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〔特　　集〕膵癌化学療法の新たな展開

切除不能膵癌に対するFOLFIRINOX治療の実際

大川　伸一*

要　旨：切除不能膵癌に対する化学療法は長らくゲムシタビン（GEM）が標準治療であった．これに続いてGEM＋Erlotinib併用療法，S-1が用いられるようになったが，3つのレジメンには治療成績において大きな差はなかった．FOLFIRINOX治療はフランスで行われたGEMとの比較試験で生存期間に大きな差を持って優越性を示し，欧米では迅速に標準治療の一つに加えられた．日本でもほぼ同様のレジメンで治験が行われ，良好な成績を得たため2013年12月に膵癌に使用が承認された．抗腫瘍効果に優れており，実地医療でも使用され始めているが，4種の薬剤を用い，また薬剤によっては用量も多いため，これまでのレジメンに比べて骨髄抑制を始めとして多くの副作用を伴う．このため実地医療において対象となる膵癌患者の選択には慎重かつ十分な検討が必要であり，治療経過中も丁寧な観察と有害事象に対する迅速な対応が必要である．

索引用語：FOLFIRINOX　　切除不能膵癌　　化学療法

はじめに

切除不能膵癌に対する化学療法は，1997年にBurris[1]らが塩酸ゲムシタビン（GEM）と5-FUとの比較試験を報告して以来，長らくGEM単独療法が唯一の標準療法であった．GEM単独療法をcontrol armとしてGEM＋新規薬剤を比べる多くの無作為化比較試験が行われたが，GEM＋erlotinib[2]以外はことごとく優越性を証明できなかった．GEM＋erlotinibは米国では報告後まもなく一次化学療法のオプションとして承認され，ガイドライン上にも加えられたが，その後もしばらく新規薬剤が見いだせなかった．この後，日本ではS-1が膵癌に承認され[3]，一次化学療法のオプションの一つとなった．だがこれらいずれの治療もGEM単独療法と効果に大きな違いはないと考えられてきた．

2011年にConroy[4]らが報告した遠隔転移を有する膵癌に対するFOLFIRINOX療法はGEMとの比較試験として行われ，明らかな優越性を示した．この試験はGEMに対する成績の差が顕著であったこと，GEM freeのレジメンであったこと，さらに試験の質が高く評価されたことから大きなインパクトを与え新たな治療法として認知された．

FOLFIRINOX試験（PRODIGE 4/ACCORD11 trial，ACCORD 11）について

試験は第II相から開始し，続けて第III相に移行する形をとった．対象は遠隔転移を有する膵癌で，適格条件は18歳以上，ECOG（Eastern Coop-

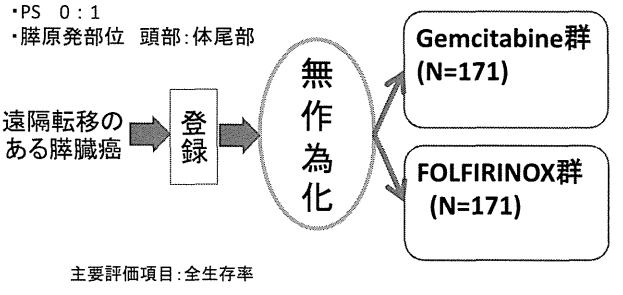

Fig. 1　FOLFIRINOX試験（ACCORD 11）試験デザイン
遠隔転移のある膵癌を対象とし，PS，膵癌の原発部位で層別化したのち，GEM群とFOLFIRINOX群に無作為に割り付けた．

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Table 1　FOLFIRINOXの有効性[4]

	FOLFIRINOX	GEMCITABINE
	N＝171	N＝171
Response Rate	31.6%（95%CI：24.7–39.1）	9.4%（95%CI：5.4–14.7）
生存期間中央値*	11.1カ月（95%CI：9.0–13.1）	6.8カ月（95%CI：5.5–7.6）
1年生存率	48.4%	20.6%

*HR（Hazard ratio）：0.57（95%CI：0.45–0.73，p＜0.001）

Table 2　FOLFIRINOXの有害事象（Gr 3，4）[4]

有害事象名	FOLFIRINOX（n＝167）	GEM（n＝169）	P値
好中球減少	45.7	21.0	＜0.001
発熱性好中球減少	5.4	1.2	0.03
血小板減少	9.1	3.6	0.04
貧血	7.8	6.0	NS
疲労	23.6	17.8	NS
嘔吐	14.5	8.3	NS
下痢	12.7	1.8	＜0.001
末梢神経障害	9.0	0	＜0.001
AST・ALT上昇	7.3	20.8	＜0.001
血栓症	6.6	4.1	NS

NS：not significant

erative Oncology Group）のPerformance Status（PS）[5]が0または1，黄疸がない，骨髄機能が保たれている（好中球数が1500/mm^{3}以上，血小板数が100000/mm^{3}以上），肝臓や腎臓などの重要臓器機能が保たれていることなどであった．除外項目としては76才以上，内分泌腫瘍や腺房細胞癌，膵癌に対する放射線治療歴のあるものなどとされた．

登録された対象をPS（0 vs 1）と原発の部位（膵頭部vs体尾部）で層別化した上で無作為にFOLFIRINOX群とGEM群に分けた（Fig. 1）．FOLFIRINOX群は，使用する薬剤として5-FU，レボホリナートカルシウム（*l*-LV），オキサリプラチン（L-OHP），イリノテカン（CPT-11）の4剤である．治療開始後3日目から14日目までを休薬とし，これを1サイクルとして繰り返した．有害事象に応じて薬剤の減量は詳細に規定された．また2サイクル以降は好中球減少に対して適宜G-CSF製剤が予防的に使用された．

GEM群は1000mg/m^{2}を週1回，連続7週間投与した後，1週休薬，その後は3週投与して1週休薬を繰り返した．

第II相部分の主要評価項目は抗腫瘍効果，副次評価項目は安全性とした．第III相では主要評価項目が全生存期間，副次評価項目が無増悪生存期間，抗腫瘍効果，安全性，そしてquality of lifeであった．

2005年の12月から2009年の10月までフランス国内の48施設から登録された．奏功率（Table 1）はFOLFIRINOX群で31.6%，GEM群で9.4%であった（p＜0.001）．生存率の観察期間中央値は26.6カ月であった．全生存期間はFOLFIRINOX群で11.1カ月，GEM群で6.8カ月であった．死亡のHazard Ratio（HR）は0.57，95%信頼区間は0.45から0.73，p＜0.001であった．6，12，18カ月時点での生存率はFOLFIRINOX群で75.9%，48.4%，18.6%，GEM群で57.6%，20.6%，6.0%であった．progression free survival（PFS）はFOLFIRINOX群で6.4カ月，GEM群で3.3カ月であった（HR＝0.47）．

二次化学療法はFOLFIRINOX群で80例，GEM群で85例に行われた．治療内容はFOLFIRINOX群ではGEMまたはGEM basedのレジメ

Table 3　ACCORD 11[4]と日本の治験[8]の比較

	ACCORD 11	日本の治験
N	171（FOLFIRINOX群）	36
有効性		
奏効率（%）	31.6	38.9
病勢制御率（%）	70.2	69.4
奏効期間	5.9（月）	170（日）
生存期間中央値（月）	11.1	10.7
有害事象		
好中球減少(Gr 3以上, %)	45.7	77.8
発熱性好中球減少（%）	5.4	22.2
G-CSF使用率（%）	42.5	52.8
貧血（Gr 3以上，%）	7.8	11.1

ンであったのに対し，GEM群では様々であった．二次化学療法開始からの生存期間は両群で差は見られなかった（各群4.4カ月）．

安全性としてgrade 3以上の有害事象については，好中球減少，発熱性好中球減少，血小板減少，下痢，末梢神経障害がFOLFIRINOX群で有意に高率であった．一方，AST・ALT上昇はGEM群で有意に高率であった(Table 2)．両群において胆管ステントの有無による血液学的な有害事象や感染症のリスクは同じようなものであった．G-CSFはFOLFIRINOX群で42.5%，GEM群で5.3%に投与された．Quality of Life（QOL）はEORTCの調査票であるQLQ-C30[6]で測定した．base lineの時点では両群に有意な差は見られなかった．しかし治療開始後6カ月の時点では，FOLFIRINOX群で31%が低下したとされたが，GEM群では低下した割合は66%に上った．QOLについては後解析でさらに詳細な報告がなされた[7]．

日本の治験について

ACCORD11の結果を受けて我が国でも同じレジメンで試験が行われた[8]．

試験は主要評価項目を奏効率とする第II相試験として行われた．36名が参加してレジメン，減量規定などほぼ同様で行われた．ACCORD11と異なる点は適格条件の年齢，好中球数などであるが大きな違いはない．奏効率は14/36＝38.9%，病勢制御率（Disease Control Rate，DCR）は69.4%であった．

