にある[1]. しかし，胆管と膵臓との重複癌の報告例は，両疾患の予後がともに不良であるためか極めてまれである.

重複癌は1889年にBillroth[2]によって初めて報告された. 現在，重複癌の定義としては，1932年のWarren & Gatesの基準[3]が広く用いられている. 1）各腫瘍が悪性組織像を呈する，2）各腫瘍は互いに離れた位置に存在する，3)一方の腫瘍が他方の腫瘍の転移ではない，という3条件を満たすものが重複癌と定義される. さらに，Moertelら[4]は両腫瘍の発生間隔が6か月以内のものを同時性，それ以上のものを異時性としている. しかし，本邦では両腫瘍の診断ないし発見までの期間が1年未満のものを同時性，1年以上のものを異時性としていることも多い[5][6].

膵癌の重複癌の発生率は，切除膵癌症例の3.2%，剖検例では5.6%と報告されている[7][8]. 重複する癌としては胃癌，甲状腺癌，前立腺癌の順に多かったと報告されているが，剖検例では膵癌と胆管癌との重複は認められなかった[8].

医学中央雑誌およびPubMedにて胆道系悪性腫瘍と膵悪性腫瘍の重複癌について検索したところ，膵管内乳頭腺癌の症例を除き12例の報告を認めた. このうち，胆嚢癌症例を除くと，膵癌と胆管癌の重複例は自験例を含め6例のみであった(Table 1)[1][7][9]~[11]. 初発症状としては黄疸発症例が多く，術前より重複癌と診断された症例は3例のみであった. それ以外は膵癌もしくは胆管癌の術前診断にて手術施行後，

Table 1 Reported cases of double cancers occurring in bile duct and pancreas

No	Author (year)	Age/ gender	Com-plain	Period	Diagnosis of double cancer	Biliary duct (stage)	Pancreas (stage)	R	Pancreati-co-biliary maljunc-tion	Progno-sis
1	Yoshii[7] (1989)	71/M	Icterus	Synchro-nous	Post operation	Bi pap (unknown)	Ph poor (unknown)	R0	—	un-known
2	Akiyama[9] (1992)	68/F	Icterus	Synchro-nous	Pre operation	Bsrl pap (T1N0 stageI)	Phb well (T3N1 stageIII)	R2	—	Dead (8M)
3	Kitagawa[1] (1994)	77/F	Weight loss	Synchro-nous	Post operation	Bm tub1(T1N0 stageI) Gf tub2(T2N0 stageII)	Ph moder-ately (T3N1 stageIII)	R0	—	Dead (7M)
4	Sato[10] (2003)	74/M	Icterus	Synchro-nous	Pre operation	Bi tub3(T4N3 stageIVa) Gn tub1(T1N0 stageI)	Ph muci-nous (unknown)	Un-known	—	Dead (8M)
5	Kato[11] (2007)	78/M	Icterus	Synchro-nous	Post operation	Bims sig (T4N2 stageIVa)	Ph well (T2N3 stageIVb)	R0	—	Alive (14M)
6	Our case	73/M	Ab-dominal pain	Synchro-nous	Pre operation	Bi tub2 (T4N0 stageIVa)	Ph moder-ately (T3N0 stageIII)	R0	—	Alive (84M)

切除標本にて同時性重複癌が証明された症例であった．そのため，ほとんどの症例が胆管病変は中下部胆管，膵病変は膵頭部領域の腫瘍であった．術前より胆管および膵病変をそれぞれ別に診断することは困難であると考えられた．また，全症例とも膵胆管合流異常を認めなかった．膵癌発生に関して合流異常の関与は明らかではないが，胆道癌においては合流異常による膵液の胆道内への逆流が発癌に寄与するといわれている[12)13)]．今回の6例においては合流異常を認めず，膵癌と胆管癌の重複癌発生機序について合流異常の関与は低いと考えられた．全体の予後については6例中3例が1年以内に死亡していることより予後不良であると考えられる．膵癌，胆管癌の両疾患自体の予後が不良であることより，重複癌となると，より予後不良であると考えられた．

胆管癌および膵癌の独立した予後因子として，治癒切除の有無，リンパ節転移，神経周囲浸潤，組織学的分化度などさまざまな因子が報告されている[14)~18)]．その中でも治癒切除およびリンパ節転移は胆管癌，膵癌ともに，もっとも重要な予後因子の一つとされている[14)~18)]．重複癌報告例5例のうち，秋山らの症例は膵癌，胆管癌ともに比較的低い病期であったが，非治癒切除症例であった．Satoらの症例は大動脈周囲リンパ節転移陽性例であり，北川らの症例もN1症例であったため，予後不良であったと考える．加藤らの症例は大動脈リンパ節転移陽性であったが，Gemcitabineによる術後化学療法を施行しながら1年生存が得られている．自験例においては，胆管癌はT4，膵癌はT3症例であったが，外科的根治切除可能であり，N0症例であったため，2群リンパ節郭清を付加した外科的治癒切除により長期生存が得られたと考えられる．

