ている術後再発リスク分類の表[46, 64]を示す（表3）．筋層浸潤が1/2以内（Ia-Ib期）でG1-2の低リスク群では再発率が低く，術後全骨盤照射の必要はない[45]．

Christopherら[48]のI期子宮体癌に対する最近の最も症例数の多い研究では，リンパ節転移のない子宮体癌Ia-c期に対する術後照射4,080例において，術後照射非施行群に比較し照射群は，Ic期Grade1と，Ic期Grade3，4で生存率が有意に改善した．

術後照射群と経過観察群に関する3つのランダム化比較試験のうち1つは1980年Aaldersら[49]が腟腔内照射例を対象に，腟腔内照射単独（A群）と腟腔内照射および外部照射（B群）のrandomized trialを施行し，腟および骨盤内再発を有意に減少させたが，5年生存率に差はなかったと報告した．最近の2つのランダム化比較試験（PORTEC trial，GOG99）でも，照射群は非照射群と比較し，骨盤内制御率は良好であるが累積生存率は改善しなかった[50-52]．Creutzbergら[50, 51]はPORTEC trial（Postoperative Radiation Therapy in Endometrial Carcinoma）で，I期60歳以下や，Grade2でも筋層浸潤が浅い症例は術後照射の適応ではないと述べている．

表3 子宮体癌の術後再発リスク分類

低リスク群
類内膜腺癌 G1あるいはG2で筋層浸潤1/2以内
頸部浸潤なし
腹腔細胞診陰性
脈管侵襲なし
遠隔転移なし
中リスク群
類内膜腺癌 G3で筋層浸潤1/2以内
類内膜腺癌で筋層浸潤1/2を超える
頸部浸潤あり
腹腔細胞診陽性
脈管侵襲あり
漿液性腺癌，明細胞腺癌あるいは未分化癌
遠隔転移なし
高リスク群
付属器・漿膜・基靭帯進展あり
腟壁浸潤あり
骨盤あるいは傍大動脈リンパ節転移あり
膀胱・直腸浸潤あり
腹腔内播種あり
遠隔転移あり

文献46, 64より引用一部改変

Keysら[52]はGOG99（Gynecologic Oncology Group）で，子宮体癌Ib-IIb期の中リスク症例で術後全骨盤照射を施行し，照射群は非照射群と比較し，生存率に有意差はなかったが，高—中リスク群において骨盤内再発率および累積生存率の改善が認められたと報告した．Straughnら[53]はIb期321例の術後経過観察のうち局所再発は9例のみ（5%）で全例放射線治療で救済されたとしている．宇田川ら[63]は手術単独群に比較し術後照射群は新III期がんで3年生存率が高い傾向にあったと報告している．Nelsonら[54]もIIIc期の術後照射で5年生存率72%の良好な成績を報告している．

分化度や筋層浸潤の深さなどから骨盤内再発のリスクと放射線療法の有害事象のリスクを考慮し，術後照射の適応を検討すべきであろう．一方，高リスク群を対象としたランダム化比較試験はいまだ報告がなく，さらに研究が必要である．

3）傍大動脈リンパ節照射

Calvinら[61]はII期全骨盤術後照射後の骨盤外再発のうち55%がPANであり，骨盤外再発のハイリスク症例に対するPANの予防照射または化学療法を検討すべきとしている．Nelsonら[62]もPEN転移陽性のIIIc期術後照射群から12%のPAN再発を認めており拡大照射野の必要性を示唆している．しかし，照射による晩期の合併症であるイレウスや腰椎圧迫骨折などの問題もあり検討が必要である．現在わが国では，PANに対する予防照射の適応に関するコンセンサスは得られていない．

4）照射方法

術後の予防照射は外部照射が主体である．腟断端再発の予防には腟内照射を行う．外部照射の照射野は全骨盤照射野とし，総線量は45～50Gy/4.5～5週とする．全骨盤照射による骨盤内制御は良好であるため，照射後は腟断端照射の追加は不要と考えられている．一方，Ic期でも骨盤リンパ節転移陰性の場合，腟内照射単独で十分という意見が多い[46]．腟内照射は腟内アプリケータ（主にオボイド）を用い，粘膜下5mmで低線量率では45～50Gy/3～4回，高線量率では24Gy/5回照射する．

5）化学療法

子宮体癌のハイリスク群の術後再発形式としては遠隔転移が多く，その予防には化学療法が重要となる．進行・再発子宮体癌に対する多剤併用化学療法のなかで現時点での標準療法はAP療法（ドキソルビシン，シスプラチン）である．しかし，ドキソルビシンは放射線との同時併用により粘膜反応を増強させるため，留意すべきである．術後補助療法についてはJGOGのアンケート結果[64]によれば，わが国ではTC療法（パクリタキセル，カルボプラチン）が広く用いられている．現在，適切な術後療法の検証のために，JGOG2043研究として，「子

宮体がん再発高危険群に対する術後化学療法としてのAP療法，DP（ドセタキセル，シスプラチン）療法，TC療法のランダム化第III相試験」を施行中である．

子宮体癌の術後療法として，放射線療法と化学療法のいずれを選択すべきかに関して，2005年のASCOでわが国より，JGOGが行った，中リスクを有する子宮内膜癌症例に対する全骨盤照射（WPI）とcisplatinを用いた化学療法（CAP）とのランダム化比較第III相試験（IGOG2033）の結果が報告された．WPI群とCAP群の5年無再発生存率（RFS）は84.0%，82.1%，5年粗生存率（OS）は85.9%，87.1%と各群に有意差はなかった．すなわち，術後補助療法として，CAP療法はWPIと同等の有用性があった．今後，有害事象についての長期経過観察結果も検討しながら，どの症例にどの術後補助療法を行うかを検討すべきであろう．

Randallら[2]は，GOG122で子宮体癌III，IV期の術後遺残（腫瘍径2cm以下）症例に，放射線療法（全腹部照射；WAI）をドキソルビシンとシスプラチンによる併用療法（AP）と比較した．AP群はWAI群に比較し，5年生存率は上回っていた（54% vs 43%）．しかし，全腹部照射はわが国で施行されることはまれで，APのプロトコール完遂率が低いなどよりこのエビデンスはわが国では推奨できない．次期のGOG184では照射野を限局した放射線療法（骨盤±PAN）に加えてパクリタキセルを導入した化学療法（AP vs TAP）の併用が進行中であることから，進行子宮体癌に対する放射線療法と化学療法の併用療法が重要になってくると考えられる．

5．標準的な治療成績

5．1　根治的照射

I期の5年生存率は50～100%，II期は26～100%，III期は0～37.1%，IV期は0～20%と，施設間にばらつきがある（表4）．欧米のデータはpacking法による低線量率腔内照射が主体であるが，近年高線量率腔内照射の報告[3][4]がある．手術例と比較すると高齢や他病死の影響で，早期でも良好とはいえないが，I期の無病生存率は最近の報告では79.6～100%と比較的良好である．腫瘍が子宮頸部へ進展するII期では子宮体部は腫瘍で充満し，CT/MRI画像なしでは腫瘍の形状に合わせた線量分布作成が困難となる[5]．腫瘍体積の大きい進行期の治療成績は不良である．患者背景，適応選択の基準の違いや腔内照射と外部照射の比率，照射線量などが異なるため施設間の比較は困難であるが，たとえ体癌であっても早期例であれば治癒の可能性が高く，最適な放射線治療手技の確立が重要である．また進行例においても放射線と手術や化学療法を併用する集学的治療が大切である[6]．

5．2　術後照射

わが国における術後照射の成績は日産婦婦人科腫瘍委員会による全国集計（1997年治療開始例）では，腺癌に関してI期82.1%，II期64.7%，III期58.8%であり，国立国際医療センター[7]，東京女子医大[8]では，I期65～83%，II期65～100%，III期53%，IV期50%と比較的良好である．

6．有害事象

6．1　急性期有害事象

子宮頸癌の放射線治療とほぼ同様で，食欲不振，宿酔，軟便，下痢，膀胱炎などが一般的な急性障害である．通常は対症的治療で対処可能で，高度な場合は照射を休止する．アプリケータ挿入時の子宮穿孔をCTなどで確認した場合は，ただちに腔内照射を中止し，抗生剤の投与で感染を予防する．一般に数日後には腔内照射は遂行可能である．

6．2　晩期有害事象

子宮頸癌の放射線治療とほぼ同様に膀胱・直腸・小腸・骨・下肢の合併症の他に，体癌では子宮底部の線量分布が広がることより，S状結腸の出血・狭窄の可能性がある．根治的放射線治療による晩期有害事象[9]の頻度はII度以上は欧米で2.8～18.4%[10][11]，わが国で8.6～33.3%[12][13]である．術後照射による晩期合併症の頻度は3.1～18.6%[14]である．

7．おわりに

わが国では子宮体癌に対する根治的放射線治療は子宮頸癌と異なり，いまだ確立された照射方法や照射手技はない．しかし，近年の子宮体癌の増加や，たとえ手術の技術が進歩しても，合併症のために手術不能な症例には症例数は少ないながら，放射線治療の必要性がある．

近年，照射技術の向上により子宮体癌に対する線量分布は改善され，また画像診断の進歩により病巣線量の評価も可能となっており，その治療成績の向上が期待されている．今後，子宮体癌においては基準点の線量評価法とアプリケータのさらなる改善が必要と考えられ，子宮体癌に対する最適放射線治療の確立にむけて努力すべきである．