ACCORD 11と比較してみると奏効率，病勢制御率ともACCORD 11とほぼ同様であったが，有害事象ではGrade 3以上の好中球減少の発現率に大きく差があり日本の場合に高率であった．これに伴いG-CSF使用率にも差が見られた（Table 3）．このため日本の試験においては，5-FUのbolusのdose intensityは15.86%と低率であった．

FOLFIRINOX治療の評価・比較

前述したように膵癌の化学療法は，1997年[1]以来GEMがkey drugとされてきた．その後GEMをbaseとした併用療法において唯一GEM単独治療に対して優越性を示したGEM＋erlotinib併用療法は，日本では安全性の担保の整備に時間がかかり，2011年に漸く使用が認められた．

またS-1をGEMと比較するGEST試験[9]が膵癌に対する日本で初めての第III相試験として行われ，S-1単独療法のGEMに対する非劣性が示された．これらの結果から我が国の膵癌診療ガイドラインでは，膵癌の一次化学療法の選択肢としてGEM，GEM＋erlotinib，S-1と3種類の治療法が存在する[10]．しかしこれらはいずれも同等に近い治療成績であり，使い分ける根拠に大きな違いはないとも言える．日常臨床において患者には3つの治療法を提示し，肺の障害の有無，臓器機能，PS，患者の希望，人生観，life styleなどを考慮して決めることが多い．

FOLFIRINOXはそのすぐれた成績から大きな

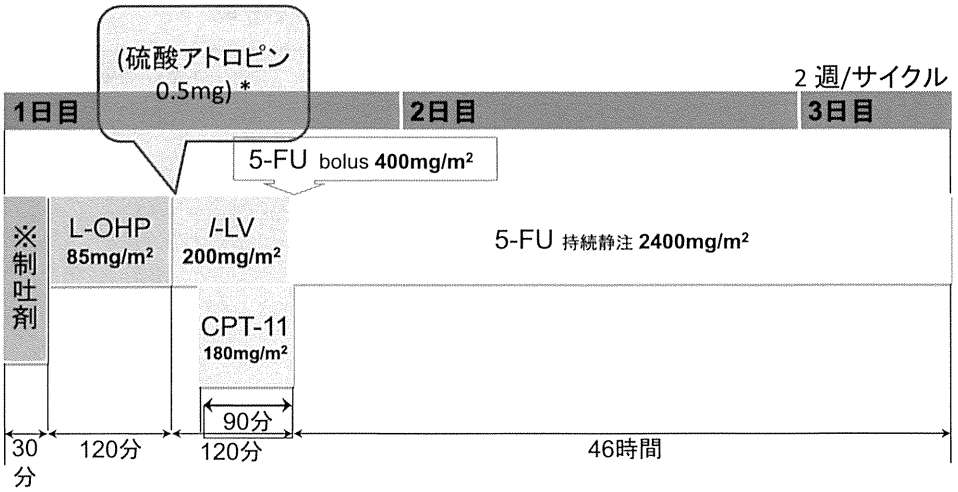

Fig. 2　実臨床における投与法の例
Highly emetogenic chemotherapy として扱い，制吐剤を3剤併用投与．L-OHP を2時間で85mg/m² を投与，続いて *l*-LV を2時間で200mg/m² を投与，*l*-LV の投与開始から30分後に CPT-11 を90分で180mg/m² 投与する．さらに続いて5-FU の400mg/m² を bolus で投与後，2400mg/m² を day2，3に46時間かけて投与する．投与終了後から14日までは休薬し，14日間を1コースとする．Day 15から次のサイクルになる．また CPT-11 によるコリン作動制症候を示した場合は，次のコースから投与前に硫酸アトロピンを予防で投与する．
L-OHP：オキサリプラチン，*l*-LV：レボホリナートカルシウム，CPT-11：イリノテカン塩酸塩
※制吐剤：5-HT_3 受容体拮抗剤，ステロイド，アプレピタント
* CPT-11 によるコリン作動性症状を来す場合に前投与

衝撃を与え，また試験の質も高く評価されたこともあり，進行膵癌に対する一次治療のオプションの一つとして NCCN の guideline[11]に迅速に記載された．日本でも膵癌診療ガイドライン2013年版の出版時点では未承認であったが，2013年12月に承認され，現在一次治療の選択肢の一つとなっている．

しかし多剤併用療法のため，薬剤による副作用が多くかつ多様なことから，これまでのレジメンと比して有害事象の対策に相当な注意を払う必要がある．特に日本の治験では Grade 3 以上の好中球減少を80％近くに生じ，発熱性好中球減少も20％以上見られ，G-CSF 製剤は50％以上に使用されている．従って治療経過中に胆管炎を発症する頻度の高い疾患である膵癌に対しては，重篤化を避けるために迅速な対応が必要である．また非血液毒性以外の有害事象として嘔気，嘔吐などの消化器症状の頻度が高いこと，また治療経過とともに増加する末梢神経障害は，治療意欲に影響の出やすい事象である．このようなことから，FOLFIRINOX の適応や治療の実際に当たっては多岐にわたり慎重な配慮が必要と考えられる．

FOLFIRINOX 治療の実際

実際の治療の適応は今までの化学療法に比べて，より PS が良いこと，年齢が若いことが条件となる．また UGT1A1 検査，中心静脈ポートの設置，開始数日間の吐き気などの有害事象に対する処置などから，治療導入においては入院が望まれる．また膵癌の治療経過中にしばしば発生する胆管炎は好中球の減少を来しやすい治療であるため医師側も入念なチェックと迅速な対応が必要である．しかし一方で優れた治療効果からこの治療の恩恵を受けられる方もいることを念頭に置いて治療法の決定に当たる必要がある．

実臨床での投与法は，まず前投薬として制吐剤を投与した後，オキサリプラチンを85mg/m²，2時間で静脈内投与，レボホリナートカルシウムを

400mg/m^2, 2時間で静脈内投与し，オキサリプラチン投与終了30分後から，イリノテカンを180 mg/m^2, 90分かけて静脈内投与する．さらにこれらの投与終了後すぐに5-FUをまず400mg/m^{2}でbolus投与し，続けて2400mg/m^{2}を46時間かけて投与する(Fig. 2)．初回治療は現段階では入院で行っている．特に支障がない限りFull doseで開始し，有害事象により適宜減量を行っているが2サイクル目の投与は好中球減少により予定どおりに行われることは少ない．経過中G-CSFは半数以上で必要になると考えて良い．まれに無顆粒球症に近い状態を経験するので，迅速な対処が必要である．治療前のUGT1A1遺伝子検査は必須であるが，野生型及びUGT1A1*6または*28のいわゆるsingle heteroまでなら治療対象としている．

CPT-11の高用量投与時によりコリン作動性症状（発汗，しびれ，ろれつが回らないなど）を生じる場合は，アトロピンで適宜対処する(Fig. 2)．

また投与開始から数日間は多くの例が嘔気などの消化器症状に苦しむため，予防的制吐剤の使用は必須である．薬剤は中催吐性[12]のもののみで構成されているが実態は催吐性が大変高いためhighly emetic chemotherapyに対する方法で行うべきであると考えられる[13](Fig. 2)．また治療が奏効して長期間になると末梢神経障害が出現してくる．この有害事象は治療意欲に影響しやすいためできるだけ早期から対処するべきである．

Modified FOLFIRINOX，適応拡大について

治療効果は優れているものの血球減少を初めとした有害事象の多さから，承認された直後より欧米でも最初から減量したレジメン（modified FOLFIRINOX）での報告がされている．多くは5-FUのbolusを除くものやCPT-11を減量したものであり，有害事象が減じ安全性が向上したが有効性はオリジナルに劣らなかったと言う報告もある[14]．日本でもbolusを除いたmodifiedレジメンの試験が行われているが，未だ結果は出ていない．

またACCORD 11や日本の試験の対象が遠隔転移を有する膵臓癌であるため，局所進行膵癌に対する効果[15~17]や，高い抗腫瘍効果に着目して術前化学療法，特にborder line resectable膵癌に対する試験や経験の報告がされている[18,19]．いずれも治療成績の向上が期待できるとしている．さらには2次化学療法としてFOLFIRINOXを用いた報告もある[20]．しかしこれらはまだ高いエビデンスを有するものではなく今後の重要な検討課題である．

膵臓癌化学療法の今後の展開予想

FOLFIRINOX治療はPSが良く，臓器機能が十分保たれている非高齢者にはこの恩恵を受けられる可能性があり，大変期待される治療法である．強力な化学療法の出現は，すべての癌腫の中でもっとも治療に抵抗する膵癌に対して朗報であることは間違いない．一方で，がん性疼痛，食欲低下，体重減少など多くの臨床症状を有する膵癌において，我が国でFOLFIRINOX療法が適応となる割合がどのくらいになるかは未知数である．すでに以前から使用されている海外においても，膵癌全体の30%程度の対象にしかならないとも言われており，一方でmodified FOLFIRINOXの治療成績の報告が多く見られている．今後はどのくらいの症例に対してどの程度の薬剤量が適切なのかなどの検証が必要である．