自験例の重複癌の診断について，上記のWarren & Gatesの基準に合わせると，1) 2)については病理学的に証明されているが，3)については完全に証明することは困難であった．しかし背景膵組織内にはPanIN2–3の異型を示す成分が散見され完全な膵管内腺癌巣も認めることや，胆管腫瘍と膵腫瘍はどちらも中分化型管状腺癌であるものの，組織像が異なることより重複癌と診断した．

胆管癌，膵癌の重複癌に対し外科的治癒切除後7年無再発生存中の1例を経験した．胆管癌および膵

癌の重複癌であっても，リンパ節郭清を付加した外科的根治切除により長期生存が得られる可能性があり，根治切除を目指すことが重要であると考えられた．

文献は医学中央雑誌（1983年から2010年まで）にてキーワードを「胆管癌」,「膵癌」,「重複癌」として，PubMed（1950年から2010年まで）にて「bile」,「pancreas」,「double cancer」として検索し，さらに検索文献より引用文献を検索した．

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CASE REPORT

A Case of Double Synchronous Common Bile Duct Cancer and Pancreas after 7 Postoperative Recurrence-Free Years of Survival

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A 69-year-old man was found in enhanced abdominal computed tomography and magnetic resonance imaging to have an enhanced thickened inferior bile duct and an enhanced tumor in the pancreatic head. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance (MR) MRCP showed a stenotic common bile duct but a normal pancreatic duct and no anomalous pancreaticobiliary ductal arrangement. Based on a diagnosis of advanced inferior bile duct carcinoma with lymph node metastasis, we conducted subtotal stomach-reserving pancreatoduodenectomy. Macroscopically, resected material showed a tumor in the common bile duct and in the pancreas head. Histopathologically, moderately differentiated tubular adenocarcinoma was found in the common bile duct and pancreas head, but the two tumors were somewhat distinct and had no continuation, yielding a diagnosis of double cancer of the bile duct and pancreas. A pancreatic fistula was identified postoperatively. Discharged on postoperative day 38, the man is doing well, without signs of recurrence 7 years later.

Key words: bile duct carcinoma, pancreatic carcinoma, double cancer

〔Jpn J Gastroenterol Surg. 2011;44(4):428-434〕

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Accepted: October 20, 2010

JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(8)964–972
doi:10.1093/jjco/hyr088
Advance Access Publication 7 July 2011

Efficacy of Concurrent Chemoradiotherapy as a Palliative Treatment in Stage IVB Esophageal Cancer Patients with Dysphagia

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Received April 16, 2011; accepted May 25, 2011

Objective: To retrospectively assess the efficacy and safety of palliative chemoradiotherapy in Stage IVB esophageal cancer patients with dysphagia due to the primary lesion.
Methods: Forty patients with dysphagia caused by metastatic esophageal cancer, which had been treated between January 2004 and June 2009, were retrospectively investigated. The treatment consisted of two courses of chemotherapy (5-fluorouracil and cisplatin) and concurrent irradiation of 40 Gy in 20 fractions to the esophageal primary tumor. The grade of dysphagia was evaluated; nutrition-support-free survival was evaluated using the status of nutritional support of patients. Response to treatment, overall survival, progression-free survival and toxicities were also evaluated.
Results: Dysphagia score improved in 75% of the patients. Seventeen of the 20 patients (85%) who had required nutritional support at baseline improved their oral intake to no longer need the support, in a median time of 43 days. The median nutrition-support-free survival was 301 days in the 20 patients who had had adequate oral intake before the treatment. Disease control rate of the primary lesion was 95%, including 12 patients (30%) who achieved a complete response. The overall response rate was 55%. The median survival was 308 days, and the 1-year-survival rate was 45.0%. The median progression-free survival was 139 days. Toxicities were generally well tolerated. Major toxicities (Grade 3 or 4) involved hemoglobin (23%), leukocytes (15%), neutrophils (20%), anorexia (10%), nausea (3%), esophageal perforation (5%) and febrile neutropenia (3%). Two patients (5%) died within 30 days of terminating radiotherapy.
Conclusions: Palliative chemoradiotherapy using 5-fluorouracil plus cisplatin combined with concurrent 40 Gy irradiation effectively improved the symptom of dysphagia in Stage IVB esophageal cancer with acceptable toxicity and favorable survival.

Key words: esophageal cancer – squamous cell carcinoma – Stage IVB – dysphagia – palliative chemoradiotherapy

INTRODUCTION

Esophageal cancer is the sixth most common form of cancer in male and the sixth most common cause of all cancer death. In 2008, estimated 482 600 new cases are diagnosed, and the estimated deaths were 406 800 worldwide (1). In Japan, 11 669 patients died of esophageal cancer in 2007 (2). For 8.6% of the patients, the disease has already spread to other organs of the body at the time of diagnosis (3), and a cure is not expected. Most of these metastatic patients experience dysphagia due to the progression of the primary lesion.

Dysphagia is the most common and serious symptom of esophageal cancer. It severely affects the patient's quality of life and necessitates nutritional support, such as intravenous

infusion or feeding through percutaneous gastrostomy or nasogastric tube, when inadequate oral intake persists. For patients with unresectable, metastatic esophageal cancer, long-term relief of dysphagia is one of the most important issues in their daily life (4).

