随時 UPDATE するデータベースと連動

Case Library Series

症例から学ぶ 乳癌 最新治療ストラテジー

監修
佐伯俊昭
埼玉医科大学国際医療センター
包括的がんセンター 乳腺腫瘍科教授

メディカルレビュー社

23 1) 温存術後

埼玉医科大学国際医療センター放射線腫瘍科教授 鹿間 直人

症例	40歳代	診断名	右乳房の浸潤性乳管癌(硬癌)	初診	2010年	合併症	乳腺症
初診時TNM分類	cT1N0M0, cStage I						
内因性サブタイプ	ER陽性, PgR陽性, HER2陰性(Luminal A-like)						

現病歴・家族歴・既往歴

現病歴：40歳代の閉経前女性．乳腺症で経過観察中に超音波検査にて右乳房の腫瘤を指摘され，精査・加療目的に紹介．
家族歴：乳癌の家族歴なし．
既往歴：特記すべき既往歴はなく，2回の出産歴がある．

診　断

来院時所見：右乳房A領域に約10 mm大の腫瘤を触知．
診断：MRI画像にて右乳房A領域に9×8×10 mmの辺縁が微細鋸歯状の結節を認め，腫瘤は造影された．原発巣の生検標本の病理組織所見より，浸潤性乳管癌，ER陽性，PgR陽性，HER2陰性(luminal A-like)，cT1N0M0，Stage Iと診断．

治療方針

乳房部分切除と腋窩のセンチネルリンパ節生検が計画・施行された．病理の結果，pT1bN0M0，Stage I，ER陽性，PgR陽性，HER2陰性(luminal A-like)，切除断端5 mm以内に腫瘍細胞はなく切除断端陰性と診断．センチネルリンパ節生検は陰性(0/2)．術後放射線療法とその後のホルモン療法が計画された．

治療経過

両上肢の挙上に問題なく，創部の離開や乳房内の液体貯留も認めなかった．患者には，既往歴に膠原病がないことを確認し，また照射期間中の妊娠は絶対に避けるよう指示した．

3次元治療計画を用いて，4 MVの超高圧X線を使用した接線照射を計画．乳房内の線量の不均等性を補正するため，高線量域をカットした小さい照射野(10 MVのX線を使用)を作成し，通常の全乳房照射の照射野と組み合わせて照射した(field-in-field法)．1回2 Gyで週5回，5週間の全乳房照射を行った後，腫瘍床へ電子線で1回2 Gyで5回，計10 Gyの追加を行った．途中，照射を休止することなく放射線治療を完了したが，最終週には皮膚炎(Grade 2)が生じ，擦らないことを患者に指示し，かゆみと軽度の痛みがあったためステロイド軟膏を処方した．

放射線療法の実際

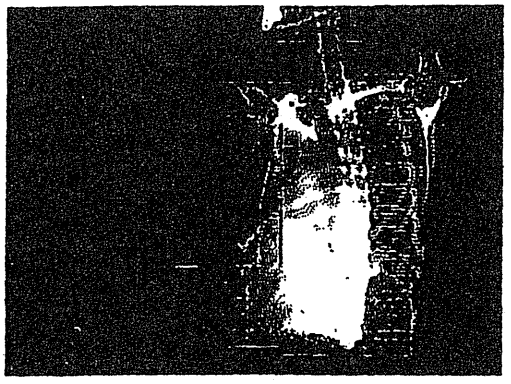

図1 接線照射野
右乳房全体を含めた照射野

図2 Field-in-field法
乳房全体を含めた接線照射のみでは高線量域が生じるため高線量域を避けた小さめの照射野を作成し，全乳房用の照射野と組み合わせることで線量の均等性を上げる工夫をしている．

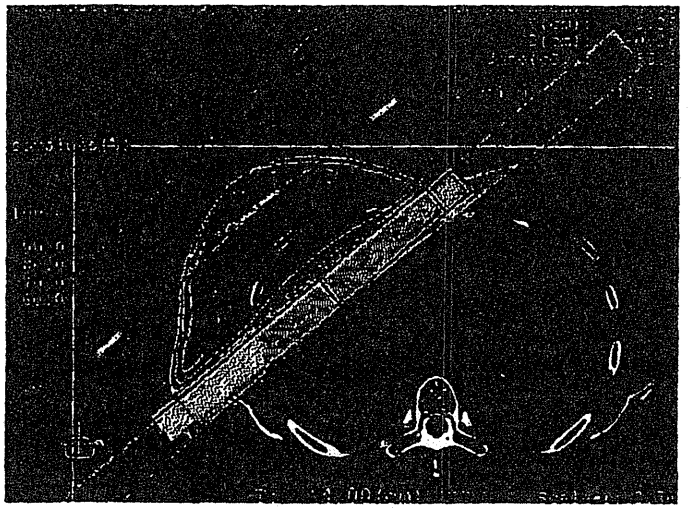

図3 線量分布図
横断面図で，青い95%線量域が乳房全体をほぼカバーしていることがわかる．

副作用マネジメント

治療後半からステロイド軟膏の塗布を行ったが改善せず，照射終了後3日目にはGrade 3の皮膚炎が生じ疼痛と一部感染を伴っていた．感染を伴う不良な皮膚を微温湯に浸したガーゼで剥離し，洗浄を行った．その後，白色ワセリンと亜鉛華軟膏の混合剤とガーゼを用いて保湿するよう指示した．毎日入浴し，弱酸性の石鹸を泡立てた後，患部を優しく撫り洗浄するよう指示した．1週間後には皮膚炎はGrade 1にまで改善した．