膵癌の化学療法はこの10年以上，やや閉塞感があったが，FOLFIRINOXが登場し，さらには近い将来使用できる可能性のあるナブパクリタキセル[21]も期待されるレジメンであり，これらを踏まえてまた新たな展開期に入ったと思われる．

おわりに

我が国における膵癌による死亡者数は平成25年に30672人と，ついに3万人を突破し肝臓癌を抜いて癌死亡の第4位の順位となり，なお増加中である．膵癌は診断時に進行しており非切除例の割合が多いため治療には化学療法が重要であることは言うまでもない．膵癌の治療成績の向上のためには膵癌の早期発見と同じく，化学療法のさらなる発展が強く望まれる．

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The current status of FOLFIRINOX for unresectable pancreatic cancer

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Key words: FOLFIRINOX, Unresectable pancreatic cancer, Chemotherapy

For a long time, gemcitabine hydrochloride (GEM) had been used as standard care for unresectable pancreatic cancer. Subsequently, GEM plus erlotinib, and S-1 were added as other standard therapies in Japan, but there were no large differences in efficacy among these 3 regimens. FOLFIRINOX clearly showed superiority of survival over GEM by the randomized study that was conducted in France, and was rapidly added as a new option of standard care for the first line of unresectable pancreatic cancer. In Japan, a phase II study was conducted following the similar regimen, and since it showed favorable results, FOLFIRINOX was approved for treatment of unresectable pancreatic cancer in December 2013. FOLFIRINOX shows a good response rate, but it is composed of 4 drugs and has many adverse events. It should be used with intensive and prompt care to minimize side effects when compared with the other regimens. It is necessary for the physician to examine the eligibility of each individual case before practical use.

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Clinical Characteristics of Adenosquamous Carcinoma of the Pancreas

A Matched Case-Control Study

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Objectives: Adenosquamous carcinoma of the pancreas (ASC) is a variant of pancreatic ductal adenocarcinoma (PDAC), but the prognosis remains unclear. The purpose of this study was to clarify the prognosis of ASC using a matched case-control design.

Methods: We evaluated clinical characteristics of ASC treated between 2001 and 2011 in our institution. As controls, PDAC cases matched with ASC cases for sex, age, pretreatment Eastern Cooperative Oncology Group performance status, location, initial therapy and American Joint Committee on Cancer TNM staging for pancreatic cancer were also evaluated.

Results: Of the 914 cases of pancreatic neoplasm, 28 cases (3.06%) of ASC were identified, and 56 cases of PDAC were matched as controls. Median overall survival (OS) was significantly worse for ASC (8.38 months) than for PDAC (15.75 months; hazard ratio [HR], 1.94; 95% confidence interval, 1.07–3.51; $P = 0.026$). Of the 22 unresected cases, median OS was again significantly worse for ASC (4.67 months) than for PDAC (12.36 months; HR, 2.39; 95% confidence interval, 1.27–4.51; $P = 0.007$).

Conclusion: These results demonstrate that ASC is more aggressive than PDAC.

Key Words: adenosquamous carcinoma of the pancreas (ASC), pancreatic ductal adenocarcinoma (PDAC), endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA), matched case-control study, pancreatic cancer

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Pancreatic neoplasms may exhibit more than one line of cellular differentiation.[1–3] Adenosquamous carcinoma of the pancreas (ASC) is one such mixed neoplasm, exhibiting both glandular and squamous differentiation.[4–6] Herxheimer[7] reported the first case of ASC in 1907, but despite the accumulation of reports, most descriptions have been from case studies[8] and small surgical series.[9] Adenosquamous carcinoma of the pancreas has anecdotally been considered aggressive and has shown poor prognosis compared with pancreatic ductal adenocarcinoma (PDAC). However, as 2 recent population-based analyses reported,[10,11] whether ASC is actually more aggressive than PDAC remains unclear. Furthermore, many clinical trials have treated both PDAC and ASC equally. The purpose of this study was therefore to clarify the clinical features and prognosis of ASC using a matched case-control design.

MATERIALS AND METHODS

We evaluated the pathological and clinical records of ASC and PDAC treated in our institution between 2001 and 2011. All cases were diagnosed based on cytological or histological confirmation from a surgical specimen or endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA). Pathological diagnosis of ASC was made based on the following criteria for surgical and EUS-FNA specimens. In the surgical specimen, the tumor exhibits both glandular and squamous differentiation, with the squamous component accounting for at least 30% of the neoplasm.[4,5] In the EUS-FNA specimen, aspirate shows both glandular and squamous differentiation characterized by an infiltrating sheetlike arrangement of polygonal cells with keratinization, confirmed by cytological or histological examination (Fig. 1).[12] To distinguish between primary ASC and metastasis from another site,[13] patients with any history of squamous cell carcinoma or other cancers were excluded from this analysis.

The procedure for EUS-FNA has been described previously.[14] After the procedure, one slide was air-dried and examined immediately with a rapid staining method (Diff-Quik stain; International Reagents, Kobe, Japan) to verify adequacy of the specimen and provide a presumptive diagnosis, if possible. Multiple passes were made in each case to provide specimens for cytological studies with Papanicolaou stain. Samples were also exposed to 10% formalin and then processed as a tissue block for histopathological evaluation using hematoxylin-eosin staining.

As controls, PDAC cases matched in a 2:1 ratio to ASC cases for pretreatment Eastern Cooperative Oncology Group performance status (0–1 or ≥2), initial therapy and tumor staging were also included in this study. Data were abstracted from medical records by 2 reviewers (T.O. and T.O.) who were blinded to case-control status. Two reviewers independently assessed these data, and disagreements were resolved by discussion with a third reviewer (K.Y.). In surgical cases, tumor staging was made based on pathological findings. In unresectable cases, staging was made based on computed tomographic results. In both situations, staging was performed in accordance with the American Joint Committee on Cancer staging system for pancreatic cancer. Tumor response and lymph node status were determined according to the Response Evaluation Criteria in Solid Tumor.[15]

Statistical Analysis

All values represent mean ± standard deviation. Bivariate analysis was performed using the Student *t* test for continuous

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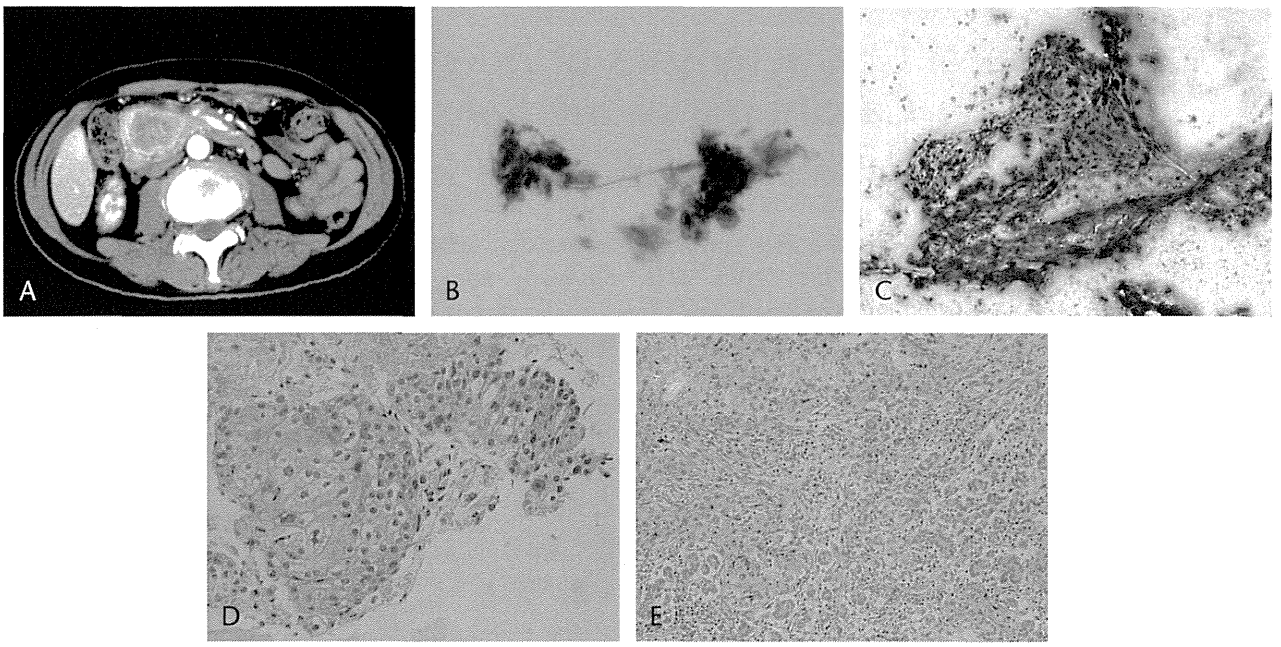

FIGURE 1. Representative images of ASC pathology. A, Computed tomography shows a large heterogeneous mass in the head of the pancreas. In the EUS-FNA specimen, aspirates show atypical keratinized cells with hyperchromatic nucleus and cytoplasmic orangeophilia (Papanicolaou stain, original magnification ×400; B), tissue fragments of neoplastic cells with cytoplasmic opacity and glandular differentiation against a necrotic background (Diff-Quik stain, original magnification ×200; C), and prominent squamous differentiation (hematoxylin and eosin stain, original magnification ×400; D). E, In the surgical specimen, both glandular and squamous differentiation are present (hematoxylin and eosin stain, original magnification ×200).

variables, and using the χ^2 test or the Fisher exact test for categorical variables. Survival was evaluated using the Kaplan-Meier method, and hazard ratios (HRs) were calculated using Cox proportional hazards model. $P < 0.05$ was considered statistically significant, and all P values are 2 sided. Data were analyzed using STATA version 11.1 statistical software (StataCorp, College Station, Tex).