Of the multiple treatment options for dysphagia, radiotherapy and metallic stent placement have been considered to be the standard of care. When rapid relief of dysphagia is required, stent placement is the preferred treatment; however, its efficacy is short term due to the fact that the tumor masses are only pressed mechanically. Stent deployment in inoperable patients has been reportedly associated with a median survival time of only 13–20 weeks (5–7). For patients in better health, radiotherapy could offer a more prolonged effect (8).

According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology™ v.1.2010, palliative chemotherapy is proposed as the standard treatment in metastatic patients, with the aims of controlling tumor growth, improving quality of life and prolonging survival. Response rates to chemotherapy alone ranged from 16 to 43% for metastatic disease (9–14). However, there is little evidence to suggest that chemotherapy alone improves survival and/or quality of life including dysphagia in patients with metastatic disease (9,15,16).

With respect to palliative chemoradiotherapy in patients with further advanced esophageal cancer, including metastatic cases, previous studies have shown considerable effects in the improvement of dysphagia (17–23). However, there have been only a few studies covering exclusively Stage IVB esophageal cancer.

The aim of this retrospective study was to provide basic data on the efficacy and toxicity of palliative chemoradiotherapy in Stage IVB esophageal cancer. We especially focused on the improvement of dysphagia, and survival time without nutritional support, because these parameters reflect clinically relevant symptomatic indices in patients suffering from dysphagia due to incurable, metastatic esophageal cancer.

PATIENTS AND METHODS

Patients

The subjects were recruited from our database of patients who were treated at National Cancer Center Hospital East (Kashiwa, Chiba, Japan) between January 2004 and June 2009, according to the following criteria: (i) histologically confirmed squamous cell carcinoma of the esophagus; (ii) metastatic disease classified as Stage IVB, according to the TNM classification of malignant tumor of UICC, sixth edition; (iii) radiation therapy consisted of 2 Gy fractions (Fr) daily for 20 days (total 40 Gy); (iv) chemotherapy consisted of 5-fluorouracil (5-FU) and cisplatin (CDDP); (v) primary lesion present in thoracic esophagus; (vi) age 20–75 years; (vii) performance status (PS) ≤ 2 on the Eastern Cooperative Oncology Group scale; (viii) no previous history of chemotherapy or radiotherapy; (ix) white blood cell count between 4000 and 20 000/μl; (x) platelet count 100 000/μl or more; (xi) adequate liver function, as indicated by serum concentrations of total bilirubin ≤ 2.0 mg/dl, aspartate aminotransferase ≤ 200 IU/l and alanine aminotransferase (ALT) ≤ 200 IU/l; (xii) serum creatinine concentration ≤ 1.5 mg/dl. The metastatic lesions were confirmed with computed tomography scans. The presence of a measurable metastatic lesion was not mandatory. Patients with other active synchronous carcinomas or concurrent uncontrolled medical illness were excluded. The study was performed in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiological research. We obtained an institutional review board (IRB) waiver to conduct this study from the chairperson of the IRB.

Treatment Schedule

Chemotherapy comprised protracted infusion of 5-FU combined with a 2 h infusion of CDDP with adequate hydration and antiemetic coverage. In general, patients were treated with 5-FU 700 mg/m^2 on days 1–4 and 29–32, and CDDP 70 mg/m^2 on days 1 and 29 (Fig. 1). Doses were modified according to the judgment of the attending physician: the doses of 5-FU and CDDP were generally reduced to 50–80% when Grade 4 hematological or Grade 3 or 4 non-hematological toxicity occurred. Once serious toxicity was observed, treatment was suspended until recovery.

Radiation treatment (10 MV) was administered for 4 weeks (5 days/week) at 2 Gy/day with a total radiation dose of 40 Gy/20 Fr, concomitantly with chemotherapy (Fig. 1). The chemotherapy and radiotherapy were started within 7 days of each other. The targeted area for irradiation included only the primary tumor with a 3 cm superior and inferior margin and a 2 cm lateral margin. Metastatic lesions were not included in the targeted area. Irradiation was applied in anterior and posterior opposed fields.

When there was a need, nutritional support was provided by fluid administration including intravenous hyperalimentation or feeding through a percutaneous gastrostomy tube.

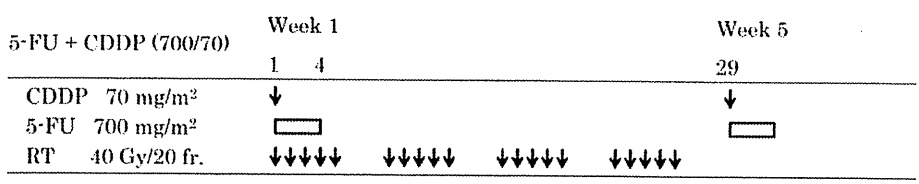

Figure 1. Treatment schedule. 5-FU, 5-fluorouracil; CDDP, cisplatin; RT, radiotherapy.

For patients who showed an objective response to treatment, additional courses of chemotherapy alone were administered, which consisted of the same regimen or protracted infusional 5-FU 800 mg/m^2/day on days 1–5 and a 2 h infusion of CDDP 80 mg/m^2/day on day 1. These treatments were repeated every 4 weeks until disease progression, development of unacceptable toxicity or the patient's refusal to continue. Further additional courses of chemotherapy were optional. When disease progression or unacceptable toxicities were observed, second-line chemotherapy was initiated.