治療経過画像

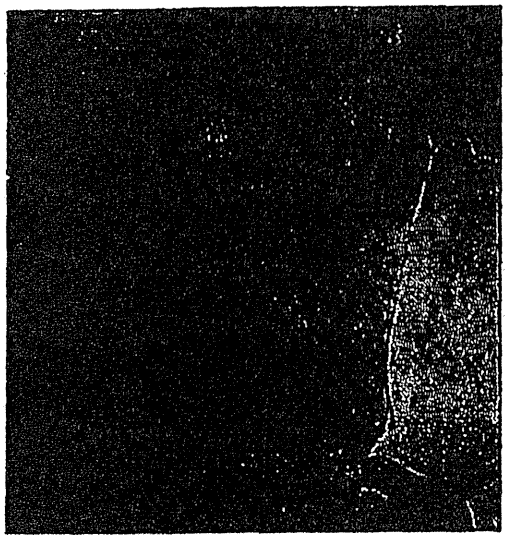

図４　照射終了後３日目の外観
腋窩を中心に皮膚が剥けており，易出血であり，一部感染を伴っていた．

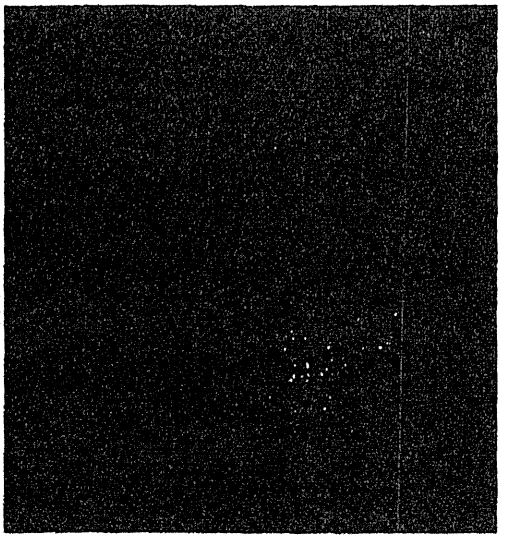

図５　腋窩の拡大図

図６　処置開始１週間後の外観
皮膚のデブリードメントと軟膏塗布による処置を施行し，１週間後には皮膚炎の改善がみられた．

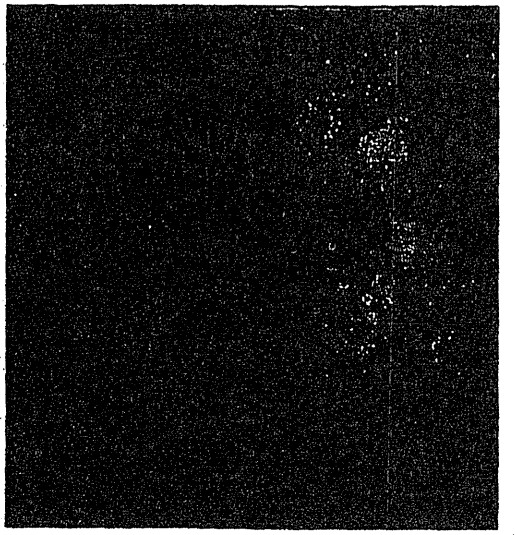

図７　腋窩の拡大図(１週間後)

治療のアウトカムのまとめ

照射期間中から終了後早期にかけては，皮膚炎以外の重篤な副作用(宿酔，肺臓炎など)はみられなかった．皮膚炎の出現と頻度は患者による因子(体型など)や治療の因子(用いる放射線のエネルギー，線量など)の影響で大きく変わる．腋窩部は発汗や腕の運動による擦過により皮膚炎が生じやすい部位である．6 MV の超高圧 X 線を用いた場合には 4 MV に比べ皮膚線量が下がり皮膚炎の程度や頻度は下がる．しかし，施設の保有する装置などの事情もあり，4

MV のX線を用いざるを得ない場合もある．2つのX線のエネルギー(4 MV/10 MV，または6 MV/10 MV)を使用できる装置では低いエネルギーと高いエネルギーを併用することでできるだけ皮膚線量を下げる工夫を行う．皮膚炎に対しては洗浄，保湿を行うことで多くの症例で，約1週間程度で改善する．

現在の状況

2年半が経過しているが皮膚炎の再燃はなく，また肺臓炎や肋骨骨折，上肢の浮腫などの副作用もみられていない．乳房の疼痛もなく，通常の日常生活を送っている．現在もTAMの内服を継続している．

25 1）脳転移

埼玉医科大学国際医療センター放射線腫瘍科教授　鹿間　直人

初診時 TNM 分類	cT2N1M0, cStage ⅡB
初回治療時の病理・内因性サブタイプ	ER 陽性，PgR 陽性，HER2 陰性(Luminal B-like(HER2 陰性))
初回治療の内容	・左乳房切除術，腋窩郭清術． ・術後補助化学療法(TC 療法) ・術後補助内分泌療法(アロマターゼ阻害薬)
転移臓器・転移個数	脳，転移個数：1 個
現在の PS　PS 0	現在の年齢　50 歳代
DFI　1 年	積極的治療希望　あり

現病歴・家族歴・既往歴

現病歴：50 歳代の閉経後女性．2009 年に乳房切除術が施行され，術後化学療法が行われた．2010 年に言葉が出づらいことを自覚し受診．

家族歴：乳癌の家族歴なし．

既往歴：特記すべき既往歴はなく，1 回の出産歴がある．

診　断

来院時所見：全身状態は良好で麻痺などもなし．

診断：頭部 MRI 検査にて左前頭葉に T1 強調画像で低信号，T2 強調画像で辺縁が低信号，中心部が高信号の 16 × 18 mm の結節を 1 つ認め，周囲には広汎な浮腫を伴っていた(図 1)．造

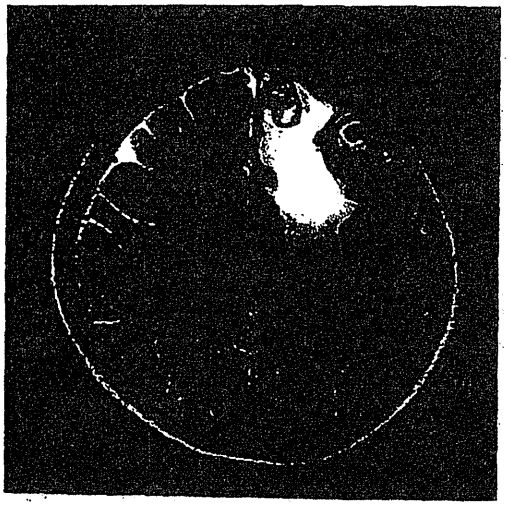

図 1　治療開始前の頭部 MRI 検査　T2 強調画像

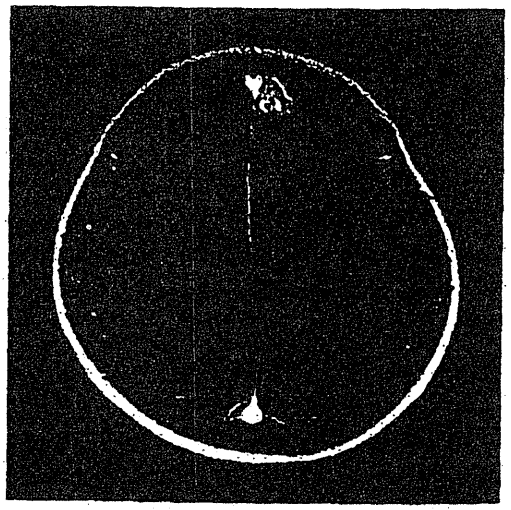

図 2　治療開始前の頭部 MRI 検査　T1 強調画像，造影後

図3　定位手術的照射後1ヵ月の頭部MRI検査 T2強調画像

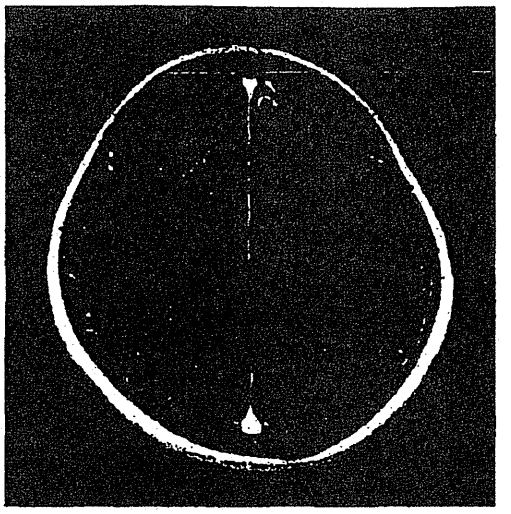

図4　定位手術的照射後1ヵ月の頭部MRI検査 T1強調画像，造影後

影後には不均一に造影され，単発性の脳転移と診断された(図2)．全身検索で脳以外に転移病巣はなかった．

治療方針

単発性脳転移で他臓器転移もなく，全身状態も良好なことから定位手術的照射を行うこととなった．腫瘍＋2 mmマージンの体積の95%が24 Gyの線量域に囲まれるように治療計画を立て，単回の定位手術的照射を行った．1ヵ月後の頭部MRI検査では腫瘍は著明に縮小し失語症も改善した(図3，4)．