RESULTS

First, we examined clinical characteristics of ASC based on our diagnostic criteria. Of the 914 cases of the pancreatic neoplasms treated between 2001 and 2011, a total of 28 cases (3.0%) of ASC were identified. Patients' characteristics are summarized in Table 1. Median age at diagnosis was 64.0 years (range, 44–79 years). The American Joint Committee on Cancer tumor staging was IIA in 5 patients (17.8%), IIB in 2 patients (7.1%), III in 5 (17.8%), and IV in 16 patients (57.1%). Adenosquamous carcinoma of the pancreas was slightly more common in the body-tail of the pancreas (57.1%). The initial treatment for ASC was curative resection in 6 patients, palliative chemotherapy using gemcitabine (Gem) in 16 cases, Gem plus S-1 in 1 case, 5-fluorouracil-based chemoradiotherapy in 1 case, S-1-based chemoradiotherapy in 1 case, and best supportive care in 3 cases. For the 6 cases of patients (21.4%) who underwent curative resection, pathological tumor staging was IIA in 4 cases and IIB in 2 cases. Three of these cases were located in the pancreatic head, and the others were in the pancreatic body-tail. Five of these cases showed no recurrence, with only 1 case showing recurrence 13.5 months postoperatively (median observation period, 36.6 months [range, 7–90.7 months]).

Next, we clarified the clinical features and prognosis of ASC using a matched case-control study. Characteristics of the control group in the matched case-control study are also shown in Table 1. Demographic and baseline disease characteristics of patients were similar in both ASC and PDAC groups. However, fewer measurable target lymph nodes metastases were seen in the ASC group than in the PDAC group (42.8% vs. 17.8%, $P = 0.014$). In the stage IV patients with ASC, the most common metastatic sites were the liver (81.2%) and lymph nodes (75%). In patients with PDAC, the most common sites were the same, but with different proportions (liver, 59.3%; and lymph nodes, 31.2%). Median duration of follow-up was 14.9 months (95% confidence interval [CI], 11.6–18.1). Median overall survival (OS) was 8.3 months (95% CI, 3.8–16.6 months) in the ASC group, compared to 15.7 months (95% CI, 12.3–32.7 months) in the PDAC group (HR for death, 1.94; 95% CI, 1.07–3.51) (Fig. 2). Overall survival rates at 6, 12, and 24 months were 53.3%, 38.7%, and 12.1%, respectively, in the ASC group compared with 86.9%, 65.3%, and 42.0%, respectively, in the PDAC group.

In unresected patients, the median OS was 4.6 months (95% CI, 3.8–11.8 months) in the ASC group and 12.3 months (95% CI, 8.9–16.0 months) in the PDAC group (HR for death, 2.39; 95% CI, 1.27–4.51) (Fig. 3). Overall survival rates at 6, 12, and 24 months were 43.2%, 24.7%, and 0.0%, respectively, in the ASC group, compared with 83.1%, 55.0%, and 26.9%, respectively, in the PDAC group. Among patients receiving either chemoradiotherapy or chemotherapy, the objective response rate was 10.5% in the ASC group and 13.5% in the PDAC group ($P = 1.000$). On the other hand, among patients receiving palliative chemotherapy using Gem, the objective response rate was 6.25% in the ASC group and 12.5% in the PDAC group ($P = 0.652$). In patients with stage IV disease, the median OS was 3.9 months (95% CI, 3.1–8.3 months) in the ASC group and 9.3 months (95% CI, 6.9–14.8 months) in the PDAC group (HR for death, 2.27; 95% CI, 1.07–4.83). In patients with liver

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TABLE 1. Patient Characteristics

	ASC (n = 28)	PDAC (n = 56)	*P*
ECOG performance status score, %			
0–1	27 (96.4)	54 (96.4)	
≥2	1 (3.5)	2 (3.5)	1.000
Initial treatment			
Curative resection	6	12	
Chemoradiation	2	4	
Gem	16	32	
Gem+S-1	1	2	
BSC	3	6	1.000
Tumor stage (AJCC)			
IIA	5	10	
IIB	2	4	
III	5	10	
IV	16	32	1.000
Age, mean ± SD, yr	64.5 ± 9.1	63.8 ± 8.7	0.639
Sex, %			
Male	19 (67.8)	38 (67.8)	
Female	9 (32.1)	18 (32.1)	1.000
Location, %			
Head	12 (42.8)	24 (42.8)	
Body-Tail	16 (57.1)	32 (57.1)	1.000
Measurable metastatic sites, %			
Liver	13 (46.4)	19 (33.9)	0.266
Lymph node	12 (42.8)	10 (17.8)	0.014
Lung	1 (3.5)	6 (10.7)	0.416
Peritoneal	5 (17.8)	12 (21.4)	0.780
Size, mean ± SD, mm	40.6 ± 13.6	35.1 ± 16.3	0.929

BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; GEM, gemcitabine; SD, standard deviation.

metastasis, the median OS was 3.9 months (95% CI, 2.4–8.3 months) in the ASC group and 10.4 months (95% CI, 7.4–14.8 months) in the PDAC group (HR for death, 3.03; 95% CI, 1.26–7.28).

DISCUSSION

Adenosquamous carcinoma of the pancreas is a variant of PDAC that accounts for 3% to 4% of malignant neoplasms of the pancreas.[16–18] Adenosquamous carcinoma of the pancreas has been considered to show poor prognosis owing to its aggressive behavior,[19–21] but the clinical features of ASC have been based primarily on case studies[8] and small surgical series with early-stage cancers.[9] Thus, whether ASC is actually more aggressive than PDAC has remained controversial. Two population-based analyses of ASC have recently been reported.[10,11] Boyd et al[10] described OS after surgical resection of ASC as significantly worse compared to that after resection of PDAC. On the other hand, Katz et al[11] reported that median OS for ASC was 4 months, similar to that for PDAC. They also mentioned that treatment of patients with ASC by surgical resection was associated with a favorable prognosis.[11] These reports about the prognosis of ASC have shown several problems. One is the prejudiced staging of disease. Although ASC has been regarded as a more progressive malignancy, reports have mainly mentioned locoregional disease, not metastatic disease. The other drawback is a

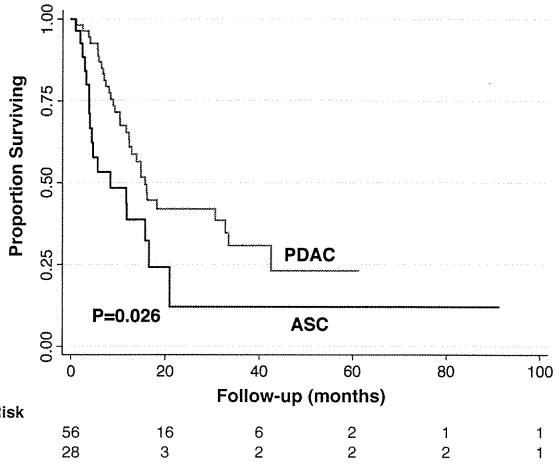

FIGURE 2. Kaplan-Meier curve comparing ASC with PDAC. Kaplan-Meier estimates show overall survival, with median values of 8.3 months in the ASC group and 15.7 months in the PDAC group.

lack of specific information about treatment. Based on registry data, they did not mention detailed palliative treatments in unresectable cases. This information seems essential to clarify the real clinical characteristics and behaviors of ASC. This study therefore examined the clinical characteristics and prognosis of ASC in a matched case-control study.