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表4　子宮体癌の根治的放射線治療成績

M. Sklodowska-Curie Warszawa (Roustowski J, et al, 1981)[30]	1952～1971	488	Ⅰ(196) Ⅱ(74) Ⅲ(218)	EBRT＋LDR	Ⅰ 51.5% Ⅱ 50.0% Ⅲ 37.1%			
Mallinckrodt Institute of Radiology (Grigsby PW, et al, 1985, 1987)[31,32]	1960～1981	69	Ⅰ(69)	LDR±EBRT	76.80%		13%	膀胱Ⅱ度 2%，直腸Ⅱ-Ⅲ度 16.4%
	1960～1983	26	Ⅱ(26)	LDR±EBRT	48%	53%	L 7.7%，L＋D 26.7%，D 7.3%	直腸：S 状結腸：Ⅰ度 4%，Ⅱ度 15%
Univ. of North Carolina (Varia M, et al, 1987)[33]	1969～1980	73	Ⅰa(21) Ⅰb(20) Ⅱ(32)	LDR±EBRT		Ⅰ 57% (G1：72%，G2：59%，G3：31%) Ⅱ 26%	Ⅰ：39% Ⅱ：59%	大腸：Ⅲ度：4.1% 小腸：Ⅲ度：4.1% 尿管：Ⅲ度：1.4%
Centre Alexis Vautrin in Nancy (Taghian A, et al, 1988)[34]	1975～1984	104	Ⅰa(41) Ⅰb(38) Ⅱ(15) Ⅲ(4) Ⅳ(6)	LDR±EBRT	Ⅰ 65.7% Ⅱ 37.3% Total 51.6%	72.2% 56.2%	Ⅰa(2.4%) Ⅰb(10.5%) Ⅱ(6.7%) Ⅲ(25%) Ⅳ(33.3%)	17.30%
Montpellier Cancer Institute (Pourquier H, et al, 1990)[35]	1968～1978	116	T1a(12) T1b(58) T2(7) T3(38) T4(1)	EBRT＋LDR /HDR		T1a 50% T1b 54% T2 14% T3 34.2% T4 0% Total 44%	T1a(8.3%) T1b(22.4%) T2(57.1%) T3(36.8%) T4(100%) Total：28.4%	消化管＋膀胱Ⅱ-Ⅲ度：10.3%
Strahlenabteilung Univ (Rotte K, et al, 1990)[29]	1972～1988	227	Ⅰ(103) Ⅰ(109) Ⅲ(15)	HDR	79.6% 74.3% 33.3%			膀胱 1.7%，直腸 5.2%
M. D. Anderson Hospital (Kupelian PA, et al, 1993)[36]	1960～1986	152	Ⅰ(120) Ⅱ(17) Ⅲ～Ⅳ(15)	LDR±EBRT	55%	87% 88% 49%	Ⅰ(20.8%) Ⅱ(17.6%)	膀胱：Ⅱ度 0.7% 直腸：Ⅱ-Ⅲ度 1.3% 小腸Ⅱ度 2%，他Ⅲ度 1.3%
Univ. Massachusetts Medical School (Rose PG, et al, 1993)[37]	1974～1992	63	Ⅰa(13) Ⅰb(22) Ⅱ(22) Ⅲ(2) Ⅳ(4)	EBRT＋LDR	Ⅰa 60% Ⅰb 64.5% Ⅱ 34.7% Ⅲ 0% Ⅳ 0%			小腸：Ⅱ度 3.1% 直腸：Ⅱ-Ⅲ度 9.4%
Mallinckrodt Institute of Radiology (Chao CKS, et al, 1996)[38]	1965～1990	101	Ⅰ(101)	LDR±EBRT	66%	84%	L：3.0% D：5.9% L＋D：6.9%	膀胱：Ⅲ度 1.0% 直腸：Ⅲ度 2.0%，Ⅳ度 1.0%
Univ. of Vienna (Knocke TH,et al, 1997)[39]	1981～1992	280	ⅠA(116) ⅠB(119) Ⅱ(37) Ⅲ(8)	HDR	63.9% 47.3% 40.2%	84.9% 73.3% 68.6%	L：16% D：2.5% L＋D：2.1% LN：2.1%	膀胱：Ⅱ度 0.5%，Ⅲ/Ⅳ度 0.9% 直腸：Ⅱ度 2.8%，Ⅲ/Ⅳ度 0.4% 小腸：Ⅱ度 3.0%，Ⅲ/Ⅳ度 3.5% (5 年の時点)
東北大（小川・他，1989)[11]	1976～1988	35	Ⅰ(4) Ⅱ(6) Ⅲ(19) Ⅳ(6)	EBRT±HDR (3 例：EBRT 単独)	Ⅰ 75% Ⅱ 53.3% Ⅲ 44.9% Ⅳ 0%		Ⅰ L：0%，D：25% Ⅱ L：33.3% Ⅲ L：52.6%，D：15.8% Ⅳ L：66.7%	膀胱：Ⅱ度 2.9% 直腸：Ⅱ度 2.7% 小腸：Ⅱ度 2.9%
東京女子医大，放射線科（兼安・他，1994)[16]	1969～1990	15	Ⅰ(5) Ⅱ(4) Ⅲ(3) Ⅳa(3)	EBRT＋LDR	Ⅰ 100% Ⅱ 100% Ⅲ，Ⅳa 0% Total 59.3%		局所：7.7% 遠隔：23.1%	膀胱，直腸：Ⅱ-Ⅲ度 33.3%
放射線医学総合研究所（中野・他，1997)[17]	1962～1994	44	Ⅰ(5) Ⅱ(13) Ⅲ(12) Ⅳa(14)	EBRT＋LDR /HDR	Ⅰ 100% Ⅱ 30.8% Ⅲ 16.7% Ⅳ 0%		Ⅰ 0% Ⅱ 38.5% Ⅲ 75% Ⅳ 100%	
全国子宮体癌調査成第 1-3 報（日産婦子宮癌委員会，1980)[40]	1966～1976	183	(Ⅰ-Ⅳ：183)		Ⅰ G1：77.2%，G2：47.6%，G3：29.6% Ⅱ 50.2% Ⅲ 18%			
全国子宮体癌調査成第 4 報（日産婦子宮癌委員会，1999)[41]	1989～1990	40	不明		18.6%			
全国子宮体癌治療年報（日産婦婦人科腫瘍委員会，2009)[42]	1997	32（腺癌）	Ⅰ(11) Ⅱ(6) Ⅲ(10) Ⅳ(5) (Total：32)		Ⅰ 46% Ⅱ 0% Ⅲ 10% Ⅳ 20% (Total：22%)			
放射線医学総合研究所（大久保・他，2009)[28]	2002～2006	10	T1-2	EBRT±HDR (1 例：EBRT 単独)	90%	100%	0%	0%（直腸-S 状結腸 1 度：2 例，膀胱 1 度：1 例）

L: local recurrence, D: distant metastasis

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2 肺（体幹部定位照射）

永田 靖／木村智樹

セットアップ上の注意

1. 患者固定法について

現在，わが国で入手可能な体幹部定位放射線照射用固定具は，脱気型発砲スチロールの固定具を使用したものと真空密着型タイプの物である．近年，画像誘導装置の進歩で，治療中の患者体位固定について軽視する考え方もあるが，通常30分程度の照射時間中に体位保持の安楽さを確保するためにも，個別の固定具作成は必須であろう．

2. 呼吸の調整について

肺腫瘍においては，腫瘍の呼吸性移動を無視するわけにはゆかない．患者の呼吸移動に対応した照射法を大きく分けると，1）息止め法，2）呼吸制限法（腹部圧迫法），3）呼吸同期法，がある．これらのいずれかよって，腫瘍の呼吸性移動（IM）を縮小させる試みが体幹部定位放射線照射には不可欠である．1）息止め法とは，患者に音声や光による合図で呼吸を一時的に停止させて，その間に照射することをくり返す音声同期間歇照射法である．2）呼吸制限法は，板状の固定具やベルトを用いて季肋部を圧迫することによって，患者の大きな横隔膜の動きを抑制する．ただ，現実に肺癌で8～10 mm以上呼吸移動し，呼吸抑制を必要とするのは全患者の20～25％程度である．3）呼吸同期法は，患者に自由に呼吸をさせながらも，照射を呼吸位相（主に呼気相）に同期させるために開発された方法である．具体的には，患者の胸壁にセンサーを付着させたり，腫瘍内に金マーカーを刺入したりして患者呼吸を感知しながら照射する方法である．

Target入力上の注意

肺定位照射におけるGTVは，肺野条件のCT画像で確認できる体積である．CTVとはGTVの周辺に位置するがん細胞の微少な浸潤を含む体積であるが，孤立性肺腫瘍の場合はGTVと同一とされる．腫瘍の肋膜への連続性浸潤いわゆるpleural indentationについてはターゲットに含めるべきとされるが，炎症性変化との境界設定に苦慮する症例があるのも事実である．ITVとは呼吸や心拍動などによる病変の体内移動を含めた体積，PTVとは毎日の治療時における患者のベッド上での位置再現の誤差（セットアップマージン：SM）などを含めた体積である．CT撮像条件については上記の治療時の呼吸条件にあわせた撮像法で行うべきであるとされる．同期法や息止め法の場合はそれに準じてCTを撮像する．また呼吸抑制法の場合は，できるだけ照射時の条件に近似させる目的で4秒程度のスキャン時間をかけて1枚のスライス画像をゆっくり撮像する，いわゆるLong time scan CTないしSlow scan CT撮像法が用いられる．その他，深吸気位と深呼気位のCT画像を2回撮像してITVを決定する方法もある．近年，すべての患者呼吸位相を反映した四次元CT撮像法も普及しつつある．肺定位照射でLong time CTスキャン法を用いた場合，PTVマージンは腫瘍の軸方向周囲が5～10 mm，腫瘍の体軸方向は患者呼吸移動に応じて10～20 mm程度のマージンを設定し，かつ5 mm程度のリーフマージンを設定することが一般的である．