Response and Toxicity Evaluation

The grade of dysphagia was determined by the dysphagia score as described previously and shown in Table 1 (24,25). Improvement of dysphagia was defined as a decrease of at least 1 point in dysphagia score.

Objective responses of measurable metastatic lesions were evaluated according to the response evaluation criteria in solid tumors (RECIST v 1.0) guideline. Tumor response was evaluated using computed tomography scan every 8 weeks after the initiation of treatment. Response of the primary tumor was evaluated by the criteria of the Japan Esophageal Society (26,27). Complete response (CR) of the primary lesion is judged, using endoscopy, with the fulfillment of all of the following conditions: (i) disappearance of all endoscopic findings that suggest the presence of tumor, such as irregular erosive lesions, ulcerative lesions or obvious elevated lesions; (ii) no histologic findings of malignant cells by endoscopic biopsy from the area where the primary tumor had been; (iii) the entire esophagus can be observed by endoscopy; and (iv) no findings of active esophagitis by endoscopy. Progressive disease (PD) of the primary lesion means distinct tumor growth or progression in esophageal stenosis during treatment. Incomplete response/stable disease (IR/SD) means that the response of the primary lesion does not meet the conditions for CR or PD.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). Toxicity was assessed on a weekly basis during chemoradiotherapy and then biweekly during the subsequent chemotherapy.

Table 1. Dysphagia score

Score	Swallowing status
0	Asymptomatic
1	Eat solid diet with some dysphagia
2	Eat semi-solid diet
3	Drink liquid diet
4	Complete dysphagia

Statistical Analysis

Overall survival was calculated from the initiation of treatment to the date of death or the last follow-up day in survivors. Progression-free survival was calculated from the initiation of treatment to the detection of disease progression or death from any cause. In patients who had not required

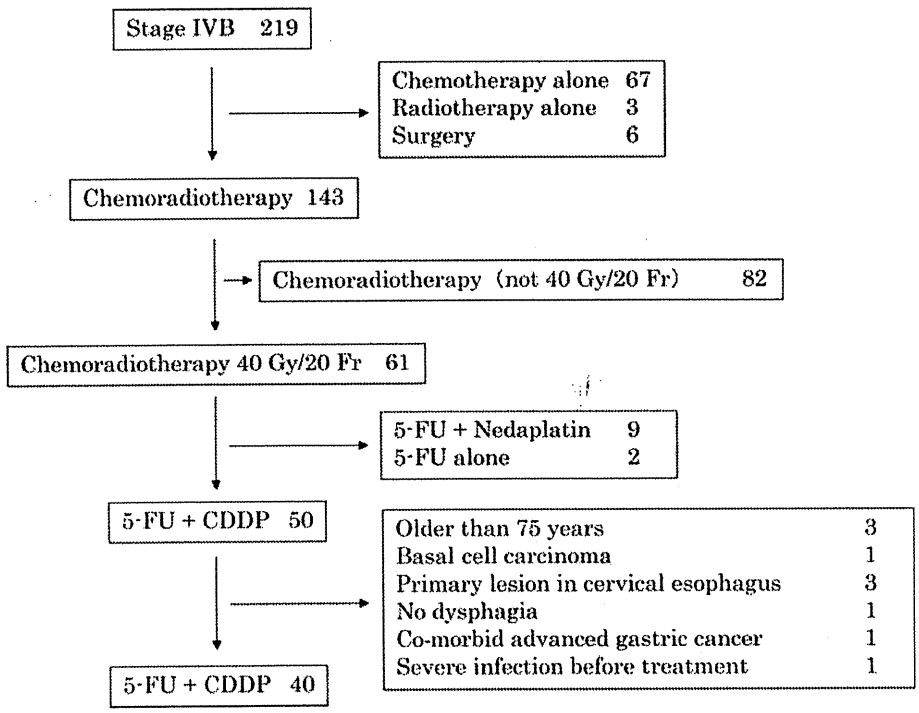

Figure 2. Between January 2004 and June 2009, 219 patients with Stage IVB esophageal cancer were treated at National Cancer Center Hospital East.

nutritional support before chemoradiotherapy, nutrition-support-free survival was calculated from the initiation of treatment to the date when nutritional support was first started. The oral intake of patients who had initially required nutritional support was considered to have improved when nutritional support could be stopped. Overall survival, progression-free survival and nutrition-support-free survival were calculated using the Kaplan–Meier method and the SPSS software program.

RESULTS

Patients' Characteristics and Treatment

From January 2004 to June 2009, 219 patients with Stage IVB esophageal cancer were treated in our hospital. Of these 219 patients, 143 patients were treated with chemoradiotherapy, 67 with chemotherapy alone, 3 with radiotherapy alone and 6 received palliative surgery as initial management (Fig. 2).