The present study examined the clinical characteristics and prognosis of ASC. Among all pancreatic neoplasms, 28 cases (3.06%) of ASC were identified. Adenosquamous carcinoma of the pancreas predominantly affected males (67.8%), and the mean age at diagnosis was 64.5 years. These findings resemble the results from other reports for ASC[17,22] and shared clinical characteristics with conventional PDAC. On the other hand, our matched case-control study showed that ASC metastasizes to lymph nodes more frequently than PDAC. Although the difference was not significant, tumors also tended to be larger in ASC than PDAC. Boyd et al[10] reported in a population-based analysis that ASC was more likely to be larger and node

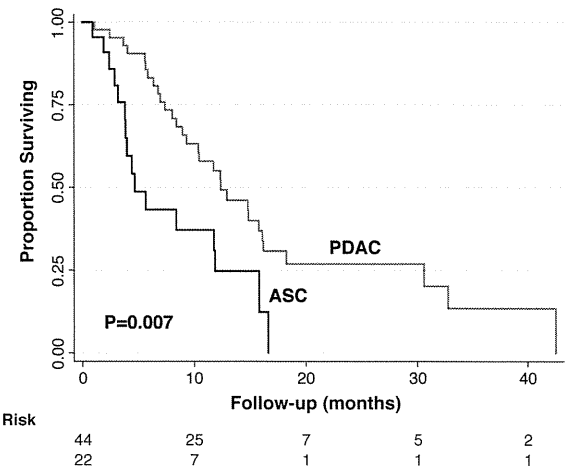

FIGURE 3. Kaplan-Meier curve comparing ASC with PDAC in unresected patients. Kaplan-Meier estimates show overall survival, with median values of 4.6 months in the ASC group and 12.3 months in the PDAC group.

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positive compared with PDAC. Results from our matched case-control study support their findings. Because we used cancer stage as a matching valuable, we could not examine the frequency of distant metastases in patients with ASC compared with PDAC. However, ASC being more likely to be larger and node-positive may indicate more aggressive behavior of ASC compared with PDAC.

Our results clearly show that ASC was more progressive than conventional PDAC. The median OS was significantly worse for ASC (8.38 months) than for PDAC (15.75 months). Of the 22 unresected cases, OS was significantly worse for ASC than for PDAC, with an HR of 2.39 (95% CI, 1.27–4.51; $P = 0.007$; median, 4.67 months vs 12.36 months). This seems attributable to the aggressive behavior of ASC. As previously mentioned, ASC tends to metastasize to lymph nodes more frequently than PDAC, even within the same cancer stage. Furthermore, in patients with stage IV disease, simultaneous metastases to the liver and lymph nodes were seen more frequently in the ASC group (43.7%) than in the PDAC group (3.1%, $P = 0.001$). This aggressiveness may contribute to the poor prognosis. We suppose that stronger chemotherapy is one promising option for patients with ASC. In this study, Gem was the most frequently administered agent as palliative chemotherapy. However, Gem shows modest survival benefit in patients with pancreatic cancer. Other newer combination chemotherapeutic regimens, such as GEM+erlotinib[23] and FOLFIRINOX,[24] may thus offer promising therapies for ASC.

In summary, we investigated the clinical characteristics and prognosis of ASC using a matched case-control study. The present results show that ASC was more progressive than conventional PDAC. Conversely, in resectable cases, surgical resection can provide a better prognosis for these patients.

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OPEN

Natural History of Branch Duct Intraductal Papillary Mucinous Neoplasm With Mural Nodules

A Japan Pancreas Society Multicenter Study

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Objective: This study aimed to elucidate the natural history of intraductal papillary mucinous neoplasm (IPMN) of the pancreas with mural nodules (MNs) in branch duct IPMN (BD-IPMN).

Methods: Among the 402 registered patients with BD-IPMN on long-term follow-up at 10 institutions in Japan, 53 patients with MNs of less than 10 mm in height detected by endosonography were included in this study. The morphological changes of the BD-IPMN in these patients and histologic findings of the resected specimen were investigated.

Results: The median height of the MNs at the initial diagnosis was 3 mm (range, 1–8 mm), and 12 (23%) of the 53 patients showed an increase in the height of the MNs during follow-up (mean duration, 42 months). Six patients underwent surgery because of an increase in the height of MNs, yielding high-grade dysplasia in 1 patient and low-grade dysplasia in 5 patients. No patients developed invasive carcinoma derived from IPMN, and distinct pancreatic ductal adenocarcinoma developed in 1 (2%) patient. The incidence of the development of malignancy in BD-IPMNs, including distinct pancreatic ductal adenocarcinoma, was similar to that of those without MNs.

Conclusions: In patients who have BD-IPMN with MNs of less than 10 mm in height, observation instead of immediate resection is considered to be possible.

Key Words: intraductal papillary mucinous neoplasm, natural history, follow-up, endoscopic ultrasonography, pancreatic ductal adenocarcinoma

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The authors declare no conflict of interest.

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Abbreviations: BD-IPMN - branch duct intraductal papillary mucinous neoplasm, CT - computed tomography, ERCP - endoscopic retrograde cholangiopancreatography, EUS - endoscopic ultrasonography, IPMN - intraductal papillary mucinous neoplasm, MD-IPMN - main duct intraductal papillary mucinous neoplasm, MN - mural nodule, MPD - main pancreatic duct, MRCP - magnetic resonance cholangiopancreatography, PDAC - pancreatic ductal adenocarcinoma, US - ultrasonography

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According to the international consensus guidelines 2012[1] for the management of intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms of the pancreas, main duct IPMN (MD-IPMN) and branch duct IPMN (BD-IPMN) are significantly different with regard to the prevalence of carcinoma, and therefore, the classification has prognostic implications. When MD-IPMN is diagnosed in a patient, surgical treatment should be considered. In BD-IPMN, however, it is important to differentiate low-grade dysplasia from high-grade dysplasia (carcinoma in situ) or ordinary invasive pancreatic ductal adenocarcinoma (PDAC) to avoid excessive surgery.

The presence of mural nodules (MNs) has reportedly been the most important factor for predicting malignancy and determining the indication for surgery of BD-IPMN. However, there is a paucity of data on the morphological and histologic changes in patients with BD-IPMN with MNs during follow-up. The aim of this study was to evaluate long-term follow-up results of patients with BD-IPMN who had MNs on initial imaging in a retrospective multicenter series for better management of patients with BD-IPMN.

MATERIALS AND METHODS

Patients

The working group of the Japan Pancreas Society for the investigation of the natural history of IPMN,[2] 5 university hospitals and 5 tertiary referral institutions, collected information on 417 follow-up patients for more than 1 year who had undergone endoscopic ultrasonography (EUS) at the time of initial diagnosis during the period from November 1993 to February 2008. Those patients who had been followed up due to an inoperable PDAC derived from IPMN were excluded.

The indications for follow-up were based on the suggestions described in the international consensus guidelines 2006[3]; these are as follows: BD-IPMNs with no symptoms such as abdominal pain, jaundice, or pancreatitis, MNs of less than 10 mm in height, cyst size of less than 3 cm, and main pancreatic duct (MPD) dilation of less than 10 mm. Ten patients with an initial

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cyst size of 3 cm and 5 patients with that of more than 3 cm were included.

Among the 417 follow-up patients, 15 were excluded from the analysis because they did not satisfy the inclusion criteria, which are as follows: follow-up periods of less than 1 year in 4 patients, MPD dilation of more than 10 mm in 5 patients, histologically diagnosed as non-IPMN in 3 patients, MN height of more than 10 mm in 1 patient, and incomplete data in 2 patients. Accordingly, 402 patients with BD-IPMN without MNs of 10 mm or greater in height on EUS at the time of initial diagnosis who had been followed up by several surveillance imagings for 1 year or more were eligible for this study.[2] Finally, a total of 53 patients with BD-IPMN with MNs of less than 10 mm in height who underwent EUS, ultrasonography (US), and/or computed tomography (CT) at least twice, including the initial EUS during follow-up, were included.

Definitions

A diagnosis of IPMN was made by imaging when a dilated MPD or a cystically dilated branch duct was recognized in association with secretion of mucin from the major or minor papilla or mobile filling defects in the pancreatic duct on endoscopic retrograde cholangiopancreatography (ERCP) or when multilocular cystic lesions were recognized on EUS, magnetic resonance cholangiopancreatography (MRCP), and/or CT. Branch duct IPMN was defined as a condition in which the main lesion was a cystically dilated branch duct with an MPD diameter of less than 10 mm. The size of the dilated branch duct was measured en bloc in patients with multilocular cysts. The presence or absence of MNs in cystic branches was determined based on morphological features on EUS at the initial diagnosis. Color Doppler imaging or contrast-enhanced EUS was not applied in most of the cases because of the dominant use of a mechanical radial scanner. The change in the height of MNs was assessed essentially by follow-up EUS at registration, as available. In patients who underwent surgery after follow-up, the diagnosis of IPMN was confirmed histologically. Pathologic results were determined by the World Health Organization criteria published in 2010[4]; these are as follows: low-grade dysplasia ("intraductal papillary mucinous adenoma"), intermediate-grade dysplasia ("IPMN with moderate dysplasia"), high-grade dysplasia ("intraductal papillary mucinous carcinoma, noninvasive," "carcinoma in situ"), and PDAC. The highest pathologic grade was adapted when there were multifocal lesions.

Pancreatic ductal adenocarcinoma was divided into 2 types, as reported by Yamaguchi et al,[5] 1 derived from IPMN ("IPMN with an associated invasive carcinoma") showing a histologic transition between IPMN and invasive carcinoma and the other concomitant with IPMN in which invasive carcinoma developed at a site in the pancreas different from that of the IPMN, according to the radiologic images and macroscopic or microscopic findings.