放射線治療計画

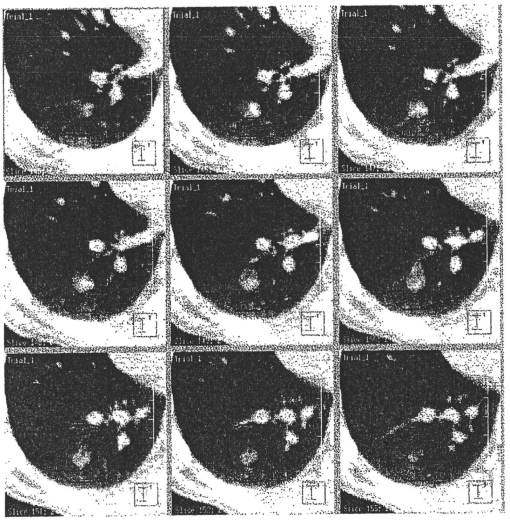
1. 治療計画について

体幹部定位照射においては，Beam's eye viewやRoom's eye viewなどの再構成三次元画像を用いることによって，照射方向や門数，放射線のエネルギーなどさまざまな要素を組み合わせて照射野を決定する．ノンコプラナー三次元固定多門照射法や多軌道回転原体照射（SMART）が用いられることも多い．通常6門以上の固定多門照射でも400°以上の回転照射でも，ほぼ類似した線量分布が実現可能である．筆者らは，固定多門照射を行う場合は，コプラナーから2～4門，ノンコプラナーから2～4門選択している．計画の目標値は，ターゲット内の線量の均一性（10％以内）と20 Gy以上照射肺容積（V20）の縮小（＜15％）である．むろん，フレームによる線量の減弱補正や，肺による不均質補正を行った三次元線量計算は必須である．また線量表記法についてはわが国では通常はアイソセンターを線量評価点とする場合が多いが，欧米では（80～90％）辺縁線量で表示される場合があるので注意を要する．

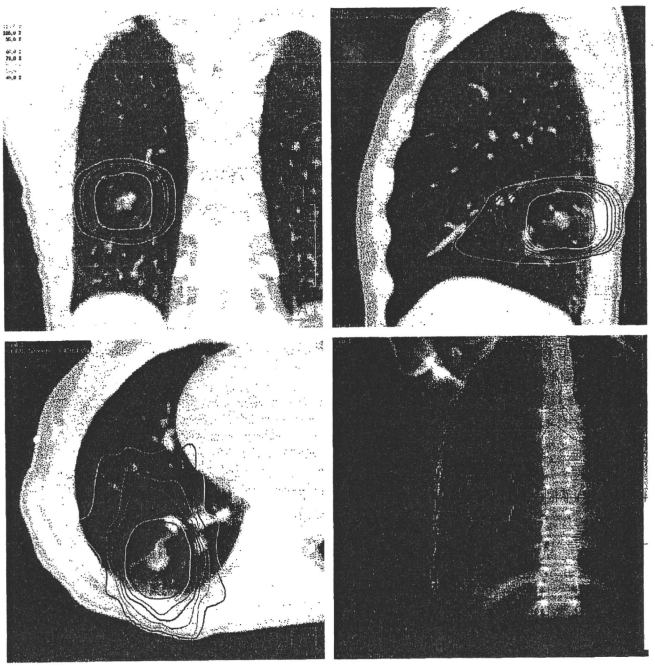
2. 治療前照合法について

放射線治療において毎回の照射前には，適切な部位に照射されるかどうかを高エネルギーX線画像やポータルビジョン，治療室内同室CTなどで照合画像を作成し確認する．特に定位放射線照射では，大線量小分割照射を行うために，毎回照射前の照合を行うことが不可欠である．以前は正面と側面のリニアックグラフィーを撮像して，治療計画時のシミュレーションフィルムとの体位の再現性を再確認することが一般的であった．しかし，近年はCTを放射線治療装置と同じ部屋に設置して毎回の治療前にCTで位置照合を行う施設（CT on rails）や，画像誘導放射線治療装置（IGRT）に付設されたX線装置を利用してCBCT（コーンビームCT）を撮像することにより，治療前位置照合を行う施設も増加している．

連続する9枚の典型的なCT画像でのターゲットと，三次元治療計画画像



種々の断面による線量分布図



左上：coronal
右上：sagittal
左下：axial
右下：beam's eye view

Evaluation of the Prognostic Factors and Significance of Lymph Node Status in Invasive Ductal Carcinoma of the Body or Tail of the Pancreas

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Objective: We evaluated prognostic indicators for distal pancreatectomy with regional lymph node dissection in pancreatic body or tail carcinoma.

Methods: Between 1993 and 2008, 50 patients with ductal carcinoma of the body or tail of the pancreas who underwent distal pancreatectomy with regional lymph node dissection were retrospectively analyzed. Clinicopathological factors associated with patient survival were evaluated.

Results: No in-hospital deaths occurred among the study patients. The overall 5-year survival rate was 19.3%, and median survival was 22.6 months. Univariate analysis revealed that lymph node metastasis, intrapancreatic neural infiltration, peripancreatic nerve plexus infiltration, and tumor differentiation affected patient survival significantly. Multivariate analysis validated lymph node metastasis as an independent prognostic factor. Moreover, the lymph nodes attached to the pancreas were the most frequent metastatic nodes, and the number of metastasis in the lymph nodes attached to the pancreas was significantly associated with survival after surgical resection.

Conclusions: Lymph node metastasis was a significant and independent prognostic factor for the surgically resected pancreatic body or tail carcinoma. Furthermore, the lymph nodes attached to the pancreas were the most frequent metastatic nodes, and these lymph nodes were potential indicators predicting both tumor extension and survival after surgery for pancreatic body or tail carcinoma.

Key Words: pancreas cancer, distal pancreatectomy, lymph node metastasis, pancreatic body and tail of carcinoma, lymph nodes attached to the pancreas

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Despite recent advances in diagnostic imaging and chemotherapeutic treatment strategies, carcinoma of the pancreas remains a challenging disease. In particular, carcinoma located in the distal pancreas is usually diagnosed at an advanced stage, and a lower survival rate has been reported even in surgically resected cases.[1–3] Accumulating evidence suggests that successful surgical resection is one of the most important parameters in the treatment of pancreatic cancers.[4,5] For pancreatic carcinoma of the body or tail, distal pancreatectomy with dissection of the regional lymph nodes is a common procedure. However, regardless of the multidisciplinary treatment strategy, the outcomes for patients with pancreatic body or tail carcinoma are unsatisfactory, even when aggressive surgical resection is performed.[4,5]

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Previous studies involving a small number of patients have demonstrated that 5-year survival rates are around 10% in pancreatic cancer resected by distal pancreatectomy.[2,5] However, little is known about the prognostic indicators in patients who undergo surgery for carcinoma of the pancreatic body or tail. Moreover, although the status of lymph node involvement is an important parameter in determining progression of the disease, few reports demonstrate the frequency and pathway of lymph node metastasis in pancreatic body and tail carcinoma. The aim of this study was to evaluate the clinicopathological features and long-term outcomes in patients with pancreatic body or tail carcinoma after distal pancreatectomy with regional lymph node dissection. Furthermore, we discuss the frequency of lymph node involvement and its significance with respect to patient survival.

MATERIALS AND METHODS

Patients

We conducted a retrospective analysis of patients who underwent distal pancreatectomy for pancreatic body or tail carcinoma between November 1993 and June 2008. During this period, a total of 534 patients had a diagnosis and underwent pancreatic resection. Among these, 67 (12.5%) underwent distal pancreatectomy, and 58 (10.8%) were histologically proven to have ductal adenocarcinoma of the pancreatic body or tail. The patients' medical records were reviewed to identify the clinical stage of the disease, surgical procedures, histopathological findings of the lesions, incidence of postoperative events, and outcome.

Diagnostic Studies

Extent of the tumors was examined preoperatively using conventional ultrasonography, dynamic thin-slice computed tomography, and magnetic resonance imaging. In some cases, endoscopic retrograde pancreatography and angiographic imaging studies were combined to evaluate local tumor extension to major vessels and small hepatic metastases.

In most cases, perioperative washing cytological examination was carried out routinely immediately after laparotomy. Briefly, saline solution was instilled into the pelvis using a bulb syringe, and after agitation of the abdomen, the cytological specimens were aspirated from the pouch of Douglas into a sterile tube. A positive peritoneal cytological finding was not considered to be a contraindication for surgery. Perioperative assessment remained consistent throughout the period of the study.

Surgical Procedure

Surgical procedures consisted of distal pancreatectomy with regional lymph node dissection. Regional (N1) and peripancreatic lymph nodes (N2) were routinely dissected.[6] Lymph nodes

TABLE 1. Patient Characteristics

Variables	n	%
Age, yr		
≤60	18	36
60<	32	64
Sex		
Male	28	56
Female	22	44
Tumor size		
≤4 cm	33	66
>4 cm	17	34
Lymph node status		
Node positive	30	60
Node negative	20	40
Stage of disease*		
IA	3	6
IB	4	8
IIA	8	16
IIB	31	62
III and IV	4	8

*Sixth UICC classification system.

along the common hepatic artery, splenic artery, or inferior margin of the pancreas, or those at the splenic hilum, were classified as belonging to the regional lymph node group, N1. Lymph nodes along the left gastric artery, around the celiac artery, along the superior mesenteric artery, or along the middle colic artery were classified as belonging to the peripancreatic lymph node group, N2. The precise areas of the paraaortic lymph nodes (N3) were defined according to the fifth edition of the *General Rules for the Study of Pancreas Cancer*,[7] in which lymph nodes located along the aorta and between the superior and inferior mesenteric arteries are classified as N3 paraaortic nodes.