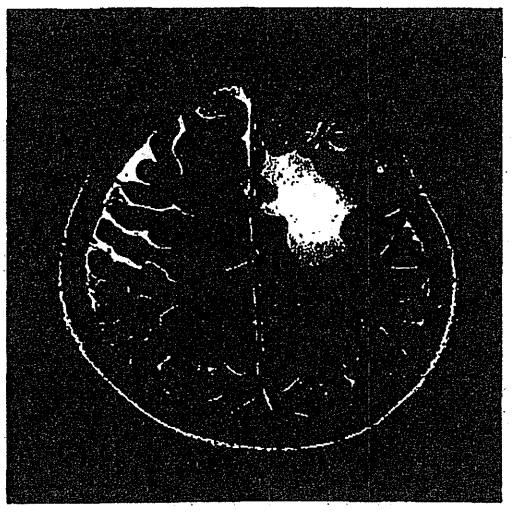

図5　定位手術的照射後，半年後の頭部MRI検査　T2強調画像
同部位の再発病巣と周囲に浮腫を認める．

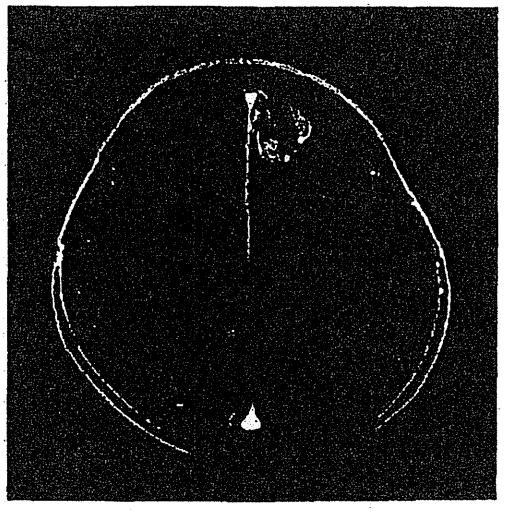

図6　同時期　T1強調画像，造影後

治療経過

初回の定位手術的照射で腫瘍の縮小と症状の改善が得られたが，半年後の頭部MRI検査で同部位の病巣の再増大が認められた(図5，6)．開頭腫瘍摘出術が施行され，病理学的に腺癌と診断され乳癌からの転移と判断された．本人の希望で術後放射線治療は行わず経過観察となった(図7，8)．術後4ヵ月には見当識障害，失語，右片麻痺が出現し，頭部MRI検査およびCT検査で前回摘出部に腫瘍の再増大を認め(図9，10)，再切除術が行われた．術後経過は良好で今回は術後照射を行うこととなった．脳外科医と放射線治療医との話し合いの結果，他

図7　開頭腫瘍摘出術後の頭部MRI検査
T2強調画像

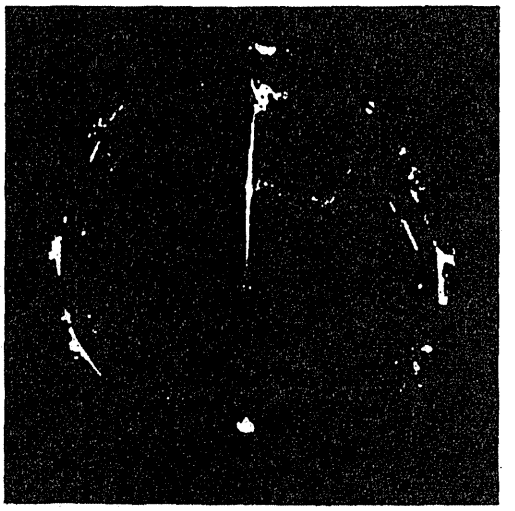

図8　開頭腫瘍摘出術後の頭部MRI検査
T1強調画像，造影後
造影部分は手術後の変化と考えられた．

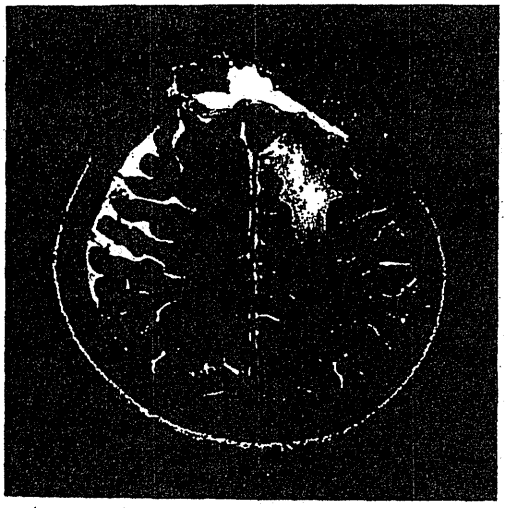

図9　開頭腫瘍摘出術後，4ヵ月の頭部MRI検査　T2強調画像

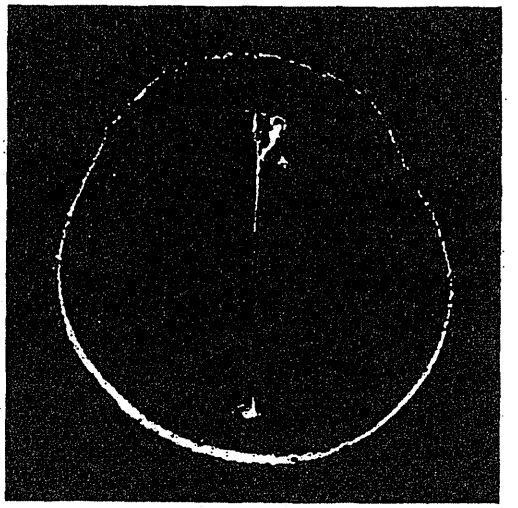

図10　開頭腫瘍摘出術後，4ヵ月の頭部MRI検査　T1強調画像，造影後
切除部位に新たな再発病巣を認めた．

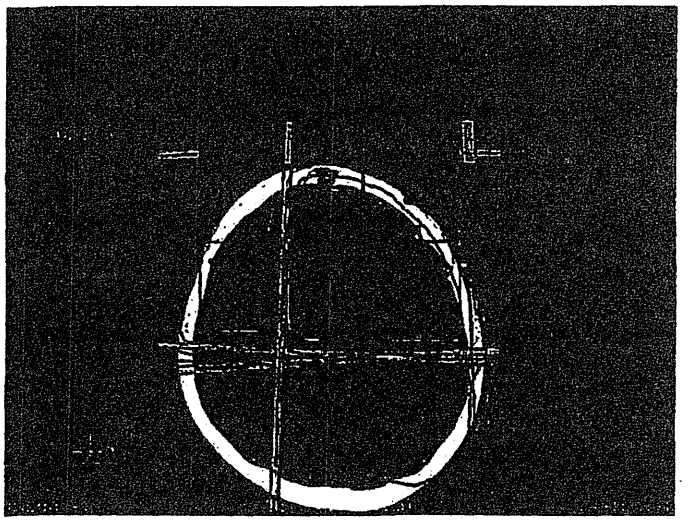

図 11　術後局所照射(線量分布図)
3 方向からの切除部位中心の照射を行った.

臓器転移がなく全身状態も比較的良好であることから長期予後も期待できると考え，全脳照射ではなく手術部位を中心とした局所照射(37.5 Gy/15 回 /3 週間)を通常のリニアック装置で行った(図 11)．術後照射施行後半年で再度，同部位に腫瘍の増大が認められたが頭蓋内の他部位には新たな病巣は認めなかった.