Of the 143 patients treated with chemoradiotherapy, 50 were treated with the palliative regimen of chemotherapy with 5-FU and CDDP and 40 Gy/20 Fr of irradiation to exclusively the primary lesion. Of these 50 patients, 10 were excluded from our study: 3 were older than 75 years; 1 had basal cell carcinoma; 3 had a primary lesion located in the cervical esophagus; 1 did not experience dysphagia; 1 had advanced gastric cancer; and 1 developed a severe infection immediately before treatment started. The remaining 93 patients had been treated with other regimens, such as 5-FU and CDDP combined with 50.4 or 60 Gy irradiation, or 5-FU plus nedaplatin with radiation.

The characteristics of the 40 eligible patients are shown in Table 2. Most of the patients (95%) had good PS of 0 or 1.

Table 2. Patients' characteristics ($n = 40$)

Characteristic	
Age (years), median (range)	64 (43–74)
Sex	
Male	36
Female	4
PS	
0	24
1	14
2	2
Primary tumor site[a]	
Ut	8
Mt	20
Lt	12
Macroscopic type	
1	3
2	18
3	18
4	1
T stage	
T1	0
T2	0
T3	24
T4	16
Tumor length (cm), median (range)	8 (3–17)
Tumor circumference	
<1/3 of circumference	1
≥1/3 and <2/3 of circumference	7
≥2/3 of circumference, but not entire circumferential	9
Entire circumferential	23
Metastatic organs	
Lymph nodes	24
Distant organs	16
Liver	10
Lung	8
Others	4

PS, performance status; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus.
[a]Anatomical subsites of esophagus are defined according to the TNM classification of malignant tumors, seventh edition.

Compliance and Efficacy

All patients completed the planned radiotherapy. Radiation schedule was interrupted for 1 day or more in seven cases (18%) because of infection or high fever (Grade 1 or 2), but all completed the program after an intermission.

The median number of courses in the initial regimen of chemotherapy was four, ranging from one to seven courses. Treatment discontinuation within two courses was observed in two patients. The regimen was changed to 5-FU and nedaplatin in one patient at the physician's discretion. Chemotherapy was terminated in the other patient because of disease progression after the first course of chemotherapy. In seven patients, the dose was reduced (to 50–80%) for the second course because of toxicities observed in the first course.

The responses of the primary lesions are shown in Table 3: 12 patients (30%) achieved a CR in their primary lesion and 26 (65%) were categorized as having IR/SD. Of these patients, 24 demonstrated apparent regression of the primary lesion, which means that 90% of the patients showed volume reduction in the primary lesion after chemoradiotherapy. As for the overall response including metastatic lesions, objective improvement was seen in 22 patients, a 55% response rate (Table 4).

Evaluation of Dysphagia and Survival

All patients were assessable for degree of dysphagia, history of oral intake, toxicity, overall survival and progression-free

Table 3. Response of the primary lesion ($n = 40$)

Response of primary lesion	No. of patients
CR	12 (30%)
IR/SD	26 (65%)
PD	0 (0%)
NE	2 (5%)
Disease control rate	95%

CR, complete response; IR/SD, incomplete response/stable disease; PD, progressive disease; NE, not evaluated.

Table 4. Overall response to treatment ($n = 40$)

Overall response	No. of patients
CR	2 (5%)
PR	20 (50%)
SD	10 (25%)
PD	6 (15%)
NE	2 (5%)
Response rate	55%

PR, partial response.

Table 5. Change in dysphagia score after treatment ($n = 40$)

Improved	Unchanged	Worsened	Improvement rate
30	7	3	75%

survival. Nutrition-support-free survival could also be assessed in all patients. Twenty patients who had received nutritional support of total parenteral nutrition or percutaneous gastrostomy at the onset of treatment were assessable for improvement in oral intake.

The overall improvement rate of dysphagia score was 75% (30/40) (Table 5). The nutrition-support-free survival of the 20 patients with initially adequate oral intake is shown in Fig. 3. The median nutrition-support-free survival was 301 days (10.0 months). The median overall survival in this group of patients was 410 days (13.7 months). Of the other 20 patients who had initially required nutritional support, 85% (17/20) were relieved from nutritional support: median overall survival was 249 days (8.3 months). Of the 17 patients who were relieved from nutritional support, the median time until relief of nutritional support was 43 days (1.4 months) and the median nutrition-support-free duration was 137 days (4.6 months).

The median follow-up period was 617 days in survivors at the time of analysis. The overall survival time is shown in Fig. 4. The median survival time was 308 days

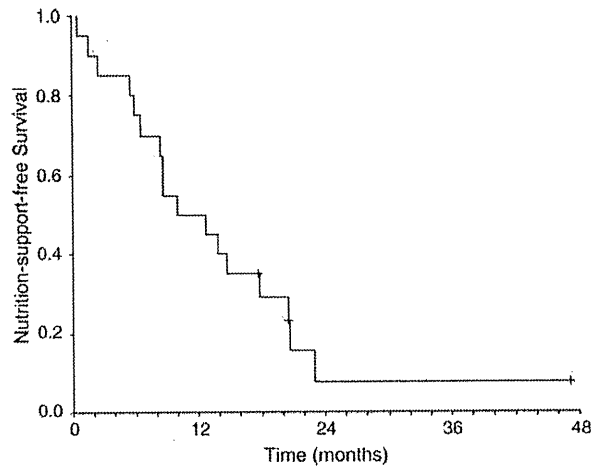

Figure 3. Nutrition-support-free survival ($n = 20$).