Histopathological Evaluation of the Resected Specimens

Histopathological findings that potentially affect patient survival were classified as follows: tumor size, serosal invasion, retropancreatic tissue invasion, splenic or portal vein invasion, splenic artery invasion, extrahepatic nerve plexus invasion, lymph node involvement, differentiation of the tumor, lymphatic invasion, venous invasion, and intrapancreatic nerve invasion. Histopathological evaluation was carried out by at least 2 specialized pathologists. Pancreatic cancer occasionally involves small lymph nodes located below the serosal layer of the pancreas with close attachment to the pancreatic parenchyma, and precise determination of the anatomical location of these nodes is usually difficult. Therefore, for detailed evaluation of lymph node metastasis, we subdivided the regional N1 lymph nodes into the lymph nodes attached to the pancreas and other nodes. Lymph nodes attached to the pancreas were defined as a group of lymph nodes having both of the following features: (1) located under the serosal layer of the pancreas and (2) within 3 mm of the parenchyma, being recognized only on histopathological evaluation. The tumors were staged according to the sixth edition of the Union Internationale Contre le Cancer (UICC) TNM classification system.[8]

Statistical Analysis

Survival estimates were calculated using the Kaplan-Meier method. All univariate comparisons of the survival curves were made using the log-rank test. Associations were considered statistically significant if $P \leq 0.05$. A multivariate regression analysis was carried out using the Cox proportional hazards model, and variables with a $P < 0.05$ were entered into the final model. All statistical analyses were performed using SPSS for Windows version 11.5 software (SPSS, Chicago, Ill).

RESULTS

Follow-up of the patients, including clinical evaluation and laboratory tests, was carried out, and adequate survival data were obtained for 50 of 58 patients who underwent distal pancreatectomy and had a histological diagnosis of ductal adenocarcinoma of the body or tail of the pancreas.

Patient characteristics of these 50 patients are shown in Table 1. Fifty-six percent of the patients were men, and 44% were women; the mean age of all patients was 64.2 years (range, 40–81 years). Thirty-three patients (66%) had tumors smaller than 4 cm in diameter, and 27 patients (34%) had larger tumors, and mean diameter was 40.2 cm. Ninety percent of patients underwent R0 resection of the tumor, whereas the remaining 10% of the patients underwent R1 resection. No in-hospital deaths occurred. Histopathological evaluation of the resected specimens revealed that 30 patients (60%) had metastatic lymph nodes. The disease stage was classified according to the sixth edition of the UICC TMN classification system.[8] Three patients (6%) had a diagnosis of stage IA; 4 (8%), stage IB; 8 (16%), stage IIA; 31 (62%), stage IIB; and 4 (8%), stage III or IV.

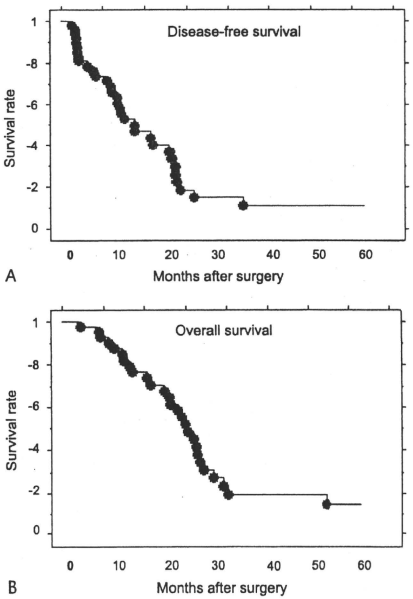


FIGURE 1. Five-year disease-free (A) and overall survival (B) curves (Kaplan-Meier) for 50 patients who underwent pancreatectomy for ductal adenocarcinoma of the body or tail of the pancreas.

Cumulative survival curves are shown in Figure 1. Disease-free survival rates were 52.6%, 14.7%, and 11.1%, and overall survival rates were 84.8%, 55.1%, and 19.3%, at 1, 3, and 5 years, respectively. The median survival time was 22.6 months. One patient (2.0%) survived for more than 10 years, and 3 patients (6.0%) survived for more than 5 years. Eighteen patients (36%) had no postoperative tumor recurrence during the follow-up period. The median follow-up period was 22.2 months (range, 1–139.8 months).

To explore their potential prognostic significance, various clinical and pathological parameters (tumor size; serosal, retropancreatic tissue, splenic vein, splenic artery, extrapancreatic nerve plexus, lymphatic, venous, and intrapancreatic nerve invasions; tumor differentiation; and lymph node metastasis) were investigated. The results of the log-rank test are shown in Table 2. Results of the univariate analysis revealed that factors such as extrapancreatic nerve plexus invasion ($P = 0.006$), intrapancreatic nerve invasion ($P = 0.024$), tumor differentiation (grade 1 vs 2 or 3; $P = 0.018$), and the status of lymph node metastasis ($P = 0.011$) were significant indicators of survival in patients after operation.

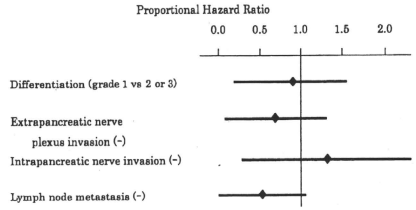
TABLE 2. Prognostic Factors of Survival in Distal Pancreatectomy Univariate Analysis

Variables	n	1-yr Survival, %	5-yr Survival, %	P
Tumor size				NS
≤4 cm	33	86.7	24.0	
<4 cm	17	79.2	16.4	
Serosal invasion				NS
Negative	38	83.2	20.6	
Positive	12	82.2	10.4	
Retropancreatic tissue invasion				NS
Negative	17	81.3	27.5	
Positive	33	82.2	10.4	
Splenic vein invasion				NS
Negative	26	82.9	28.9	
Positive	24	88.2	0.0	
Splenic artery invasion				NS
Negative	37	100	20.7	
Positive	13	81.1	0.0	
Extrapancreatic nerve plexus invasion				$P = 0.0067$
Negative	35	88.2	26.6	
Positive	15	76.9	0.0	
Lymphatic invasion				NS
Negative	33	89.5	20.6	
Positive	17	72.9	15.2	
Venous invasion				NS
Negative	19	82.5	36.1	
Positive	31	81.9	12.0	
Intrapancreatic nerve invasion (ne0, 1 vs ne2, 3)				$P = 0.0246$
Negative	23	84.5	36.2	
Positive	27	85.2	6.7	
Differentiation				$P = 0.0183$
Well differentiation	14	100	36.7	
Moderate or poor differentiation	36	77.6	9.1	
Lymph node metastasis				$P = 0.012$
Negative	20	86.7	43.8	
Positive	30	83.9	0.0	

ne indicates intrapancreatic nerve plexus invasion; NS: not significant.

TABLE 3. Multivariate Analysis Using Cox Proportional Hazards Model

Variables	Hazard Ratio	95% CI	P
Differentiation (grade 1 vs 2 or 3)	0.570	0.210–1.548	0.26
Extrapancreatic nerve plexus invasion	0.444	0.160–1.230	0.11
Intrapancreatic nerve invasion (ne0, 1 vs ne2, 3)	0.912	0.315–2.367	0.86
Lymph node metastasis	0.387	0.139–1.035	0.05



To further evaluate the significance of these 4 factors, multivariate analysis was carried out. Results of the multivariate analysis with the Cox proportional hazards model showed that lymph node metastasis was an independent prognostic factor (hazard ratio [HR], 0.387; 95% confidence interval [CI], 0.139–1.035; $P = 0.05$) for survival (Table 3).

The multivariate analysis showed that lymph node status was one of the most important prognostic factors. To evaluate the significance of the status of lymph node metastasis, we further investigated the lymph node status according to the anatomical location of the tumor, based on the categories used to subdivide regional N1 lymph nodes into the lymph nodes attached to the pancreas and other nodes, as described in Materials and Methods. The results for the lymph node status are shown in Figure 2. In total, 1461 lymph nodes were resected from 50 patients (mean, 29.2 nodes per patient), and 89 lymph nodes (6.1%; mean, 1.8 nodes per patient) were histologically diagnosed as metastatic nodes. Of these, the lymph nodes attached to the pancreas were the most frequent node both in the total number of dissected nodes (633/1461 nodes, 43.3%) and in the number of total metastatic lymph nodes (69/89 nodes, 77.5%).

Next, to address the correlation between the location of the tumor and the lymph node status, we classified the tumor location in the pancreas as follows: the body of the pancreas (Pb), the tail of the pancreas (Pt), and both the body and the tail of the pancreas (Pbt). Among the 50 patients, 25 patients (50%) were classified as Pb, 17 patients (34%) as Pbt, and 8 patients (16%) as Pt. Among the Pb cases, 47 lymph nodes were histologically diagnosed as metastatic lymph nodes, primarily comprising the lymph nodes attached to the pancreas (37/47, 78.7%), the lymph nodes along the superior mesenteric artery (3/47, 6.3%), and the lymph nodes around the paraaortic area