副作用マネジメント

初回の定位手術的照射時には脳浮腫の予防のため，照射当日と翌日までステロイドと浸透圧利尿薬の投与を行い，脳浮腫による症状の出現がないことを確認し退院となった．脳表に近い腫瘍ではあったが皮膚線量を低く抑えることができ，脱毛や皮膚炎はみられず特別な処置は不要であった．再発後の術後照射時には通常のリニアックを用いるため，脱毛および軽度の皮膚炎について事前に患者および家族に説明を行い，同意を得た．照射経過中に宿酔はみられず制吐薬の投与は行わなかった．皮膚炎に対しては洗髪時に強く擦過しないよう指示し，また照射後半から生じる照射部の脱毛に対してはスカーフを用いて脱毛部を隠すなどの工夫をアドバイスした.

治療のアウトカムのまとめ

頭部以外に他臓器転移がなく全身状態も良好であったことから定位手術的照射を選択したことは問題ないと考えられた．1 回大線量であっても再発を来すことはあり，本症例も残念ながら再発を来した．再照射を試みる施設もあるが，脳壊死のリスクや再照射による制御の可能性の低さなども考慮し手術が行われた．脳転移の手術後には全脳照射は同部位および頭蓋内の他部位からの再発を抑えるために推奨されるが，本人が希望されなかったこともあり見送られた．再切除後にも同様の検討がなされたが，長期予後が期待できると判断し脳の高次機能障害を避けるため術後照射は局所照射に止めた．NCCN のガイドラインで術後の局所照射はカテゴリー 3 と全脳照射より推奨度は低いが，考慮される治療となっている．術後に全脳照射または局所照射を行うかは患者の期待される予後を，予後予測モデルなどを用いて検討することが

重要である．

現在の状況

術後照射後半年で再度，腫瘍の増大が認められ，現在，ステロイドと浸透圧利尿薬などによる対症療法が行われている．今後どこまで積極的な治療を行っていくかは，本人および家人を含め相談していく予定である．

27 3) 局所再発

埼玉医科大学国際医療センター放射線腫瘍科教授 鹿間 直人

初診時 TNM 分類	cT2N2M0, cStage ⅢA		
初回治療時の病理・内因性サブタイプ	左乳房の浸潤性乳管癌(硬癌), ER 陽性, PgR 陽性, HER2 陽性(Luminal B-like(HER2 陽性))		
初回治療の内容	・左乳房切除術, 腋窩郭清術. ・術後化学療法・内分泌療法(詳細不明).		
転移臓器・転移個数	右乳房 1 個, 下垂体 1 個		
現在の PS: PS 2	現在の年齢: 60 歳代	DFI: 12 年	積極的治療希望: あり

現病歴・家族歴・既往歴

現病歴：60 歳代の閉経後女性. 1995 年に他院で左乳房切除術が施行され, 術後化学療法と左鎖骨上窩と胸壁に術後照射が施行された. 2007 年に右胸壁に腫瘤と下垂体腫瘤に伴う尿崩症が出現した.
家族歴：母(膵臓癌).
既往歴：特記すべき既往歴はなし.

診　断

来院時所見：下垂体転移に伴う尿崩症と右目の視力低下を認めた. 軽度の意識障害あり.
診断：頭部 MRI 検査にて下垂体に腫瘤を認め, 前医ですでに desmopressin にて加療されていた. 軽度の意識障害を認め, 低ナトリウム血症と低血糖が指摘された. 全身検索で下垂体以

図 1
対側である右側乳房を置換する大きな腫瘤を認めた.

外に，右乳房の広範囲の腫瘤，右傍胸骨リンパ節，右腋窩リンパ節などに転移を認めた(図1)．

治療方針

前医では抑うつ状態があること，本人があまり積極的な治療を望まなかったことから経口抗癌剤を中心に治療が行われていた．視力低下が進行したため，2011年に経鼻経蝶形骨洞的腫瘍摘出術が施行され，乳癌の転移と診断された．今回，右乳房を置換する腫瘤による痛みに対し緩和的放射線治療と，視力確保のための下垂体部への照射を行うこととなった．

治療経過

下垂体部へは視神経および視交叉の有害事象を考慮し，1回2 Gyで週5回，5週間で総線

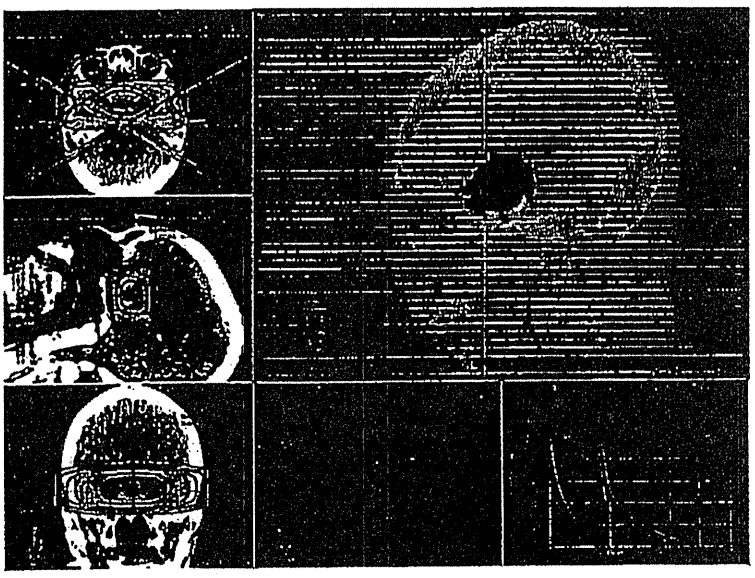

図2　下垂体部へ6方向からの局所照射を計画

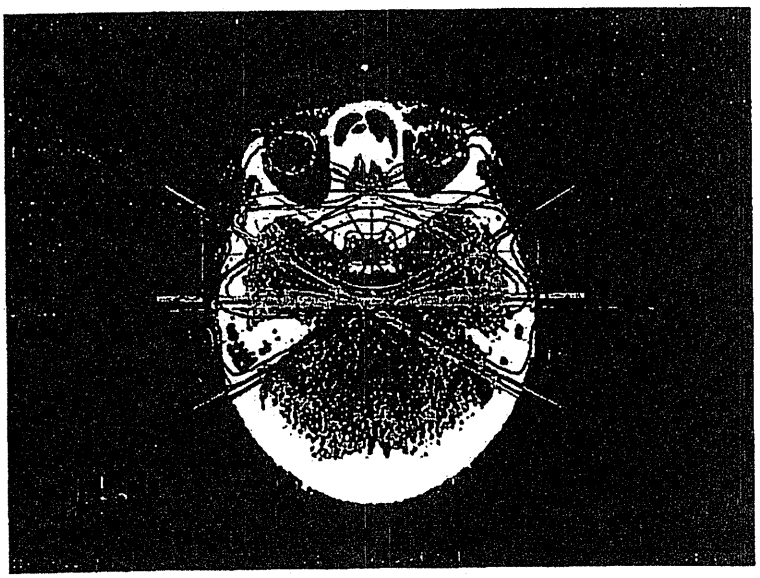

図3　下垂体部の線量分布図(軸位断像)

量50 Gyを投与することとした(図2, 3). また, 前医での左胸壁照射の詳細が不明(前医に問合せをしたが, 保存されていた資料が少なく照射方法の詳細は十分把握できなかった)であったが止血と疼痛緩和を目的とした右胸壁－腋窩照射へ30 Gy/10回/2週間を計画した(図4). 視力の回復は現時点まで認めていないが, 胸壁の腫瘤は縮小し疼痛の緩和も得られ鎮痛剤の減量が可能であった(図5). 半年後に右上肢の浮腫が出現し, 再度放射線治療について検討がなされた. 本人は抑うつ状態にあり治療に対し強い要望はなかった. 再照射となること, また痛みがないことなどから右胸壁－腋窩への再照射は行わないこととした.