Methods

In patients with evident MNs in the cystic lumen, the height of the most prominent MNs was measured by EUS. During the follow-up period, strict monitoring of BD-IPMNs was performed by EUS, US, MRCP, and/or CT at intervals of 3 to 6 months. The modality used for the monitoring of BD-IPMNs was at the discretion of each institution and on a case-by-case basis, not following a unified protocol.

The maximum diameter of cystically dilated branch ducts and MPDs was measured by EUS in combination with US, CT, and/or MRCP, as available. Morphological findings at the initial examination, including the height of MNs, size of cystic branch, diameter of MPD, and presence of multifocal lesions, were collected. The frequency of enlargement of the cystically dilated branch, progression of MPD dilation, and an increase in the height of MNs were investigated using the follow-up data. Then, the characteristics of patients with BD-IPMN showing an increase in the height of MNs during follow-up were evaluated and compared with those patients without such an increase. In patients who had undergone surgery with morphological progression during follow-up, histologic findings of the resected specimens were evaluated, and the incidence and background of the development of invasive carcinoma associated with those lesions during follow-up were investigated.

These characteristics and morphological changes in the patients with IPMN with MNs were compared with those of the patients who did not show MNs on EUS at the time of initial diagnosis. The incidences of the development of PDAC derived from IPMN and PDAC concomitant with IPMN during follow-up were compared as well. Furthermore, the factors predictive of PDAC concomitant with IPMN were investigated.

Statistical Analysis

The average age, maximum size of cystic branch, maximum diameter of the MPD, and maximum height of MNs at the initial examination were compared using Student t test. The differences in the incidence of sex, enlargement of cystic branch, progression of MPD dilation, progression of MNs height, and multifocal lesions were examined with the χ^2 test or Fisher exact test. P value of less than 0.05 was considered significant. The predictive factors for PDAC concomitant with IPMN were investigated by univariate analysis. The calculations were carried out using SPSS II for Windows (release 16.0; SPSS, Chicago, Ill).

RESULTS

Follow-up Results

The mean follow-up period of the 53 patients with BD-IPMN with MNs was 42.4 (SD, 22.2) months (range, 12–196 months). There were 28 men and 25 women, with a mean age of 66.1 (SD, 8.1) years (range, 44–83 years).

At the time of the initial diagnosis, all 53 patients underwent EUS. Computed tomography, US, MRCP, and ERCP were also carried out in 32, 30, 26, and 40 patients, respectively. At registration, EUS, CT, US, MRCP, and ERCP were carried out in 43, 25, 15, 27, and 20 patients, respectively. The mean height of MNs among the 53 patients at the start of follow-up was 3.2 (SD, 1.6) mm (median, 3 mm; range, 1–8 mm), and MN heights of less than 5 mm and those 5 to 10 mm were found in 41 (77.4%) patients and 12 (22.6%) patients, respectively. The mean maximum size of the cystically dilated branch and the mean diameter of the MPD were 2.2 (SD, 0.9) cm (range, 0.8–4.2 cm) and 3.9 (SD, 1.4) mm (range, 1–9 mm), respectively. The cystically dilated branch with the main MN was located in the head of the pancreas in 32 patients, in the body in 16 patients, and in the tail in 5 patients. Ten patients underwent surgery because of an increase in the height of the MNs (n = 6), enlargement of the dilated branches (n = 1), development of concomitant PDAC (n = 1), emergence of symptoms (n = 1), and patient's request (n = 1).

Changes in the Size of Cystic Branches

During follow-up, enlargement of the cystic branch was identified in 4 (7.5%) of the 53 patients, none of whom showed an increase in the size of the MNs (Fig. 1). One patient, a 68-year-old

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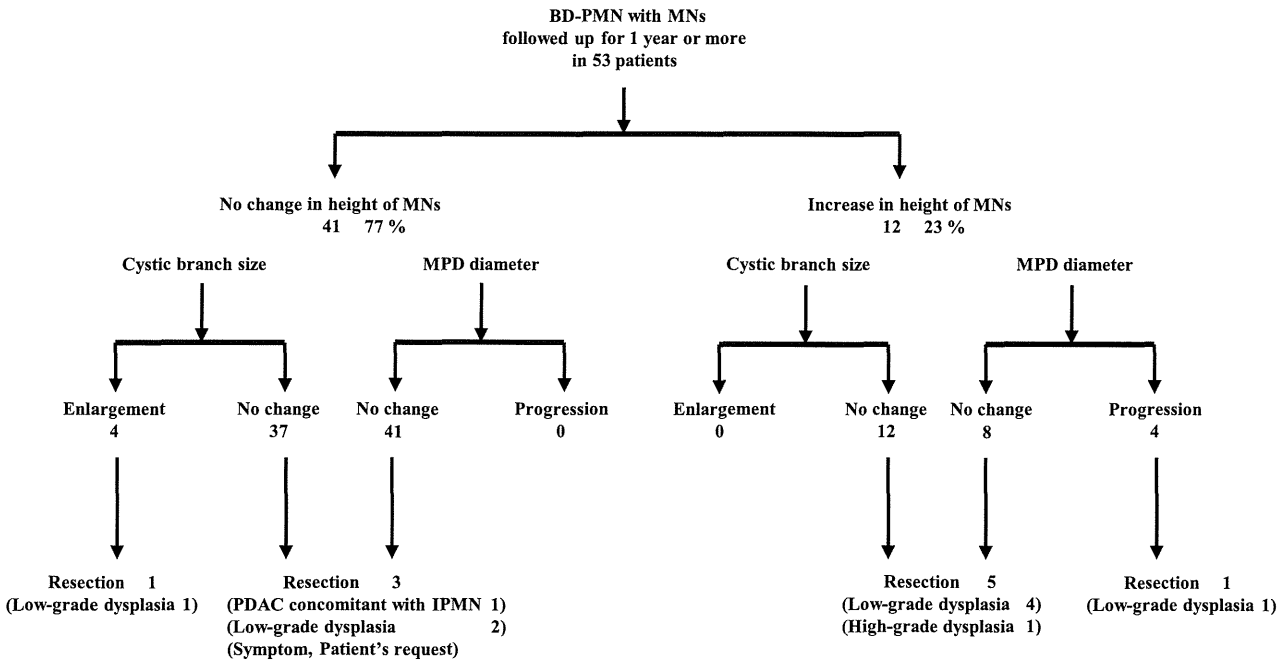

FIGURE 1. Changes in MNs, cyst size, and MPD diameter during follow-up.

man, underwent surgery because of an increase in the size of the cystic branch from 3 to 4.5 cm in 37 months, whereas the height of MN (3 mm) remained unchanged during follow-up. The histologic examination of the resected specimen verified low-grade dysplasia.

Changes in the Size of MPD

Of the 53 patients, 4 (8%) showed progression of MPD dilation during the follow-up (Fig. 1). All of these 4 patients exhibited an increase in the size of the MNs as well; these are as follows: from 3 to 6 mm, from 8 to 13 mm, from 4 to 8 mm, and from 5 to 8 mm, respectively. One patient underwent resection, leading to a pathologic diagnosis of low-grade dysplasia (patient 7; Table 1). The other patients are now under follow-up.

Changes in the Height of MNs

Of the 53 patients, 12 (23%) showed an increase in the height of the MNs during follow-up (Fig. 1). In those 12 patients, the mean size of the cystic branch, the mean diameter of the MPD, and the mean height of the MNs at the initial examination were not significantly different from those in the group without an increase in the size of the MNs during follow-up (Table 2). Furthermore, none of these 12 patients showed an enlargement of the cystic branch during follow-up. The frequency of progression of MPD dilatation during follow-up was significantly higher in the group with an increase in the height of MNs than those in the group without (33% vs 0%, $P = 0.002$). Furthermore, there was no significant difference in the frequency of enlargement of cystic branch between the groups (0% vs 10%, $P = 0.35$).

TABLE 1. Patients With BD-IPMN Showing an Increase in Height of MNs During Follow-up (n = 12)

Patient no	Age, y	Sex	Follow-up, mo	MN Size, mm	Progression of MPD Dilation, mm	Enlargement of Cystic Branch	Resection	Histologic Findings
1	58	F	60	1 → 4	—	—	−	—
2	76	F	40	1 → 5	—	—	−	—
3	74	F	32	3 → 8	—	—	−	—
4	69	F	60	3 → 6	5 → 7	—	−	—
5	75	M	74	8 → 13	6 → 12	—	−	—
6	75	M	67	4 → 8	4 → 9	—	−	—
7	61	F	82	5 → 8	6 → 10	—	+	Low-grade dysplasia
8	56	F	24	3 → 5	—	—	+	Low-grade dysplasia
9	54	M	15	1 → 3	—	—	+	Low-grade dysplasia
10	63	M	26	7 → 13	—	—	+	Low-grade dysplasia
11	60	M	91	5 → 10	—	—	+	Low-grade dysplasia
12	72	M	71	6 → 13	—	—	+	High-grade dysplasia

F indicates female; M, male.