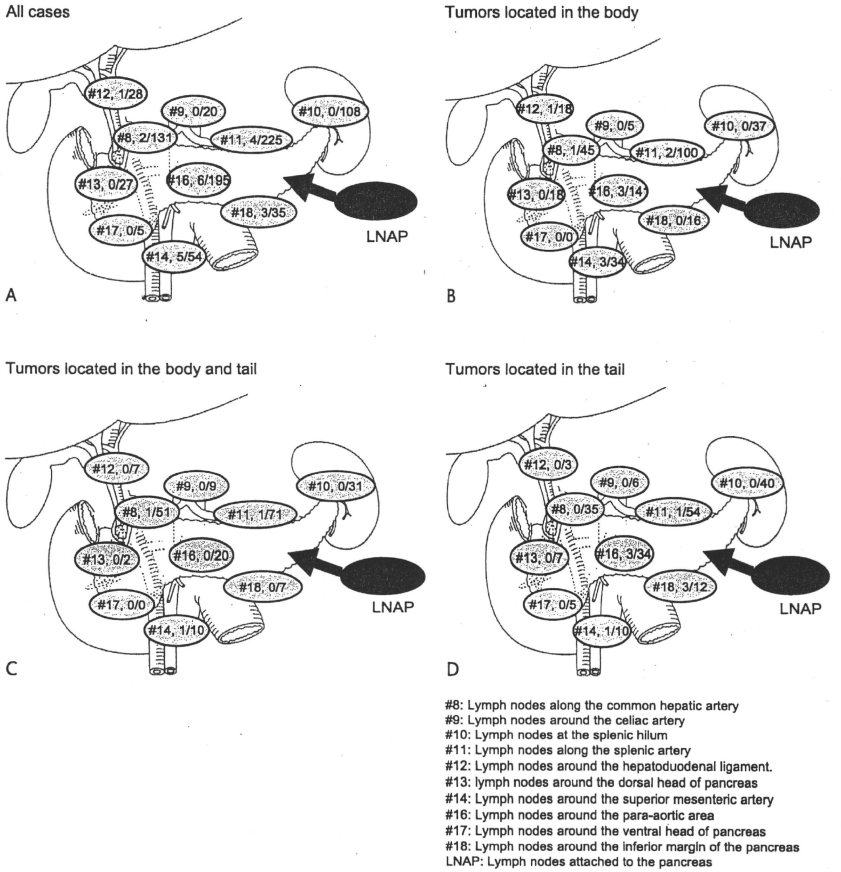


FIGURE 2. Lymph node mapping in distal pancreatectomy in patient with pancreatic body or tail carcinoma (A, all cases; B, tumors located in the body of pancreas; C, tumors located in the body and tail of pancreas; D, tumors located in the tail of pancreas).

(3/47, 6.3%; Fig. 2B). Among the Pbt cases, 21 lymph nodes were microscopically diagnosed as showing tumor metastasis. Most of these metastatic lymph nodes were the lymph nodes attached to the pancreas (18/21, 85.7%), and the remaining metastatic lymph nodes were located along the common hepatic (1/21, 4.7%), splenic (1/21, 4.7%), and superior mesenteric arteries (1/21, 4.7%; Fig. 2C). Among the Pt cases, 22 lymph nodes were microscopically diagnosed as showing tumor metastasis, and these metastatic nodes mostly comprised the lymph nodes attached to the pancreas (14/22, 63.3%), the nodes located around the inferior margin of the pancreas (3/22, 13.6%), and the nodes located around the paraaortic area (3/22, 13.6%; Fig. 2D).

Table 4 shows the distribution and the percentage of the metastatic lymph nodes. For Pb tumors, percentages of lymph node metastasis were higher in the lymph nodes attached to the pancreas (9.0%) and in nodes located along the superior mesenteric artery (8.8%). For Pbt tumors, although the total number of metastatic nodes was small, the nodes attached to the pancreas (14%) and along the superior mesenteric artery (10%) showed a higher percentage of tumor metastasis. For Pt tumors, the lymph nodes attached to the pancreas (9.6%), the nodes along the superior mesenteric artery (9.5%), and the nodes around the inferior margin of the pancreas (8.5%) showed a higher percentage of tumor metastasis. Taken together, the

TABLE 4. Distribution and Percentage of Metastatic Lymph Node in Distal Pancreatectomy for Pancreatic Body or Tail Carcinoma

Lymph Nodes	Pb (%)	Pbt (%)	Pt (%)	Total (%)
8*	1 (2.2)	1 (1.9)	0 (0)	2 (1.5)
9†	0 (0)	0 (0)	0 (0)	0 (0)
10‡	0 (0)	0 (0)	0 (0)	0 (0)
11§	2 (2.0)	1 (1.4)	1 (1.8)	4 (1.7)
12‖	1 (5.5)	0 (0)	0 (0)	1 (3.5)
13¶	0 (0)	0 (0)	0 (0)	0 (0)
14#	3 (8.8)	1 (10)	1 (10)	5 (9.2)
16**	3 (2.1)	0 (0)	3 (8.8)	6 (3.0)
17††	0 (0)	0 (0)	0 (0)	0 (0)
18‡‡	0 (0)	0 (0)	3 (25)	3 (8.5)
Nodes attached to the pancreas	37 (9.0)	18 (14)	14 (14)	69 (9.6)
Total	47 (5.7)	21 (6.3)	22 (7.2)	90 (6.1)

*Lymph nodes along the common hepatic artery.
†Lymph nodes around the celiac artery.
‡Lymph nodes at the splenic hilum.
§Lymph nodes along the splenic artery.
‖Lymph nodes around the hepatoduodenal ligament.
¶Lymph nodes around the dorsal head of the pancreas.
#Lymph nodes around the superior mesenteric artery.
**Lymph nodes around the paraaortic area.
††Lymph nodes around the ventral head of the pancreas.
‡‡Lymph nodes at the inferior margin of the pancreas.

percentage of the metastatic lymph nodes was 6.1% among all the dissected lymph nodes, and both the number and the percentage of metastatic lymph nodes were highest in the lymph nodes attached to the pancreas for all tumor locations.

Because both the number and the percentage of metastases in the lymph nodes attached to the pancreas were greater compared with that in the other N1 regional nodes, regardless of tumor location, and because lymph node metastasis was an important prognostic indicator in pancreatic body or tail carcinoma, we focused further on the lymph nodes attached to the pancreas to evaluate their potential prognostic impact in patients who underwent distal pancreatectomy. Figure 3 shows the overall survival curves related to the status of the lymph nodes attached to the pancreas in patients who underwent distal pancreatectomy. As shown in Figure 3A, significantly better survival ($P < 0.05$) was observed in patients with no metastasis in the lymph nodes attached to the pancreas. Furthermore, we examined the status of the lymph node attached to the pancreas to determine whether it affected the frequency of metastasis in extrapancreatic nodes. As shown in Figure 3B, among patients with no positive lymph nodes attached to the pancreas, 6.5% showed extrapancreatic lymph node metastasis, whereas 48.5% of patients with positive lymph nodes attached to the pancreas showed extrapancreatic metastasis, a statistically significant result ($P < 0.05$). Figure 3C shows the overall survival curves in patients with no metastatic nodes attached to the pancreas, with 1 to 2 metastatic nodes attached to the pancreas and with 3 or more metastatic lymph nodes. Significantly worse survival was observed in patients with 3 or more positive lymph nodes attached to the pancreas ($P < 0.01$) compared with the other groups. Indeed, when patients were categorized into 2 groups (metastasis involving 0–2 nodes attached to the pancreas vs ≥3 nodes attached to the pancreas), significantly better survival was observed in patients with metastasis involving 0 to 2 lymph nodes attached to the pancreas ($P < 0.001$; Fig. 3D). The multivariate analysis using the Cox proportional hazards model demonstrated that the presence of 3 or more positive lymph nodes attached to the pancreas was an independent prognostic factor in patients who underwent distal pancreatectomy for pancreatic carcinoma of the body or tail (HR, 0.349; 95% CI, 0.134–0.906; $P = 0.03$; Table 5).

DISCUSSION

Ductal adenocarcinomas of the body or tail of the pancreas are usually diagnosed at an advanced stage, which frequently results in unresectable disease due to extrapancreatic tumor involvement or distant metastasis. A prior study evaluating a large series of patients in the United Kingdom demonstrated that resection of pancreatic carcinoma of the body or tail was achieved in less than 10% of patients.[9–11] Despite multidisciplinary treatment strategies, the prognosis for patients with ductal adenocarcinoma of the body or tail of the pancreas is dismal. Previous studies have reported that 5-year survival rates ranged from 10% to 22%, and median postoperative survival was 11 to 16 months for patients with pancreatic body or tail carcinoma.[1,3–5,12,13] A recent report from a Japanese investigator demonstrated a 5-year survival rate of 19% and median survival of 22 months for patients who underwent pancreatectomy with extended lymphadenectomy for ductal adenocarcinoma of the body or tail of the pancreas. In the present study, 5-year overall survival was 19.3% and median survival term was 22.6 months,[4] which is compatible with the results of the previous studies.

In the treatment of pancreatic carcinoma, chemotherapeutic agents are becoming a more important option. The results of recent studies demonstrated that adjuvant chemotherapy could improve patient survival in pancreatic cancers.[14,15] Previous studies have shown significant improvement in survival for patients with pancreatic cancer who received adjuvant chemotherapy after R0/R1 resection for pancreatic cancer,[16] and a recent trial has also demonstrated the beneficial effect of adjuvant chemotherapy.[17] Thus, although the improvement in survival obtained by adjuvant chemotherapy is not yet satisfactory, it is clear that adjuvant chemotherapy is essential in the treatment of pancreatic cancer.