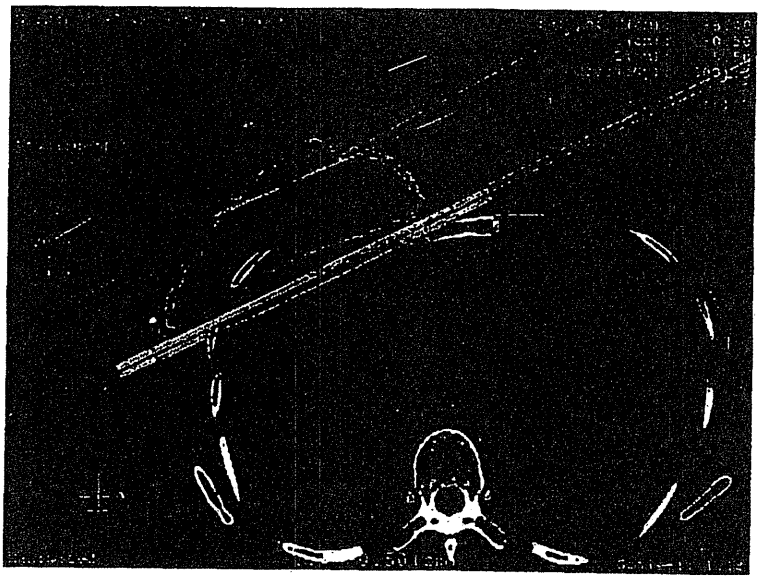

図4　右乳房を置換する腫瘤に対する接線照射

内側の照射野内側縁が腫瘤に近接しているが, 前回左胸壁への照射の既往があるため過線量を避けるために図のような治療計画とした.

図5　照射後2週間の右胸壁

腫瘤は著明に縮小した.

副作用マネジメント

照射の既往がある反対側の胸壁・乳房への照射を行う際には，前回の照射野，線量などを詳細に検討する必要がある．しかし，過去の症例で治療計画装置を用いずX線シミュレータのみで治療計画が立てられた症例のようであり，詳細な資料が現存していなかった．姑息的照射でもあり，十分なマージンを取った照射は有害事象を増やすと考え病巣部ぎりぎりの照射野となった．

下垂体への照射は視神経や視交叉があるため，注意深い治療計画が必要である．リスク臓器である視神経や視交叉は54 Gy前後が耐容線量と考えられており，今回もそれ以下に設定した．多門照射を用いることで正常組織への高線量を避けるよう配慮した．

治療のアウトカムのまとめ

他臓器転移があること，下垂体転移より視力低下があり全身状態も不良であり，また本人の抑うつ状態から，治療選択には全身療法や放射線療法を含め苦慮する状況であった．緩和的治療では本人の負担軽減は重要な課題であり，本症例でも本人の苦痛を最小限にとどめる放射線治療とした．本症例では，胸壁再発に対する照射で腫瘍の縮小が得られたが，症例によっては，照射終了時にはすでに照射野外に腫瘍が出現してしまうこともあり治療に苦慮する．現時点では局所再発例に対する標準的な照射スケジュールは確立しておらず，症例ごとに検討するしかないのが現状である．

現在の状況

現在は，右胸壁の腫瘤はある程度落ち着いていたが，他臓器転移もみられ緩和ケア中心の医療となり，自宅に近い施設に転院した．多部位にわたる疼痛のため，麻薬を中心とした疼痛緩和が行われている．

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Pancreatic cancer

Histopathological effects of preoperative chemoradiotherapy for pancreatic cancer: An analysis for the impact of radiation and gemcitabine doses

Takero Hirata [a,d], Teruki Teshima [a,*], Kinji Nishiyama [a], Kazuhiko Ogawa [d], Keisuke Otani [a,d], Yoshifumi Kawaguchi [a], Koji Konishi [a], Yasuhiko Tomita [b], Hidenori Takahashi [c], Hiroaki Ohigashi [c], Osamu Ishikawa [c]

[a] Department of Radiation Oncology; [b] Department of Pathology; [c] Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases; and [d] Department of Radiation Oncology, Osaka University Graduate School of Medicine, Osaka, Japan

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ABSTRACT

Background and purpose: Histopathological findings of patients who underwent resection for pancreatic adenocarcinoma (PC) after preoperative chemoradiotherapy (CRT) reportedly showed beneficial effects. The purpose of our study was to evaluate the correlation between histopathological effects (HE) of preoperative CRT and treatment parameters [radiation and gemcitabine (GEM) doses].

Material and methods: HE of CRT were assessed on 158 primary lesions of 157 patients with PC who underwent pancreatic resection after preoperative CRT with GEM between January 2006 and December 2011. The radiation dose delivered to the primary tumor site and surrounding regional nodal areas was 50 Gy until September 2009 followed by the dose escalation of a 10 Gy boost added for delivery with the field-in-field technique to the roots of the celiac and superior mesenteric arteries. Intravenous administration of GEM (1000 mg/m^2) was initiated concurrently on days 1, 8, and 15, every 4 weeks and generally repeated for 3 cycles. HE of CRT on the primary tumor were categorized based on the number of tumor cells destroyed.

Results: The median overall survival time was 74.5 months and 3-year and 5-year survival rates were 64.3% and 54.5%, respectively. Dose-volume parameters of radiation such as D33 with a cut-off value of 51.6 Gy were correlated significantly with HE ($p = .0230$). Lesions having received GEM > 7625 mg/m^2 before surgical resection more frequently showed positive HE ($p = .0002$). Multivariate logistic regression analysis demonstrated that both D33 and cumulative GEM dose were significant predictors of definite HE ($p = .0110$ and <.0001, respectively).

Conclusions: Our retrospective analysis showed that dose intensity of radiation and GEM is significantly related to HE of preoperative CRT for PC.

Pancreatic adenocarcinoma (PC) is one of the most fatal cancers and the fifth leading cause of cancer-related mortality in Japan with a 5-year survival rate of approximately 5% [1]. Although some patients with PC are candidates for surgical therapy, results of surgical resection alone have been unsatisfactory. Senser et al., with reference to the National Cancer Database population in the United States, reported a 5-year survival rate as low as 23.4% for patients with resectable PC [2]. The risk of locoregional and distant recurrence remains high without additional treatment, even after completion of a margin-negative resection [3]. To improve the outcomes, various multimodal approaches, including preoperative or postoperative chemoradiotherapy (CRT) for resectable or borderline resectable lesion have been tried. Previous studies have reported a decrease in viable cancer cells observed during microscopic examination of resected specimens [4–16] and lower incidences of positive margins or nodal involvement [17–19] after preoperative CRT. Therefore, preoperative CRT seems to be effective for advanced cancers, allowing for more effective surgery by reducing the number of residual cancer cells at the surgical margin or in the pancreatic tumor bed thus diminishing the risk of peritoneal tumor-cell seeding during the surgical procedure.

* Corresponding author at: Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3 Nakamichi 1-Chome, Higashinari-ku, Osaka 537-8511, Japan.
E-mail address: teshima-te@mc.pref.osaka.jp (T. Teshima).