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TABLE 2. Comparison of Characteristics Between the Patients With BD-IPMN With and Without an Increase in Height of MNs During Follow-up (n = 53)

	Height of MNs		
	Increased	No Change	
	n = 12 (23%)	n = 41 (77%)	*P*
Mean (SD) age, y	66.1 (8.3)	66.1 (8.2)	0.99
Sex (male/female)	7/5	21/20	0.66
Initial average (SD) size of cystic branch, cm	2.6 (1.0)	2.1 (0.8)	0.07
Initial average (SD) diameter of MPD, mm	4.3 (1.50)	3.8 (1.4)	0.29
Initial average (SD) height of MNs, mm	3.9 (2.4)	3.0 (1.4)	0.24
Enlargement of cystic branch	0	4 (10%)	0.35
Progression of MPD dilation	4 (33%)	0	<0.01 (0.002)
High-grade dysplasia	1 (8%)	0	
Invasive carcinoma derived from IPMN	0	0	
Invasive carcinoma concomitant with IPMN	0	1 (2%)	

Six of the 12 patients showing an increase in the height of MNs underwent surgery. Histologic examination of the resected specimens verified high-grade dysplasia in 1 patient and low-grade dysplasia in 5 patients. None of them showed development of PDAC (Table 1). Among the 6 other patients who did not undergo surgery, 1 patient with MNs of 13 mm in height refused surgery and the remaining 5 patients who had MNs of less than 10 mm in height are under follow-up.

Of the 41 patients without an increase in the height of MNs, 4 underwent surgery, 1 of whom had a new appearance of a solid mass in a different portion in the pancreas. Histologic examination of the resected specimen revealed the mass to be a PDAC concomitant with IPMN and the IPMN itself was a low-grade dysplasia (Fig. 1). In the remaining 3 patients, pathologic diagnosis was all low-grade dysplasia.

Development of Malignancy Among Surgical Cases

To summarize the 10 surgical cases, 1 (2%) patient developed PDAC concomitant with IPMN without enlargement of the cystic branch, an increase in the height of MNs, or progression of MPD dilation.

In the remaining 9 patients, 1 (2%) had high-grade dysplasia and the others had low-grade dysplasia. The patient with high-grade dysplasia showed an increase in the height of the MNs from 6 to 13 mm in 71 months without enlargement of the cystic branch or progression of MPD dilation (Fig. 1).

Comparison of Morphological Changes and Histologic Findings Between Patients With BD-IPMN With and Without MNs

Size of Cystic Branches

The comparison of morphological changes and histologic findings between patients with BD-IPMN with and without MNs is shown in Table 3. At the time of the initial diagnosis, the mean maximum size of the cystically dilated branch in the patients with and without the MNs was 2.2 (SD, 0.9) cm and 2.0 (SD, 0.9) cm, respectively. There was no significant difference between the 2 groups ($P = 0.28$). Furthermore, there was no significant difference in the incidence of enlargement of cystic branch during follow-up between the groups (8% vs 9%, $P = 0.47$).

Diameter of MPD

The initial diameter of the MPD in the patients with MNs was significantly greater than that in those without (3.9 [SD, 1.4] mm vs 3.3 [SD, 1.3] mm, $P = 0.001$). On the other hand, there was no significant difference in the frequency of progression of MPD dilation during follow-up between the groups (8% vs 7%, $P = 0.52$).

Development of Malignancy

The number of patients who underwent surgery in each group with and without MNs was 10 of the 53 patients and 29

TABLE 3. Comparison of BD-IPMNs With and Without MNs by EUS at the Initial Examination (n = 402)

MNs by Initial EUS	Present (n = 53)	Absent (n = 349)	*P*
Mean (SD) age, y	66.1 (8.1)	65.7 (10.0)	0.79
Sex (male/female)	28/25	178/171	0.80
Initial average (SD) size of cystic branch, cm	21.7 (8.8)	20.2 (9.3)	0.28
Initial average (SD) diameter of MPD, mm	3.9 (1.4)	3.3 (1.3)	<0.01 (0.001)
Enlargement of cystic branch	4 (8%)	32 (9%)	0.47
Progression of MPD dilation	4 (8%)	24 (7%)	<0.01 (0.002)
High-grade dysplasia	1 (2%)	8 (2%)	0.66
Invasive carcinoma derived from IPMN	0	1 (0.3%)	0.87
Invasive carcinoma concomitant with IPMN	0	1 (2%)	0.72

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TABLE 4. Risk Factors of PDAC Concomitant With IPMN During Follow-up by Univariate Analysis n = 402

	PDAC Concomitant With IPMN (n = 8)	Others (n = 394)	*P*
Mean (SD) age, y	69.0 (6.6)	65.7 (9.8)	0.34
Sex (male/female)	5/3	201/193	0.39
Presence of MNs	1 (13%)	52 (13%)	0.72
Initial average (SD) size of cystic branch, cm	2.0 (1.2)	2.0 (0.9)	0.81
Initial average (SD) diameter of MPD, mm	3.4 (7.4)	3.4 (1.3)	0.97
Initial average (SD) height of MNs, mm	0.3 (0.7)	0.4 (1.3)	0.69
Enlargement of cystic branch	0	36 (9%)	0.47
Progression of MPD dilation	1 (13%)	27 (7%)	0.44
Increase in height of MNs	0	38 (10%)	0.45
Multifocal lesions	2 (25%)	129 (33%)	0.49

of the 349 patients, respectively. Among the 53 patients with MNs, the PDAC derived from IPMN developed in 0 patient, the PDAC concomitant with IPMN in 1 (1.9%) patient, and high-grade dysplasia in 1 (1.9%) patient. The corresponding numbers in the group without MNs including 3 patients with unresected PDAC concomitant with IPMN were 1 (0.3%), 7 (2.0%), and 8 (2.3%). There were no significant differences in the development of malignancy—high-grade dysplasia ($P = 0.66$), PDAC derived from IPMN ($P = 0.87$), and PDAC concomitant with IPMN ($P = 0.72$)—between the 2 groups.

Factors Predictive of Development of Malignancy in BD-IPMNs During Follow-up

One patient with PDAC derived from IPMN did not show the emergence of MNs, enlargement of cystic branch, increase in the height of MNs, or multifocal lesions. However, MPD dilation progressed during the follow-up. In other patients with BD-IPMN without PDAC derived from IPMN, the frequency of progression of MPD dilation was 7%.

The factors predictive of PDAC concomitant with IPMN in the follow-up patients were investigated by univariate analysis. There was no significant difference in each morphological feature between the patients with PDAC concomitant with IPMN and those without (Table 4).

DISCUSSION

The international consensus guidelines recommend that patients with BD-IPMNs who have MNs should basically consider surgery if clinically appropriate. The subjects of the present study, however, were patients who had been observed because the height of MNs was less than 10 mm. In these patients, strict monitoring of BD-IPMNs had been performed at short intervals, which enabled investigation of the natural history of BD-IPMNs with MNs of less than 10 mm in height. Among these patients, 23% showed an increase in the height of the MNs during follow-up for over 40 months. In this group, there were no patients who showed enlargement of the cystic branch; however, all 4 patients who showed progression of MPD dilation exhibited an increase in the size of the MNs. The frequency of progression of MPD dilatation during follow-up was significantly higher in the group with an increase in the height of MNs than in the group without.

In the follow-up patients who had BD-IPMN with MNs, none developed PDAC derived from IPMN. The incidence of the development of malignancy in BD-IPMNs including a distinct PDAC was similar to that of those without MNs reported in the literature. Therefore, in those who have a BD-IPMN with MNs of less than 10 mm in height, observation instead of immediate resection is considered to be possible.

It is well known that IPMNs are characterized by slow progression and a favorable prognosis in contrast to ordinary PDAC, which is recognized as being very invasive.[6–11] Histologic studies of resected IPMNs have revealed that most IPMNs are dysplasia without parenchymal invasion such as high-grade dysplasia (carcinoma in situ), intermediate-grade dysplasia (borderline, moderate dysplasia), and low-grade dysplasia.[4] On the other hand, the presence of PDAC derived from IPMN showing parenchymal invasion has also been recognized, colloid carcinoma and tubular adenocarcinoma being its predominant histologic cell types. Therefore, the indications for surgery and determination of operative procedures based on the biologic behavior of this tumor are currently of great concern.

There are 2 opinions as to the indications for surgery in IPMN. One is that all patients with IPMN, including those with low-grade dysplasia, should undergo resection. This idea is based on the possible existence of an adenoma-carcinoma sequence in the evolution of this type of neoplasm and is also supported by the observations of oncogene activation. Yanagisawa et al[12] reported that the same point mutation was detected both in the area of carcinoma and in coexisting adenoma components. Furthermore, duct-ectatic mucinous cystic neoplasms accompany K-*ras* point mutation similar to typical exocrine pancreatic carcinomas.