Clinicopathological features in patients with ductal adenocarcinoma of the head of the pancreas have been widely investigated, whereas prognostic factors in patients with ductal adenocarcinoma of the body or tail of the pancreas, particularly based on evaluation of the frequency of lymph involvement, have not been fully addressed. Therefore, further investigation is required to elucidate the potential prognostic indicators in patients who undergo surgery for pancreatic carcinoma of the body and tail. To identify the potential prognostic factors, it is necessary to understand the clinicopathological features and patterns of the tumor spread in the distal pancreas. Reflecting the complexity of the anatomical location of the pancreas, extension of the tumors is determined by multiple factors such as vascular or nerve plexus invasion. In the present study, the status of lymph node involvement was found to be one of the most important indicators predicting patient survival after surgery. Indeed, supporting our observation, current reports have indicated that lymph node metastasis is a critical determinant of long-term survival in patients after surgery for pancreatic carcinoma of the body or tail.[4,5] Based on detailed analysis

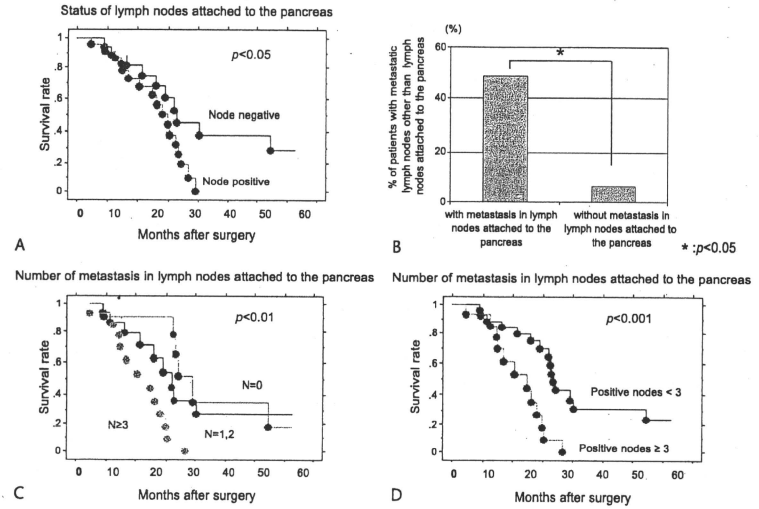


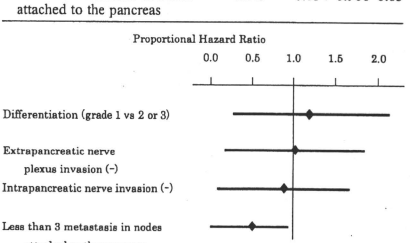
FIGURE 3. Overall survival regarding the status of lymph nodes attached to the pancreas in patients who underwent distal pancreatectomy for pancreatic body or tail carcinoma. A, Five-year overall survival curve for patients who underwent distal pancreatectomy regarding the status of lymph node metastasis. Significant differences are observed between the 2 groups (node positive vs node negative). B, Percentage of patients with metastatic lymph nodes other than lymph nodes attached to the pancreas, regarding the status of the lymph nodes attached to the pancreas. Incidences of metastasis in lymph nodes other than the lymph nodes attached to the pancreas are significantly higher in patients with metastasis in the lymph nodes attached to the pancreas. C, Significantly lower survival rate is observed for patients with 3 or more metastatic lymph nodes attached to the pancreas compared with those with less than 3 metastasis in the lymph node attached to the pancreas. D, Significantly better survival is observed for patients with more than 3 metastases in the lymph node attached to the pancreas.

of surgically resected specimens of pancreatic body or tail carcinoma, Nakao et al[15] reported that a higher incidence of lymph node involvement was observed along the splenic artery and around the superior mesenteric artery. Conversely, a low incidence of lymph node involvement was observed on the inferior pancreatic body, around the common hepatic artery, at the hilum of the spleen, and on the anterior surface of the head of pancreas. Consistent with their observations, the results of our study demonstrated a higher incidence of lymph node metastasis along the superior mesenteric artery and a lower incidence around the anterior surface of the head of pancreas, at the splenic hilum, and along the common hepatic artery. In ductal adenocarcinoma of the pancreatic head, it has been reported that lymphatic flow is strongly suspected from the tumor to the paraaortic lymph nodes via the posterior surface of the pancreatic head and around the superior mesenteric artery.[13,18] The results of the present study suggest that, on the contrary, lymph nodes around the superior mesenteric artery may be one of the major pathways to the paraaortic lymph nodes in ductal adenocarcinoma of the body or tail of the pancreas.

In the present study, the lymph nodes attached to the pancreas were the most frequently dissected nodes among the other regional nodes. For this reason, we investigated the association between tumor progression and the status of these nodes, which were only detectable on histological examination. The existence

TABLE 5. Multivariate Analysis Using Cox Proportional Hazards Model

Variables	Hazard Ratio	95% CI	P
Differentiation (grade 1 vs 2 or 3)	0.724	0.243–2.160	0.56
Extrapancreatic nerve plexus invasion	0.640	0.222–1.846	0.40
Intrapancreatic nerve invasion (ne0, 1 vs ne2, 3)	0.549	0.178–1.698	0.29
Less than 3 metastasis in nodes attached to the pancreas	0.349	0.134–0.906	0.03



of the lymph nodes attached to the pancreas had not been described previously. These nodes can be categorized as lymph nodes along the common hepatic artery, lymph nodes along the splenic artery, or lymph nodes around the inferior margin of the pancreas. Definitive classification of these nodes is difficult; however, based on microscopic evaluation, the regional N1 nodes were subdivided as lymph nodes attached to the pancreas or the other nodes. On microscopic examination, these nodes were found to be (mean ± SD) 2.75 ± 0.73 mm in size, located at a distance of 1.93 ± 0.44 mm from the parenchyma of the pancreas, and mostly undetectable by intraoperative or macroscopic observations. Notably, in both the number of dissected nodes and percentage of metastasis, the lymph nodes attached to the pancreas were found to be the most frequent nodes being considered major lymph nodes in pancreatic body or tail carcinoma.

Several studies have demonstrated the detailed lymphatic pathway of the pancreas.[2,19] The smallest lymphatic vessels, termed *intralobular lymphatics*, start within the lobules of the pancreas, and their blind beginnings lie in the thin and delicate connective tissues surrounding the smallest pancreatic ducts and blood vessels. These earliest lymphatics open into interlobular lymphatics, and larger interlobular lymphatics reach to the surface of the pancreas and enter a surface network of the lymphatic vessels that converge at the lymph node.[19] In the present study, detailed analysis of the distribution of metastatic lymph nodes revealed that the lymph nodes attached to the pancreas are the most frequent nodes removed after distal pancreatectomy. Because the lymph nodes attached to the pancreas are located nearest to the parenchyma of the pancreas among the other regional nodes, it is reasonable to suppose that the lymph nodes attached to the pancreas could be categorized as the earliest surface network nodes to which cancer cells first migrate and create metastatic foci. Furthermore, the results of the present study demonstrated that only 6.5% of patients with no positive nodes attached to the pancreas had extrapancreatic lymph metastasis, whereas 45% of patients with positive nodes attached to the pancreas had extrapancreatic nodal metastasis, a statistically significant result (Fig. 3). Moreover, among patients with positive extrapancreatic nodes, 91.6% (data not shown) of patients demonstrated lymph metastasis in the nodes attached to the pancreas. Given that paraffin-embedded pancreatic tissues were prepared as 5-mm slices and the mean diameter of the lymph nodes attached to the pancreas was less than 3 mm, metastasis in the lymph nodes attached to the pancreas was potentially more frequent in patients with positive extrapancreatic nodes.

Our study had several limitations. Some conditions of the patients may have been falsely diagnosed as negative for the lymph nodes attached to the pancreas because of the small size of both the nodes and the slices prepared for histological evaluation; therefore, excluded information could have biased the results of the study. Furthermore, our study covered an almost 15-year period, during which preoperative diagnostic accuracy and postoperative follow-up regimens differed. However, histopathological explorations were performed consistently, which may even be considered a strength of the study.

In conclusion, the results of our study indicate that (1) the status of lymph node metastasis was an important prognostic factor in patients who underwent distal pancreatectomy for ductal adenocarcinoma of the pancreatic body or tail and (2) the lymph nodes attached to the pancreas were the most frequent nodes in both the number of dissected nodes and percentage of metastasis, and these nodes were potential indicators predicting tumor extension and survival after surgery for patients with carcinoma of the pancreatic body or tail.

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ORIGINAL ARTICLE

Incidence, clinical presentation and pathological features of benign sclerosing cholangitis of unknown origin masquerading as biliary carcinoma

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Abstract
Background Benign obstructions of the liver hilum are occasionally encountered in surgically resected cases. Some of these cases are pathologically classified as benign sclerosing cholangitis and are not clearly categorized. This study aims to elucidate the clinicopathological features of benign sclerosing cholangitis of unknown origin.
Methods Patients who had undergone surgery of the proximal bile duct from 1993 to 2008 on suspicion of proximal bile carcinoma were evaluated, then their clinical presentation, histopathological and immunohistochemical findings were retrospectively analyzed.
Results One hundred seventy-six patients underwent surgery during this period. Of these, five patients were diagnosed with benign sclerosing cholangitis of unknown origin. All five patients were middle-aged with no history of autoimmune disease. One patient died of recurrent cholangitis after surgery. Histopathologically, lymphoplasmacytic infiltrations were observed in all five cases. Among them, the clinicopathological findings of one patient were compatible with IgG4-related sclerosing cholangitis, and the other two patients had unusual histopathological findings with prominent lymph follicular formation.
Conclusions Although patients with benign sclerosing cholangitis of unknown origin comprise a heterogeneous population, they can be further classified into subgroups. The response to immunosuppressive therapy, long-term prognosis and histological morphology of the disease should be considered in order to classify these cases of sclerosing cholangitis.

Keywords Hilar cholangiocarcinoma · Sclerosing cholangitis · IgG4-associated sclerosing pancreatocholangitis · Malignant hilar masquerade

Abbreviations
PSC Primary sclerosing cholangitis
IgG4-SC IgG4-associated sclerosing cholangitis

Introduction

The incidence of benign stricture of the hilar bile duct was reported in approximately 10% of surgically resected cases that were preoperatively diagnosed as cholangiocarcinoma [1–8]. Although secondary sclerosing cholangitis associated with choledocholithiasis and hepatolithiasis is responsible for bile duct stenosis [9, 10], there are still certain benign biliary obstructive conditions whose exact pathogenesis remains unclear and are occasionally diagnosed as nonspecific sclerosing cholangitis. Of these, IgG4-related lymphoplasmacytic sclerosing disease was recently found to be responsible for stricture of the bile duct in the context of autoimmune pancreatitis [11, 12]. Current reports have also suggested that IgG4-related lymphoplasmacytic sclerosing disease is responsible for hilar bile obstruction and even for extra-hepatobiliarypancreatic lesions [11, 13].