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Preoperative CRT for PC can induce histopathological changes, and Chatterjee et al. reported that favorable histopathological effects (HE) correlated with better survival of patients who underwent surgical resection of PC [13]. They divided their patients into two groups [those with pathologic complete response or minimal (<5%) residual tumor and the others] and found significant differences between the two groups in overall survival (mean 79.2 months vs. 48.2 months, $p = .0002$) and disease-free survival (mean 55.8 months vs. 36.8 months, $p = .01$). Breslin et al. also demonstrated that patients with tumors showing evidence of tumor destruction of more than 50% tended to have better survival [4]. Therefore, making every effort to achieve definite HE of CRT may lead to improved treatment outcomes for PC. Currently, new technologies such as intensity-modulated radiation therapy, stereotactic body radiation therapy and particle therapy have become available, which have the great advantage of delivering a higher dose to the target volume while reducing doses to neighboring organs at risk. As for chemotherapy, gemcitabine (GEM) has emerged as the key drug for PC, and its clinical benefits have been reported [20–23]. However, the extent of radiation dose or GEM dose which contributes to positive HE has not been determined yet. The current study was conducted to evaluate the effects of preoperative CRT for PC, especially the relationship between the number of viable cells remaining at the tumor site and the radiation and GEM doses. We believe our findings should prove useful for radiotherapy planning for patients with PC.

Materials and methods

Patients

This study is a retrospective analysis of the results of a prospective phase II clinical trial involving part of the patients with PC hospitalized at our institution [15], and was approved by the ethics committee. Written informed consent was obtained from each patient. From January 2006 to December 2011, 222 patients with PC, either resectable or borderline resectable according to the MD Anderson classification [24], were treated with CRT and sequentially underwent surgical resection. Among them, 59 patients were ineligible for radical surgical resection (One patient died of a rupture of a gastroduodenal artery aneurysm, another patient elected to discontinue CRT in mid-course, 2 patients was precluded major pancreatic surgery because of low performance status, 6 patients did not choose surgical resection voluntarily, and the others revealed that they had unresectable factors such as vascular invasion or distant metastases at restaging or intraoperative diagnosis). Consequently, 163 patients underwent radical surgical resection. We excluded six patients from analysis (one patient had lack of pathological materials, another patient underwent operation in another hospital, another patient did not undergo GEM-based CRT, and the others revealed that they did not have adenocarcinoma). Finally, 157 patients [97 males, and 60 females; median age, 66 years (range: 33–84) (Table 1)] were the subjects of our analysis.

Table 1
Patient characteristics and treatment outcomes.

Characteristics or outcomes (157 patients, 158 lesions)	*n*, value	%
Median age, *y* (range)	66 (33–84)	
Median follow-up time, mo (range)	32 (4.4–87)	
Performance status		
0	127	80.9
1	30	19.1
Sex		
Male	97	61.8
Female	60	38.2
Tumor location		
Head	90	57.0
Body or tail	68	43.0
Resectability		
Resectable	104	66.2
Borderline resectable	53	33.8
Clinical N stage		
cN0	142	90.4
cN1	15	9.55
Pathological T stage		
ypT0	6	3.80
ypT1	25	15.8
ypT2	9	5.70
ypT3	118	74.7
Pathological N stage		
ypN0	119	75.8
ypN1	38	24.2
R0 resection		
Yes	157	99.4
No	1	0.633
Lymph-vascular invasion		
yes	48	30.4
no	110	69.6
Venous invasion		
Yes	21	13.3
No	137	86.7
Perineural invasion		
Yes	85	53.8
No	73	46.2
Site of first treatment failure		
No recurrence	85	54.1
Local only	10	6.37
Local and distant	21	13.4
Distant only	41	26.1
Median GTV, cm^3 (range)	8.10 (0.500–42.4)	
Median total GEM dose, mg/m^2 (range)	8000 (980–21000)	
Histopathological effects (amount of tumor cell destruction)		
Grade Ia (<33%)	56	35.4
Grade Ib (33–66%)	74	46.8
Grade II (>67%)	22	13.9
Grade III (no viable tumor cells are present)	6	3.80
Median survival time, mo	74.5	
5-Year overall survival rates, %	54.5	
5-Year disease-free survival rates, %	40.4	

Protocol of preoperative CRT, surgical resection, and adjuvant therapy

Three-dimensional conformal radiotherapy, with the patient positioned in a body frame (Blue BAG; Elekta AB, Inc., Stockholm, Sweden) was used. Treatment planning involved the use of a multislice CT scanner with 2.5 mm slice thickness. Scanning was performed for both the expiration and inspiration phases after oral administration and intravenous injection of contrast media. The clinical target volume consisted of the primary pancreatic tumor site (with a 5–10 mm margin) which was delineated on each respiratory phase, the retroperitoneal soft tissue and surrounding regional nodal areas including the para-aortic region. A planning target volume (PTV) with an omnidirectional 5 mm margin was then created. A 10-MV linear accelerator was used for irradiation with a prescribed radiation dose of 50 Gy (2 Gy/fr) for PTV. We used the field-in-field technique for a 10 Gy (0.4 Gy/fr) radiation boost to the roots of the celiac and superior mesenteric arteries, which have been recognized as high risk areas of perineural invasion since September 2009. With this technique, a tumor close to the boost field received a dose of more than 50 Gy. The multiple fields technique and an adjustable multi leaf collimator were used to avoid delivering an overdose to the gastrointestinal tract and kidneys. Care was taken not to set an unnecessarily large PTV (not more than 300 cm^3). Typical dose distribution is shown in Fig. 1.

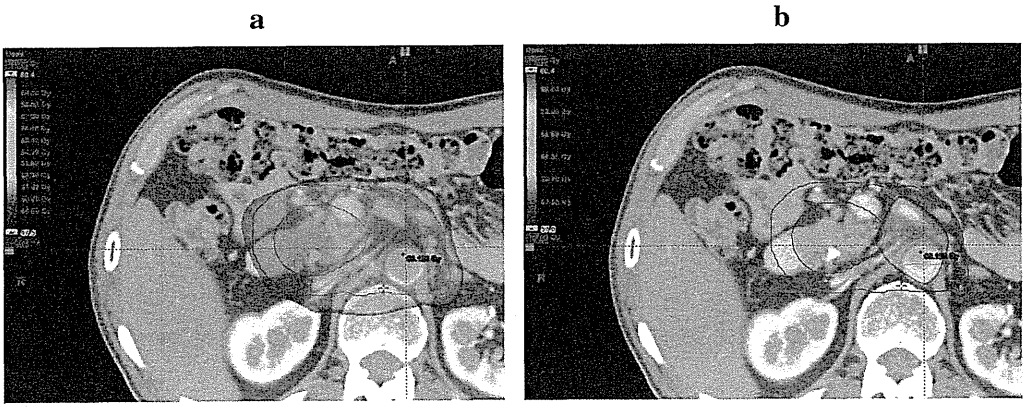

Fig. 1. Typical dose distribution. (a) Main field; (b) field of boost to the roots of the celiac and superior mesenteric arteries.

Intravenous administration of GEM (1000 mg/m^2) was initiated concurrently on days 1, 8, and 15 every 4 weeks. This procedure generally repeated for 3 cycles, so that the preoperative CRT was usually completed in 3 months after initiation.

Patients were restaged after completion of CRT and, if there was no disease progression, resection was performed. The surgical resection was accompanied by lymphatic and connective tissue clearance and postoperative liver perfusion chemotherapy [25]. For patients who were thought to have a high probability of recurrence, GEM or other chemotherapeutical drugs such as tegafur, gimeracil, and oteracil potassium were administered as the adjuvant therapy.