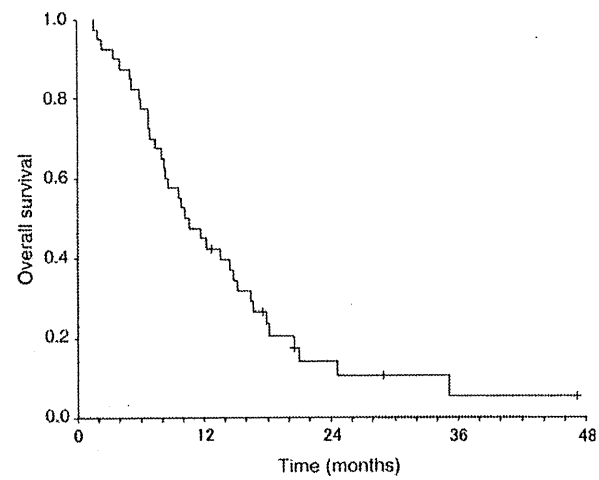

Figure 4. Overall survival ($n = 40$).

(10.3 months), and the 1-year-survival rate was 45.0%. The median progression-free survival was 139 days (4.6 months) (Fig. 5).

Toxicity

The grades of toxicity during the treatment course (radiotherapy and first and second course of chemotherapy) are summarized in Table 6. Toxicity profiles with Grade 3 and 4 are shown except for platelet. Hematological toxicities were generally mild. Anemia was the most common hematological toxicity, but only 23% of the patients experienced Grade 3 or 4 anemia. Grade 3 or 4 neutropenia and leukopenia occurred in 15 and 20% of the patients, respectively. Grade 3 or 4 non-hematological toxicities were hyponatremia (18%), anorexia (10%), nausea (3%), esophageal perforation (5%), ALT (5%), creatinine (3%), febrile neutropenia (3%), rash (3%) and constipation (3%).

No patient died during radiotherapy. However, early death, within 30 days of terminating radiotherapy, occurred

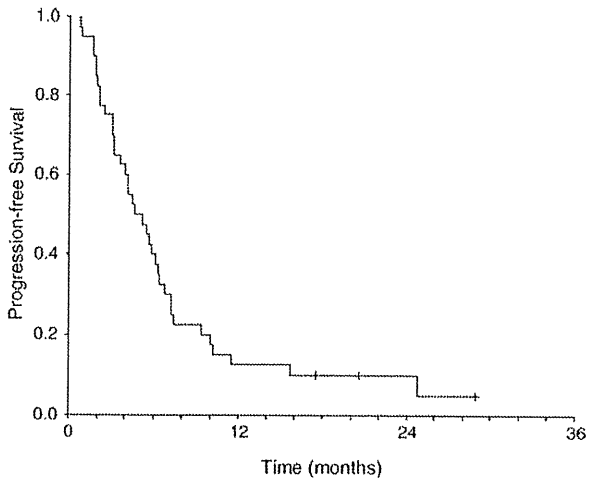

Figure 5. Progression-free survival ($n = 40$).

Table 6. Adverse events ($n = 40$)

CTCAE VER3.0	Gr. 1	Gr. 2	Gr. 3	Gr. 4	≥Gr. 3
Hemoglobin	10	17	8	1	9 (23%)
Leukocytes	13	10	5	1	6 (15%)
Neutrophils	19	13	8	0	8 (20%)
Platelet	9	5	0	0	0 (0%)
Rash	1	0	1	0	1 (3%)
Anorexia	11	8	4	0	4 (10%)
Constipation	3	2	1	0	1 (3%)
Mucositis/stomatitis	4	3	0	0	0 (0%)
Nausea	16	7	1	0	1 (3%)
Esophageal perforation	0	0	2	0	2 (5%)
Alanine aminotransferase	16	2	2	0	2 (5%)
Creatinine	8	2	1	0	1 (3%)
Hyperkalemia	21	3	1	0	1 (3%)
Hyponatremia	28	—	7	0	7 (18%)
Febrile neutropenia	0	0	1	0	1 (3%)

Two patients (5%) died within 30 days of completion of radiotherapy.
CTCAE, Common Terminology Criteria for Adverse Events.

in two patients: one was a 64-year-old man who had supraclavicular lymph node metastases. The primary tumor had not invaded adjacent organs (T3), but one metastatic lymph node had invaded the wall of the aorta. On the 13th day after terminating radiotherapy, the patient was admitted to the hospital as an emergency due to severe right pneumonia; he died the next day. Chest X-ray indicated pneumonia due to aspiration or perforation, so the probability of radiation pneumonitis was low. The other patient was a 71-year-old man who had deep cervical and supraclavicular lymph node metastases and pericardial dissemination. The primary tumor invaded the wall of the aorta, bronchus and pericardium (T4). On the 26th day after terminating radiotherapy, the patient complained of severe back pain. After a few hours, he was found in cardiac arrest. The causes of death in these two cases are not clear, but they could be related to treatment.