IgG4-associated autoimmune disease was advocated in the field of autoimmune pancreatitis [12] when focal stricture of the main pancreatic duct was observed not only

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in pancreatic cancer, but also in benign diseases with an autoimmune origin frequently associated with elevation of serum IgG4 levels. Histopathological findings of autoimmune pancreatitis were characterized by lymphoplasmacytic infiltration and categorized as lymphoplasmacytic sclerosing pancreatitis [11, 14]. In nearly half of the autoimmune pancreatitis cases, there are more than 20 IgG4-positive plasma cells per high-power field (h.p.f) [15–17]. Likewise, IgG4-positive plasma cells are prominently observed in lymphoplasmacytic sclerosing cholangitis. However, the way in which large lymphoplasmacytic sclerosing cholangitis is responsible for proximal stricture of the bile duct, which masquerades as hilar cholangiocarcinoma, has not been clarified. In fact, recent reports suggest that inflammatory biliary strictures probably represent a wider variety of pathological processes [3, 4]. This suggests that there are other types of sclerosing cholangitis regardless of the status of IgG4.

This study aims to evaluate the incidence of IgG4-positive sclerosing cholangitis among patients diagnosed with benign sclerosing cholangitis of unknown origin and to summarize the clinicopathological features of this condition. Furthermore, we review the literature and discuss the potential characteristics of this as yet uncategorized disease.

Methods

Patients

Patients who had undergone surgery for proximal biliary strictures were identified retrospectively from the database of the clinical pathology unit of the National Cancer Center Hospital East from October 1993 to July 2008.

Clinical presentation

The preoperative diagnosis was based on preoperative imaging studies, including percutaneous transhepatic cholangiography, endoscopic retrograde cholangiopancreatography, magnetic resonance cholangiopancreatography and conventional cross-sectional imaging studies (computed tomography and magnetic resonance imaging). Proximal bile duct strictures were classified according to the Bismuth–Corlette classification system. The patients' medical records were reviewed for clinical symptoms, surgical procedures, postoperative complications and long-term outcome.

Histopathological and immunohistochemical analysis

With the use of serial sections from paraffin-embedded tissue blocks, immunohistochemical analyses were performed using anti-CD3, CD4, CD8, CD20, CD79a and IgG4 antibodies (Santa Cruz Co., Santa Cruz, CA). Monoclonal antibodies against IgG4 were obtained from The Binding Site (Birmingham, UK). Immunohistochemical staining was performed in the usual manner. Briefly, the deparaffinized sections were microwaved for 20 min in EDTA buffer. After blocking the endogenous peroxidase and incubating in blocking buffer, the sections were incubated overnight with the primary antibody at 4°C. Thereafter, these sections were incubated for 2 h with the secondary antibody at room temperature. Diaminobenzidine tetrahydrochloride was used as the chromogen before counterstaining with hematoxylin (Sigma-Aldrich, St Louis, MO).

The numbers of IgG4-positive cells were counted and evaluated in at least 10 h.p.f and determined as positive in cases with more than 10 cells per h.p.f (Olympus, Tokyo, Japan). The degree of immunohistochemical positivity of cells was classified semiquantitatively. Statistical analysis was performed using the chi-square test, and $P < 0.05$ was considered statistically significant.

Two specialized pathologists (MK and TH) histologically evaluated all stained slides of the lesions. The following features were assessed during the histopathological re-evaluation on a semiquantitative basis: fibrosis (absent, minimal, mild, moderate, severe), lymphoplasmacytic infiltration (absent, minimal, mild, moderate, severe) and formation of lymph follicles (absent, mild, moderate, severe), germinal centers (absent, mild, moderate, severe) and vascular thrombi (absent, mild, moderate, severe). Evaluation of immunohistochemical staining was performed based on the presence or absence of cells positive for the markers. Distributions of IgG4-positive cells were classified as diffuse, focal and scattered.

Results

Patients

From October 1993 to June 2008, 176 patients with proximal biliary strictures underwent surgery at the National Cancer Center Hospital East. Results of histopathological analysis of the resected specimens showed that 155 (88.1%) patients had malignant neoplasms. Seven (4.0%) patients had biliary obstructive disease related to congenital biliary dilatation, two (1.1%) had biliary hamartoma, two (1.1%) had stone disease or its related glanulomatous process, five (2.8%) had other conditions, and five (2.8%) had benign bile stricture of unknown origin.

Five patients had benign nonspecific sclerosing cholangitis: three men and two women with a mean age of 54.8 (range 44–65) years. We further evaluated the clinicopathological characteristics of these five cases.

Clinical presentation

A brief summary of the clinical characteristics of the five patients with benign nonspecific sclerosing cholangitis is shown in Table 1. Obstructive jaundice was the main reason for the consultation for the symptoms in three (60%) patients, and two (40%) patients had abnormal hepatobiliary enzyme levels and a slight elevation of serum total bilirubin. None of the patients had a history of autoimmune-like disease; one patient had a history of gastric cancer. Blood examination showed no abnormal findings concerning anti-nuclear antibodies or other markers of autoimmune disease. The main lesions were located in the liver hilum in four (80%) patients. All five patients had a preoperative diagnosis of cholangiocarcinoma, and stenotic lesions were surgically removed in all cases. Of these patients, two (40%) underwent extended hepatic lobe resections, two (40%) underwent local resection of the liver hilum, and one (20%) underwent modified pancreatoduodenectomy.

The outcomes of the patients are shown in Table 2. At a median follow-up of 59.2 months (range 3–180 months), one patient had died, three were still alive, and one was lost to follow-up. As postoperative complications, two patients (40%) had moderate pancreatic fistula and transient cholangitis, both of which were successfully managed, and no special care was needed. Two patients were administered corticosteroids, and one of them showed moderate response (case 2); the other showed mild response (case 3). Case 3 had a progressive worsening of hepatobiliary enzyme levels 3 months after surgery and eventually died of liver failure of unknown origin.

Histopathological and immunohistochemical findings

A summary of the histopathological findings for these five cases is shown in Table 3. Fibroinflammatory changes were observed under the submucosal layer of the stenotic areas for all patients. Lymphoplasmacytic infiltration of

Table 1 Clinical manifestations

	Age	Gender	Symptom	Location	Surgery	AIDs	Previous history	Duration of symptom (months)
Case 1	44	M	Jaundice	Bismuth IV	Bile duct resection	–	Gastric cancer	4
Case 2	60	M	Jaundice	Bismuth IV	Bile duct resection	–	–	3
Case 3	58	F	Elevation liver enz	Bismuth III	Left hepatectomy	–	–	24
Case 4	65	F	Jaundice	Bismuth I	Pancreato-duodenectomy	–	–	4
Case 5	47	M	Elevation liver enz	Bismuth IV	Right hepatectomy	–	–	36

AIDs autoimmune disease, *NA* not applicable, + present, – absent

Table 2 Patient outcomes

	Postoperative complications	Recurrent cholangitis	Treatment with IST	Response to the IST	Late complications	Overall survival
Case 1	–	–	None	NA	None	Alive (180 months)
Case 2	–	+	Corticosteroids	Moderate	Henoch–Schonlein purpura	Unknown (75 months)
Case 3	Cholangitis	+	Corticosteroids	Mild	Liver failure	Died (24 months)
Case 4	Pancreas fistula	–	None	N/A	None	Alive (14 months)
Case 5	–	–	None	N/A	None	Alive (3 months)

IST immunosuppression therapy, *NA* not applicable

Table 3 Histopathological findings

	Histological diagnosis	Fibrosis	Lymph-plasmocycte infiltration	Lymph follicule	Germinal center	Vascular thrombus	Epithelial surface	Intrahepatic peripheral bile duct
Case 1	BSC	++	+	–	–	–	Intact	Intact
Case 2	BSC	++	++	+	–	++	Intact	Intact
Case 3	BSC	++	+++	+++	++	–	Intact	Intact
Case 4	BSC	++	±	–	–	–	Disappeared	Intact
Case 5	BSC	++	+++	+++	++	–	Intact	Intact

BSC benign sclerosing cholangitis, – absent, ± minimal, + mild, ++ moderate, +++ severe

various degrees was observed in all cases. Two patients (case 1 and 4) had prominent dense fibrosis around the stenotic bile ducts, and scattered lymphoplasmacytic inflammatory foci were observed in the fibrotic areas (Fig. 1a). However, in these two patients, the number of lymphoplasmacytes was much lower than in the other three patients; no lymph follicular formation or vascular phlebitis was observed around the lesion (Fig. 1b, c), and the margin between the fibrotic lesion and periductal area was clearly observed. However, lymph follicle formations were observed in three cases and were particularly prominent in two cases (cases 3 and 5) in which they had germinal centers (Fig. 2a). In these two cases, marked lymph follicles were circumferentially located around the fibroinflammatory layers of the periductal areas (Fig. 2b). These pathological findings were observed only in relatively large-diameter bile ducts (Fig. 2c), with no abnormal findings in the peripheral intrahepatic bile duct.

In case 2, mild lymph follicle and moderate venous thrombus formations were observed in the peripheral intrahepatic lesions (Fig. 3a). Histological examination showed vascular phlebitis and perineural lymph infiltrates (Fig. 3b, c). In all cases, nearly intact or only mildly dysplastic biliary epithelium was observed; no findings indicative of malignant neoplasms were observed. Other histopathological findings, such as "onion-skin" lesions and non-suppurative destructive cholangitis, were not observed in any of the cases.

The results of immunohistochemical staining in the five patients with nonspecific sclerosing cholangitis are summarized in Table 4. One of these patients had a small amount of lymphoplasmacytic infiltration (case 4), while in the remaining four, moderate to severe lymphoplasmacytic infiltration was observed. However, regardless of the number of infiltrating inflammatory cells, the lymphoplasmacytes of all five patients were positive for CD3, CD4, CD8, CD20 and CD79a. In contrast, IgG4-positive lymphoplasmacytes were observed in only one case (case 2) (Figs. 1d, 2d, 3d).