Histopathological examination of resected specimens

Histopathological examination was carried out by pathologists of our institute using 4-μm thick sections stained with hematoxylin and eosin. All tumors were evaluated pathologically according to the UICC classification 7th edition [26] and Classification of Pancreatic Carcinoma 3rd English edition, by The Japan Pancreas Society [27]. Evaluation of the histopathological response of the primary tumor to the preoperative CRT was categorized as follows, based on tumor cell status: Grade Ia, destruction of less than 33% of tumor cells; Ib, destruction of 33–67% of tumor cells; II, destruction of over 67% of tumor cells; and III, no viable tumor cells. This method is established based on the classification proposed by Shimosato et al. [28] and used commonly in Japan when HE of preoperative therapy are evaluated for such cancers as gastric cancer [29], esophageal cancer, colon cancer, head and neck cancer and breast cancer.

Statistical analysis

Gross Tumor Volume (GTV) was contoured by a radiation oncologist on every patient's CT images which were scanned at the expiration phase and the dose-volume histograms (DVH) were obtained with an Eclipse radiotherapy planning system (Ver.8.9.08, Varian Medical Systems, Inc., Palo Alto, CA, USA). For DVH analysis, the dose was calculated by using the Anisotropic Analytical Algorithm with heterogeneity correction. JMP software (Ver10.0.2.0; SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. We explored the optimal cut-offs for the prediction of definite HE by using the decision tree method with the algorithm engaged in the software. After the patients had been divided into groups, we compared the occurrence rates for definite HE (Grade Ib or higher) using the one-sided Fisher's exact test with a subsequent multiple logistic regression analysis. Statistical significance was defined as $p < .05$.

Results

Table 1 shows the characteristics of and treatment outcomes for the patients enrolled in this current study. Each patient's performance status and administered GEM dose were not significantly different from those of patients who were excluded from analysis. Detailed data of excluded patients and p value from the Wilcoxon rank-sum test were as follows: performance status 0/1/2; 50/14/1 patients ($p = 0.4745$), cumulative GEM dose, median 7500 (0–29000) mg/m^2 ($p = 0.4002$).

Overall survival (OS) and disease-free survival (DFS) outcomes for the 157 cases resected after preoperative CRT show that median OS was 74.5 months, and 3-year and 5-year survival rates were 64.3% and 54.5%, respectively. Corresponding results for DFS were 33.7 months, 47.6% and 40.4%. Three patients had Grade 3 (according to CTCAE ver. 4.0 [30]) complications (two had nausea and one had peptic ulcer). No patient had any Grade 4 or 5 complications.

HE of CRT are shown in Table 1. Fifty-six lesions were classified as Grade Ia, 74 as Grade Ib, 22 as Grade II, and 6 as Grade III, with 65% of the lesions graded as Ib or higher. Typical histopathological presentations after CRT are shown in Fig. 2. Effects of preoperative CRT were most obvious for high-grade lesions in terms of the destruction of large numbers of cells and a great deal of fibrosis, and organization of vascular lumens.

There was no difference in the frequency of definite HE between patients who underwent irradiation boost and those who did not (70.6% vs. 60.0%: odds ratio; 1.60 (0.818–3.13): $p = .113$). However, the recurrence rate from the roots of the celiac and superior mesenteric arteries tended to be lower in patients with boost irradiation (24.7% vs. 13.2%: odds ratio; 2.15 (0.919–5.04): $p = .0540$). In addition, a focus on details of radiation and GEM dose data disclosed several predictors of definite HE. Table 2 shows the predictive capability of HE of CRT on the basis of the dose-volume parameters of radiotherapy and cumulative GEM dose before surgical resection. Among the dose-volume parameters, D2 (dose covered 2% of GTV) >52.7 Gy and D33 > 51.6 Gy were identified as significant predictors of definite HE ($p = .0302$ and .0230, respectively). Other factors such as Dmean >51.5 Gy and D90 > 50.5 Gy also featured predictive capability but of borderline significance ($p = .0394$ and .0474, respectively; lower limit of confidence interval <1). D33 proved to be the most significant predictive factor. As for chemotherapy, among 75.0% of the patients who received more than 7625 mg/m^2 of GEM before surgical resection, 75.0% of

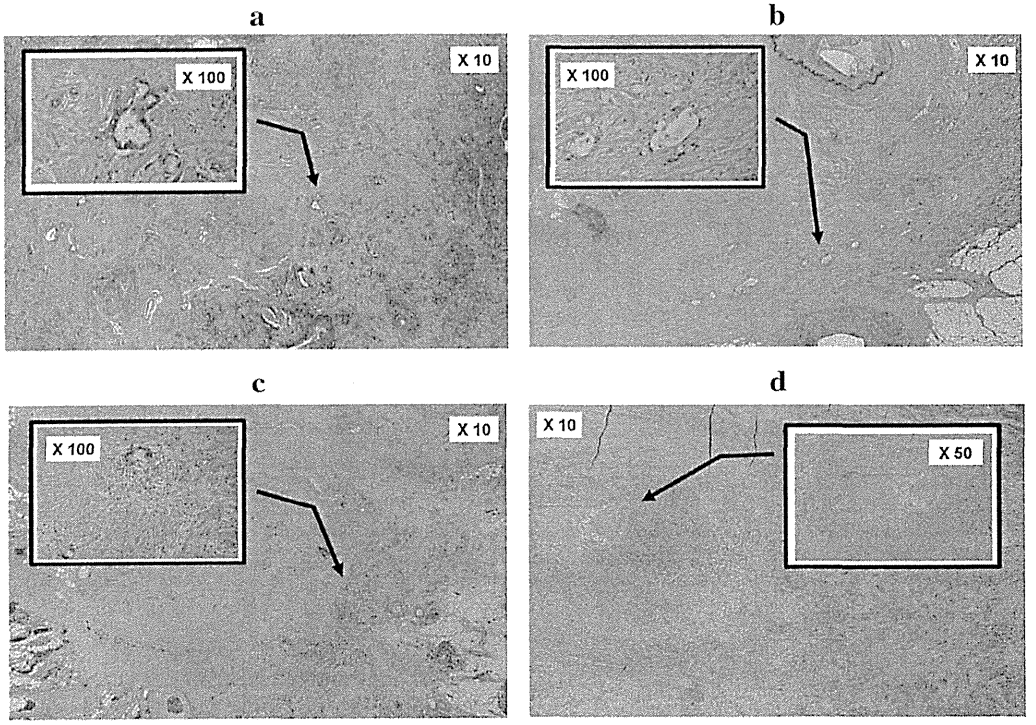

Fig. 2. Typical histopathological findings after preoperative CRT. (a) Grade Ia, little tumor cell destruction (<10%) is evident; (b) Grade Ib, 50% destruction of tumor cells; (c) Grade II, a few residual tumor cells; (d) Grade III, no viable tumor cells [fibrosis and organization of vascular lumen (splenic vein)].

Table 2
Correlation between histopathological effects and treatment parameters.