On the other hand, with the increase in clinical knowledge on the progression of IPMNs, the demand for establishing surgical indications that take the biologic behavior of such neoplasms into consideration is increasing.[13–16] There are some groups who recommend surgery only in cases of high-grade dysplasia or invasive carcinoma, avoiding excessive surgery for benign conditions.

Main duct IPMN and BD-IPMN are significantly different with regard to the prevalence of carcinoma,[13–16] and therefore, the classification has prognostic implications. In the review by Tanaka et al,[1] the frequency of invasive carcinoma in MD-IPMN and in BD-IPMNs have a mean of 43% (range, 11%–81%) and 18% (range, 1%–37%), respectively.

According to the new international consensus guidelines 2012 for the management of IPMNs,[1] when MD-IPMN is diagnosed in a patient with an IPMN, surgical treatment is strongly recommended. In BD-IPMN, however, the likelihood of invasive carcinoma is substantially less compared with that in MD-IPMNs. Thus, the differentiation of low-grade dysplasia from high-grade dysplasia or PDAC derived from IPMN would enable us to avoid excessive surgery.

Among the subjects of the present study on BD-IPMN, surgical resection was indicated according mainly to the previous international guidelines 2006,[3] which are as follows: the

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appearance of symptoms attributable to IPMN (eg, pancreatitis), a cyst size greater than 30 mm, and dilation of the MPD (>6 mm).[16–19] The usefulness of the previous consensus criteria for resection has been validated by many reports.[20–24] According to the international consensus guidelines 2012, because a cyst size of more than 3 cm is a weaker indicator of malignancy than the presence of MNs and positive cytology, a BD-IPMN of more than 3 cm in size without MNs or positive cytology can be observed without immediate resection, particularly in elderly patients.

Some researchers consider the measurement of the maximum height of the MNs in BD-IPMNs to be effective for the differentiation between high-grade dysplasia and low-grade dysplasia and have suggested the height of the papillary protrusion of 3 to 10 mm as a cutoff value for determining the indication for surgical treatment.[25,26] In our retrospective study on the relationship between the height of MNs on EUS and histologic findings,[26] most patients in whom the maximum height of the MNs was more than 10 mm experienced high-grade dysplasia (86%). Furthermore, among those who underwent surgery due to the presence of MNs, no patients with MNs of 5 to10 mm in maximum height as shown by EUS developed PDAC derived from the BD-IPMN. Considering the biologic behavior of this neoplasm, performing surgery only in cases of BD-IPMN with a maximum height of MNs of more than 10 mm is likely to be justified.

Unfortunately, these retrospective studies entailed selection bias, that is, only patients with BD-IPMN who had been considered to have indications for surgery due to the presence of MNs and had undergone surgery were included. To verify the appropriateness of surgical indications based on the maximum height of MNs, a better understanding of the developmental course and the process of invasion in IPMN is necessary. The investigation of the morphological and histologic changes in patients with BD-IPMN who have undergone follow-up studies before resection is thus indispensable.

In 2011, the same working group of the Japan Pancreas Society[2] reported long-term follow-up results of 349 patients who had no MNs on EUS at initial diagnosis. The results showed that the PDAC derived from IPMN and the distinct PDAC developed in 0.3% of the patients and 2.0% of the patients, respectively. In contrast, among the patients with MNs in the present multicenter study, PDAC derived from IPMN and PDAC concomitant with IPMN developed in 0% of the patients and 2% of the patients, respectively; that is, the incidence of the development of invasive carcinoma in BD-IPMNs with MNs was similar to that of those without MNs.

As previously reported, there may possibly be 2 developmental patterns of PDAC derived from IPMN, 1 with an increase in the height of MNs of more than 10 mm[10] and the other at a site that is rather flat.[26] Therefore, periodical surveillance is mandatory in BD-IPMNs regardless of the presence/absence and height of MNs.

Concerning the histologic type, most of the patients with PDAC had tubular adenocarcinomas showing few papillary growths, whereas approximately 30% of the patients with PDAC derived from IPMN had colloid carcinomas with high papillary protrusions. Colloid carcinoma derived from intestinal type[27] is deemed to show more expansive and slower progression compared with other invasive carcinomas.[11] Therefore, PDAC derived from IPMN shows a different invasive behavior from ordinary PDAC. Yamaguchi et al[5] reported that the median survival time of 122 patients with PDAC derived from IPMN was 46 months, which was significantly longer than what was reported (12 months) in 7605 patients with ordinary PDAC.

Another problematic issue in patients with BD-IPMNs is that a distinct PDAC may develop in patients with IPMN, either synchronously or metachronously. Ohtsuka et al[28] reported that the incidence of synchronous and metachronous multifocal occurrence of IPMNs in the remnant pancreas during follow-up evaluation after pancreatectomy for IPMNs was 20% and that of distinct PDAC was 9.9%. Izawa et al[29] stated the possibility of multicentric development of cancer in IPMN, based on the observation that hyperplasia developed multifocally in different branch ducts with a different frequency of K-*ras* point mutation. In this study, we could not detect any significant predictive factors for the development of PDAC concomitant with IPMN.

The present study has several limitations. First, because of the retrospective nature of this study, the modality used for monitoring of BD-IPMN at intervals of 3 to 6 months was at the discretion of each institution, not following a unified protocol. Second, the presence of MNs was determined based solely on morphological features on EUS without color Doppler imaging, which may have resulted in inclusion of mucus nodules. However, the requirement in the inclusion criteria to have undergone EUS, US, and/or CT at least twice is thought to have minimized this risk. Third, the number of patients with MNs included in this study was not large because the presence of MNs is considered to be the most important factor for the surgical indication of BD-IPMN regardless of its height. However, the subjects were patients who had been followed up despite having MNs, and the number is the largest in the literature to date owing to multicenter cooperation. Fourth, patients with BD-IPMN who underwent surgery and histologic examination of resected specimens included not only patients showing an increase in the MN height to more than 10 mm but also those with no change or a change within 10 mm in height of MNs during follow-up. Furthermore, there is no way to investigate the incidence of high-grade dysplasia in the 43 patients who had not had surgical resection.

In summary, no PDAC derived from BD-IPMN developed in patients with MNs of less than 10 mm in height during follow-up for over 40 months. Furthermore, the incidence of the development of malignancy in BD-IPMNs including a distinct PDAC was similar to that of those without MNs. In patients who have BD-IPMN with MNs of less than 10 mm in height, observation instead of immediate resection is considered to be possible.

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特集II 胆膵癌の化学療法の最前線

局所進行膵癌に対する化学放射線療法および化学療法を中心とした治療成績*

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Key Words : locally advanced pancreatic cancer, chemotherapy, chemoradiotherapy, gemcitabine, S-1

はじめに

膵癌は代表的な難治癌であり，患者の多くが外科切除不能な状態で発見される．膵癌患者のうち約30%が画像診断で明らかな遠隔転移を伴わず，膵周囲への局所進展により外科的切除不能と判断されるが，これを局所進行膵癌と呼ぶ．局所因子による切除不能の定義に一定の見解はないが，本邦では上腸間膜動脈，腹腔動脈幹，肝動脈への進展を切除不能とする施設が多い．

局所進行膵癌の中には進行した状況になっても遠隔転移を認めず，膵周囲組織の障害により全身状態をきたす症例があり，遠隔転移を伴う膵癌とは生物学的な背景が異なる可能性が指摘されている[1]．反対に，局所進行膵癌の中には一定の割合で画像では同定できない，微小な腹膜播種や肝転移を有する高度進行膵癌が含まれている．このように局所進行膵癌と一括りにされているが，実際は多様な集団であることを認識して治療戦略を構築する必要がある．

局所進行膵癌に対する治療は遠隔転移を有する進行膵癌と異なり，明確なエビデンスの乏しい領域である．従来，局所治療である5-FU併用放射線療法が中心的な役割を果たしてきたが，塩酸ゲムシタビン(GEM)の登場以後，放射線療法の意義についてはcontroversialである．また，最近のトピックとして，化学療法や化学放射線療法の奏効例に対する外科切除の有用性について積極的な検討が行われている．

本稿では近年，発展の著しい局所進行膵癌に対する治療について概説し，今後の展望につき考察を行う．

局所進行膵癌に対する化学放射線療法

従来，過去の小規模な無作為化比較試験に基づき，局所進行膵癌に対する標準的治療は5-FU併用放射線療法とされてきた．しかし，本治療法のrationaleは5-FUの放射線増感作用を利用して放射線治療の局所効果を高めることにあり，5-FU自体の抗腫瘍効果は期待できない．患者の多くは遠隔転移再発をきたし，生存期間中央値は約10か月と十分なものではない．予後改善には局所的な効果のみでなく，十分な全身性作用を持った治療法の開発が不可欠と考えられる．近年，GEMやS-1などの有効な薬剤の登場により5-FU併用放射線療法に代わる新たな化学放射線療法の

* Chemotherapy and chemoradiotherapy for locally advanced pancreatic cancer.

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