DISCUSSION

Palliative chemoradiotherapy using 5-FU plus CDDP combined with concurrent 40 Gy irradiation effectively improved the symptom of dysphagia in Stage IVB esophageal cancer with acceptable toxicity and favorable survival in our study.

To date, the best palliative method for dysphagia due to advanced esophageal cancer has not been established. Of the multiple treatment options, chemoradiotherapy had been reported to be effective for the palliation of dysphagia through tumor regression in advanced, incurable esophageal cancer (17–23). However, these previous studies included patients who were not uniform in terms of TNM clinical classification. In palliative chemoradiotherapy for patients with Stage IVB esophageal cancer accompanied by dysphagia, it is most important to balance management of primary and metastatic sites with tolerance of toxicity. Therefore, to prolong survival without nutritional support, it is important to establish the appropriate dose of individual agents and irradiation dose and field. Our study is one of only a few to investigate the palliative effects of chemoradiotherapy exclusively in patients with Stage IVB esophageal cancer.

In our study, the palliative chemoradiotherapy was satisfactory, with an overall improvement rate in dysphagia score as high as 75%. Of the patients who had required nutritional support at the onset of treatment, 85% no longer needed the support after the treatment. The toxicity was tolerable, and the median overall survival was 10.3 months in patients with Stage IVB esophageal cancer accompanied by dysphagia. We suggest that concurrent chemoradiotherapy of 5-FU plus CDDP combined with 40 Gy irradiation is effective in improving dysphagia.

Published reports of palliative chemoradiotherapy are summarized in Table 7 (17,18,20–23). The chemotherapy regimens in these studies are basically a combination of 5-FU and another agent, and the radiation dose ranges between 30 and 54 Gy, which is generally lower than the dose used in definitive chemoradiotherapy. Our regimen, chemotherapy with 5-FU and CDDP, and concurrent radiation of 40 Gy, can be properly categorized in the spectrum of palliative therapy. Hayter et al. (18) showed in detail the palliative efficacy of 30 Gy radiation in 10 Fr with concurrent chemotherapy consisting of 5-FU and mitomycin C in 22 patients with advanced incurable esophageal cancer. In that study, complete relief of dysphagia was observed in 68% of the patients. The median time to normalization of swallowing was 5 weeks, and the median dysphagia-free interval from the onset of improvement was 11 weeks. In the other reports, the improvement rate of dysphagia ranged

Table 7. Previous reports of palliative concurrent chemoradiotherapy for dysphagia in inoperable, advanced esophageal cancer

Literature	*n*	Pathology	Chemotherapy	Radiotherapy (Gy)	Treatment failure (%)	TRD rate (%)	Improvement rate of dysphagia (%)	Survival (months)
Coia (22)	49	SCC, Adeno	5-FU, MMC	50	NS	NS	91	8
Urba and Turrisi (23)	27	SCC, Adeno	5-FU, CBDCA	40	0	4	59	6
Hayter et al. (18)	22	SCC, Adeno	5-FU, MMC	30	NS	5	68	5
Harvey et al. (17)	106	SCC, Adeno, small cell, undifferentiated and others	5-FU, CDDP	35	5	6	78	7
Burmeister et al. (20)	24	SCC, Adeno	5-FU	30–35	17	NS	67	9
Cho (21)	27	SCC	S-1, CDDP	54	0	0	77.8	11.6
Present study	40	SCC	5-FU, CDDP	40	5	5	75	10.3

TRD, treatment-related death; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; 5-FU, 5-fluorouracil; MMC, mitomycin C; NS, not stated; CBDCA, carboplatin; Small cell, small cell carcinoma; Undifferentiated, undifferentiated carcinoma; CDDP, cisplatin.

from 67 to 91% (Table 7). The effects of our palliative regimen are comparable to those reported in these studies.

Our treatment regimen was well tolerated. No patient failed to complete radiation, and only two patients (5%) received fewer than two complete courses of the planned chemotherapy. Death within 30 days of completion of radiation was observed in two patients (5%). The rates of treatment failure and treatment-related deaths in the previous studies are shown in Table 7. As for these two parameters, the toxicity profile of our regimen is equivalent to those of the previous studies.

There have been some studies evaluating chemotherapy for locally advanced or metastatic squamous cell esophageal cancer (10–14). Bleiberg et al. (12) reported that WHO Grade 3 and 4 toxicities were observed from combined chemotherapy of 5-FU and CDDP: leukocytes in 14% of the patients and platelets in 14%. Iizuka et al. (14) evaluated the combination of 5-FU and CDDP in advanced squamous cell carcinoma of the esophagus and reported WHO Grade 3 and 4 toxicities of hemoglobin, leukocytes and platelets in 13, 8 and 5% of the patients, respectively. In our study, CTCAE Grade 3 and 4 leukocytes, hemoglobin and platelets developed in 15, 23 and 0% of the patients, respectively. The higher rates of hematological toxicities in our study seem to arise because of the concurrent radiation. In the studies of definitive chemoradiotherapy with a radiation dose of 50–70 Gy (20,28–32), Grade 3 and 4 toxicities were observed at a rate of 9–33% hemoglobin, 24–78% leukocytes and 14–20% platelets. These figures are generally higher than in our study, probably due to the higher radiation dose. Non-hematological toxicities were not severe in our study. Although Grade 3 esophageal perforation and febrile neutropenia occurred in 5 and 3% of the patients, respectively, they were properly managed.