Parameters			Grade Ia	Grade Ib or higher (%)	*p* value	OR	95% CI
D2	>52.7 Gy		16	46 (74.2)	0.0302	2.053	1.021–4.130
	⩽52.7 Gy		40	56 (58.3)			
D33	>51.6 Gy		14	43 (75.4)	0.0230	2.186	1.063–4.497
	⩽51.6 Gy		42	59 (58.4)			
Dmean	>51.5 Gy		14	41 (74.5)	0.0394	2.016	0.979–4.154
	⩽51.5 Gy		42	61 (59.2)			
D90	>50.6 Gy		10	32 (76.2)	0.0474	2.103	0.943–4.688
	⩽50.6 Gy		46	70 (60.3)			
GEM	>7625 mg/m^2		26	78 (75.0)	0.0002	3.750	1.868–7.525
	⩽7625 mg/m^2		30	24 (44.4)			
GEM > 7625 mg/m^2	D33	>51.6 Gy	4	34 (89.5)	0.0075	4.250	1.338–13.50
		⩽51.6 Gy	22	44 (66.7)			
GEM ⩽ 7625 mg/m^2	D33	>51.6 Gy	10	9 (47.4)	0.4860	1.200	0.390–3.686
		⩽51.6 Gy	20	15 (42.9)			
Total			56	102 (64.6)			

Abbreviations: OR, Odds ratio; CI, Confidence interval.

patients showed definite HE. The corresponding outcome for 7625 mg/m^2 or less of GEM was only 44.4% ($p = .0002$). The odds ratios were compared for the groups divided according to radiation dose and GEM dose to determine their interaction.

The predictive capability of the following factors was validated: sex, age, performance status, tumor location, resectability status, radiation dose (D33 > 51.6 Gy or not) and GEM dose (cumulative GEM dose >7625 mg/m^2 or not). The results of multiple logistic regression analysis then demonstrated that D33 (odds ratio; 2.767 (1.257–6.402): $p = .0110$) and cumulative GEM dose (odds ratio; 5.638 (2.552–13.13): $p < .0001$) were significant predictors of definite HE.

Discussion

In recent years, several authors have reported favorable outcomes of preoperative CRT for PC. Findings of histopathological response analyses of resected specimens have also be detailed in several reports. Supplementary Table 1 summarizes data about HE from previous studies. The results of our treatment are comparable with those reported elsewhere. As for the effect of the radiation dose, Golden et al. reported a higher radiation dose improved the likelihood of long-term survival of patients with unresectable PC [31]. This report indicates that higher radiation dose prescribed to tumor site results in more tumor cell destruction and greater

survival benefits. The impact of the GEM dose has also been examined. Several studies have shown the superiority of full-dose over lower-dose GEM regimens in terms of their systemic treatment efficacy for CRT [32,33]. In addition, combing GEM with irradiation is thought to have a synergetic effect [34,35], so that concurrent use of GEM and radiotherapy is expected to have more favorable HE on tumor sites. To the best of our knowledge, however, there have been no reports which demonstrated exactly what dose and volume of radiotherapy or dose of GEM contributes to positive HE.

For this study, we investigated the factors associated with definite histopathological changes (to Grade Ib or higher) after preoperative CRT, and found that both dose and volume of radiotherapy and cumulative dose of GEM had significant effects. GEM dose (cut-off value: total GEM dose >7625 mg/m^2) proved to be a relatively more significant factor. Furthermore, when a higher radiation dose (cut-off value: D33 > 51.6 Gy) was administered with a higher GEM dose, the resultant of definite HE became potentially the highest. In addition, a comparison of the odds ratios for the groups classified by radiation dose and GEM dose indicated that these two factors interacted positively. These findings provide the basis for the establishment of quantitative evidence in finding radiation and cumulative GEM doses needed to attain positive HE, and can be expected to be valuable for future use of CRT for PC, especially for treatment of locally advanced PC, which CRT is relatively more important because primary tumors cannot be surgically resected.

Previous studies have identified various predictive factors of recurrence or prognosis including the extent of tumor invasion of muscular vessels, perineural invasion, nodal involvement, the residual status of the tumor after surgery, tumor diameter and histological grade [12,15,36–41]. Preoperative CRT reportedly resulted in a relatively higher rate of negative margins after resection and lower lymph node positivity [19]. Several authors have identified such conditions as representing factors which yield survival benefits [15,41,42]. These findings further imply that preoperative CRT contributes making insufficient surgical resection and occurrence of lymph node metastases less likely, and thus leading eventually to better survival rates for patients with resectable or borderline resectable PC. A previous study conducted at our institute reported that positive nodal involvement was the single independent predictor significantly associated with an increased risk of distant recurrence [15]. The same study demonstrated that perineural invasion was associated with local recurrence [15]. OS and DFS after preoperative CRT at our institute were relatively higher than those reported previously as shown in Supplementary Table 1. These favorable outcomes may be partially attributed to the setting up of radiation fields including high risk areas of nodal involvement and perineural invasion, considering the boost irradiation had a tendency to lower the recurrence rate in the irradiated fields. However, the efficacy of our protocol and results of CRT need to be validated. Six of our patients showed the complete response after preoperative therapy, which implies that a radical cure is possible for the patients with medically inoperable conditions. Since we could not prove that the radiation dose significantly affected more favorable HE (Grade II or higher), our data do not constitute proof that the dose intensity of preoperative CRT of PC is directly related to survival benefits. However, the present protocol followed at our institute involves irradiation with a higher dose of 60 Gy only for the roots of the celiac and superior mesenteric arteries and a higher dose of more than 50 Gy only for the tumor site adjacent to those areas and so we hypothesize that expansion of the tumor site covered by a higher radiation dose for patients who received a relatively higher GEM dose will result in a higher frequency of more favorable HE and more extensive tumor destruction, thus contributing to survival benefits as demonstrated by Chatterjee et al. [13]. Indeed, the results of CRT have not always been gratifying, but the radioresistance of pancreatic cancer cells have become surmountable because various biomarkers related to it have been detected [43–45]. An increase of radiation dose administered to the tumor site is thus worth considering. In our experience, administration of high-dose radiotherapy is feasible if careful attention is paid to organs at risk while limits on the dose intensity of GEM sometimes need to be imposed because of myelosuppressive or other adverse effects. In recent years, radiation techniques have undergone remarkable developments, resulting in higher radiation doses being prescribed with great accuracy. Several authors reported their attempts to put intensity modulated radiation therapy or particle therapy to the treatment of PC [46–48]. Terashima et al. showed the feasibility and high efficacy of high-dose proton therapy with GEM [48]. Efforts to improve treatment outcome of PC with dose escalation of radiotherapy using high-accuracy treatment modality is expected to be active in the immediate future. Our quantitative data can thus also be useful for efforts to establish curative doses of CRT for PC.

Our study has several limitations. First, we evaluated only dose-volume parameters of tumors shown on the CT images obtained at the expiration phase and did not take into account tumor movement associated with respiratory motion. Second, we could not demonstrate whether the area irradiated with a higher dose corresponds to the area in which greater tumor destruction was observed. However, we confirmed that in some patients whose dose distribution within GTV is inhomogeneous, histopathological findings are also inhomogeneous within the tumor site (Supplementary Fig. 1). We are therefore considering conducting an analysis of correlations between dose distribution and histopathological changes by three-dimensional reconstructing dose on resected tissue. Third, continuous follow-up will be needed to determine whether our CRT protocol contributes to survival benefit, because our adoption of field-in-field technique in recent years has resulted in a shorter follow-up period. Finally, this study was based on a retrospective review and we have not performed validation cohort analysis. Therefore, our study was prone to selection or other unforeseen biases, so that a prospective study to be conducted in the future can be expected to provide more conclusive results about the actual correlation between CRT doses and associated HE.

In conclusion, our retrospective analysis showed that a higher radiation dose, combined with a specific irradiation volume for tumor sites and chemotherapy dose, contributes to definite histopathological outcomes for preoperative CRT for PC. Our quantitative data are expected to prove useful for detailed radiotherapy planning, especially in this era of high-accuracy radiotherapy.

Conflict of interest disclosure

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.01.004.

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