Regression of the primary lesion was observed in 90% of the patients and 12 (30%) achieved CR. This effect probably results in the effective improvement of dysphagia. In definitive chemoradiotherapy of esophageal cancer, the irradiation dose to the primary lesion is 50.4 or 60 Gy in Japan. The CR rates of the primary lesion following definitive chemoradiotherapy are 62% in T3 cases and 37% in T4 cases, respectively (33). The CR rate of the primary lesion in our study was lower than this, probably because of the lower radiation dose of 40 Gy. A higher dose could lead to better and longer dysphagia relief through tumor regression, but it is important to balance palliative outcome with the costs of treatment, namely toxicities of higher irradiance and the effort of hospital visits, especially in those patients who cannot expect a cure.

The prognosis of Stage IVB esophageal cancer is poor. The median survival time has been reported to be 5–11 months (7,11,17,18,22,23,29,34) in patients who receive any treatment (including chemotherapy, chemoradiotherapy or surgery). In our study, the median survival time was 10.3 months, which is relatively good compared with previous studies of palliative therapies including chemoradiotherapy (Table 7). The survival effect is an important therapeutic aim in incurable Stage IVB esophageal cancer. Our result suggests that the addition of 40 Gy of radiotherapy to palliative chemotherapy is not associated with a negative effect on survival. However, we have to accept that there could be a selection bias in our retrospective study. It should be noted that 24 out of 40 patients have only lymph node metastasis in our study, who are known to have better outcome than those with visceral metastasis.

As for the histological type of the tumor, both squamous cell carcinoma and adenocarcinoma were included in the western studies (17–20,23), whereas only squamous cell carcinoma was included in Asian studies, including ours (21). The incidence of adenocarcinoma of the esophagus has increased considerably in western countries over the past three decades (35), whereas squamous cell carcinoma remains the major histological type of esophageal cancer in Japan and most Asian countries. It has been reported that there has been no dramatic increase in adenocarcinoma in Japan (36). Our study included only patients with squamous

cell carcinoma, in order that we represent actual Japanese clinical practice.

In conclusion, our retrospective study suggests that our palliative regimen of chemoradiotherapy, 5-FU plus CDDP combined with concurrent 40 Gy irradiation, can provide effective palliation of dysphagia through tumor regression with a tolerable toxicity profile in incurable Stage IVB esophageal cancer. However, since there are inevitable biases that could not be ruled out in our retrospective study, further prospective studies are required to elucidate the most durable and swift palliation with lower toxicity and better survival.

Conflict of interest statement

None declared.

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Appendix

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JJCO Japanese Journal of Clinical Oncology

Jpn J Clin Oncol 2011;41(4)508–513
doi:10.1093/jjco/hyr012
Advance Access Publication 18 February 2011

A Pilot Study of Post-operative Radiotherapy with Concurrent Chemotherapy for High-risk Squamous Cell Carcinoma of the Cervical Esophagus

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Received November 28, 2010; accepted December 27, 2010

Objective: After complete resection of carcinomas of the head and neck, including carcinoma of the cervical esophagus, the pattern of first failure is more often locoregional than distant metastasis. We retrospectively evaluated the safety and efficacy of the combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin for high-risk squamous cell carcinoma of the cervical esophagus.
Methods: From 2005 through 2008, 34 patients with previously untreated squamous cell carcinoma of the cervical esophagus underwent cervical esophagectomy with or without laryngectomy. Of these 34 patients, 11 with disease-positive lymph nodes in the upper mediastinum (M1 lymph/Stage IV) confirmed by pathologic examination were enrolled. Patients received radiotherapy (66 Gy in 33 fractions) and concurrent low-dose cisplatin.
Results: Nine patients completed the planned radiotherapy and two or more courses of chemotherapy. Grade 3 toxicities during chemoradiotherapy were leukopenia (36% of patients), neutropenia (18%) and mucositis (9%). At a median follow-up time of 39.5 months, the overall 1- and 3-year survival rates were 91 and 71%, respectively.
Conclusions: The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is well tolerated and has the potential to improve the rates of locoregional control and overall survival in patients with high-risk advanced squamous cell carcinoma of the esophagus.

Key words: cervical esophageal squamous cell carcinoma – post-operative radiotherapy with concurrent chemotherapy – nodal M1 disease

INTRODUCTION

Locally advanced head and neck cancer is optimally treated with multimodal approach, involving resection followed by radiotherapy and concurrent chemotherapy (1). Carcinoma of the cervical esophagus has a poor prognosis, with reported 3- and 5-year survival rates ranging from 18 to 35.4% and from 12 to 33%, respectively (2). We have previously reported on the prognosis, patterns of first failure and significant clinicopathologic factors affecting survival in cases of squamous cell carcinoma of the cervical esophagus (2). In particular, the 3-year survival rate was 0% in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV). We have maintained that multimodal treatment, such as post-operative radiotherapy with concurrent chemotherapy, is essential for the treatment of cervical esophageal carcinoma (2). On the basis of the results of our previous study, we performed a pilot study and retrospectively assessed the toxic