On the basis of histopathological and immunohistochemical analyses, we classified cases of benign sclerosing cholangitis of unknown origin as follows: (1) IgG4-related sclerosing cholangitis, (2) lymphoplasmacytic sclerosing cholangitis with prominent lymph follicules and (3) nonspecific fibroinflammatory cholangitis.

Discussion

The incidence of benign biliary strictures of unknown origin varies between 2.9 and 14.3% in cases of proximal biliary strictures masquerading as cholangiocarcinoma [18]. Two studies, including this one, have described the incidence of proximal biliary strictures masquerading as cholangiocarcinoma in Japanese populations [18]; however, no clear trends were observed in a comparison of this incidence in

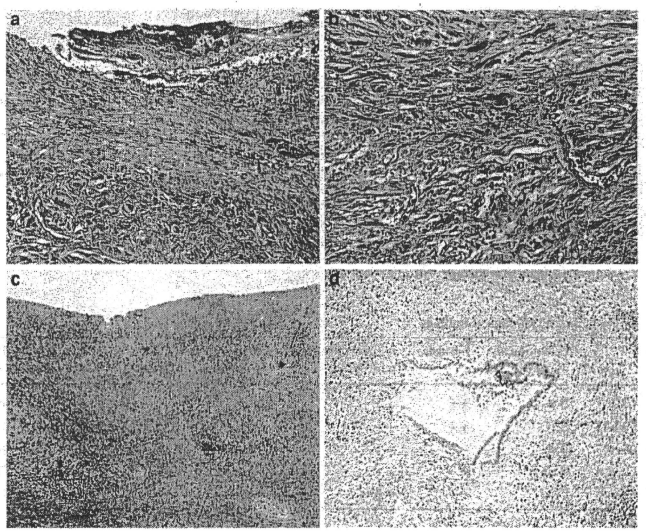

Fig. 1 Histopathological findings of case 1. **a** Stenotic area was composed of dense fibrotic tissue. **b** Scattered lymphoplasmacytic infiltrations were scattered around the inflammatory foci of the stenotic area. **c** No lymph follicular formation was observed in the inflammatory foci. **d** Immunohistochemical study found that there were no lymphoplasmacytes positive for IgG4

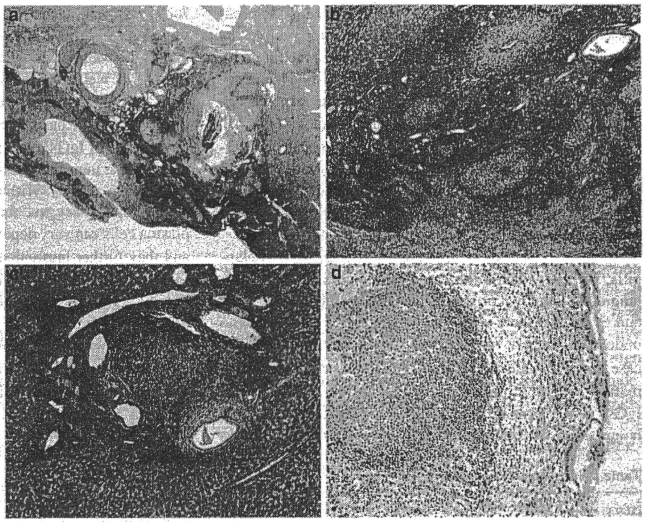

Fig. 2 Histopathological findings of case 3. **a** Inflammatory lesion was composed of follicular lymphoplasmacyte infiltration. Lymph follicule formations were prominently observed around the inflammatory lesion. **b** Lymph follicules were accompanied by germinal centers. **c** Lymphoplasmacyte infiltrations were observed only in relatively large-diameter bile ducts. **d** Immunohistochemical findings of case 3 was compatible with negative for IgG4

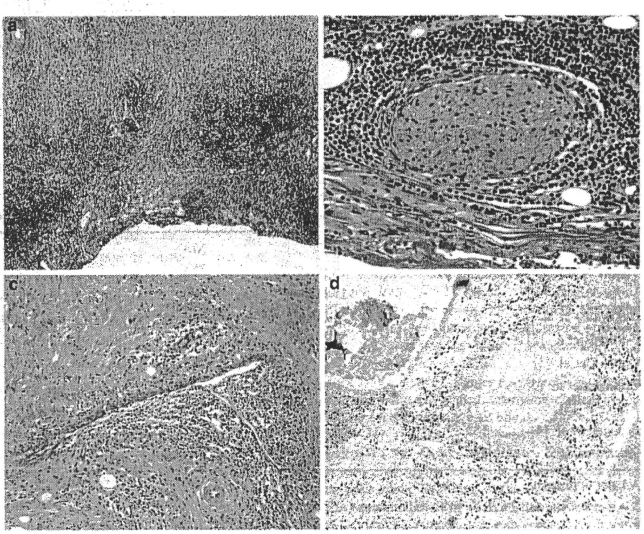

Fig. 3 Histopathological findings of case 2. **a** Inflammatory lesion was composed of diffuse lymphoplasmacyte infiltrations. Few lymph follicules were found in the lesion. **b** Histological examination showed vascular phlebitis. **c** Perineural lymph infiltrations were markedly observed around the inflammatory foci. **d** Immunohistochemical study revealed that IgG4 positive plasmacytes were diffusely observed in the lesion

Japanese, European and American patients. Most studies on benign biliary strictures of unknown origin have simply described histological findings such as chronic inflammatory infiltration. Thus, further review and a detailed histological re-evaluation may identify the epidemiological and clinicopathological features of benign biliary strictures.

Except for cases caused by obvious mechanical stimulation, most benign bile strictures are supposed to be somehow associated with the autoimmune system [9, 10, 19], and several recent studies showed that IgG4 is associated with the progression of autoimmune pancreatitis, cholangitis and other fibroinflammatory diseases [11, 20]. These intra- and extra-pancreatic lesions indicate infiltration of abundant IgG4-positive plasma cells, and treatment with steroids resulted in the disappearance of most of the IgG4 plasma cells and subsequent improvement of the affected organs [15, 21, 22].

As per our current understanding of sclerosing cholangitis, we re-evaluated the cases of benign sclerosing cholangitis of unknown origin diagnosed over the past 15 years and found that there were 5 cases among 176 patients who underwent surgery for proximal biliary stricture. Of these, case 2 had a moderate level of lymphoplasmacytic inflammation, and these plasma cells were diffusely positive for IgG4, being compatible with IgG4-related sclerosing cholangitis. On the other hand, the histopathological findings for cases 3 and 5 were similar and unusual, showing differences from those of case 2. Microscopically, in cases 3 and 5, the walls of the bile duct were thickened, and dense fibrosis as well as a marked formation of lymph follicles with germinal centers under the mucosal layer was observed. On the basis of our evaluation, both cases showed the absence of IgG4 levels; however, it is unknown whether or not these unusual cases of cholangitis consistently show the absence of IgG4. With regard to the status of IgG4, some recent reports suggest that the number of IgG4-positive plasma cells can vary depending on the status of the disease, and they further imply that there is no selective increase in IgG4-positive plasma cells in IgG4-related sclerosing cholangitis [17, 23, 24]. Therefore, we could not rule out the possibility that this lymphoplasmacytic sclerosing cholangitis with prominent lymph follicules is a variant of IgG4-related sclerosing cholangitis. Nevertheless, because the histopathological findings and profile of disease progression of this unusual lymphoplasmacytic sclerosing cholangitis varied in our study, the characteristics of the disease should be further clarified.

In our cases 1 and 4, a single focal stricture of the bile duct with no abnormal findings in other areas of the hepatobiliary system and subtle lymphoplasmacyte infiltration negative for IgG4 were found. The histological findings for these two cases indicated no vascular phlebitis or perineural lymph infiltration with no pathological findings in the peripheral intrahepatic bile duct. Thus, we could not further categorize these two cases, and they were classified as nonspecific fibroinflammatory cholangitis at this point.

Table 4 Immunohistochemical findings

	CD3	CD4	CD8	CD20	CD79a	IgG4	Distribution of IgG4(+) cells
Case 1	+	+	+	+	+	−	NA
Case 2	+	+	+	+	+	+	Diffuse
Case 3	+	+	+	+	+	−	NA
Case 4	+	+	+	+	+	−	NA
Case 5	+	+	+	+	+	−	NA

NA not applicable, + present, − absent

Table 5 Summary of cases in the literature of benign proximal stricture of the bile duct presumably diagnosed as cholangiocarcinoma

	Total number of resected specimen	Number of benign biliary stricture	Primary sclerosing cholangitis	Biliary stricture with unknown origin	Stone disease or granulomatous process
Hadjis et al. [1]	104	8 (7.7%)[a]	N/A	8 (7.7%)	0 (0%)
Wetter et al. [7]	98	8 (8.1%)[b]	N/A	3 (3.0%)	5 (5.1%)
Verbeek et al. [6]	82	11 (13.4%)[c]	N/A	11 (13.4%)	N/A
Nakayama et al. [8]	99	14 (14.1%)[d]	N/A	14 (14.1%)	N/A
Gerhards et al. [5]	132	20 (15.1%)	N/A	15 (11.3%)	3 (2.3%)
Corvera et al. [3]	275	22 (8.0%)	3 (1.1%)	8 (2.9%)	9 (3.3%)
Uhlmann et al. [25]	49	7 (14.3%)[e]	N/A	7 (14.3%)	0 (0%)
Are et al. [2]	171	9 (5.2%)[f]	N/A	8 (4.7%)	1 (0.6%)
Erdogan et al. [4]	185	32 (17.3%)	2 (1.1%)	18 (9.7%)	7 (3.8%)
Present study	176	21 (11.9%)	0 (0%)	5 (2.8%)	2 (1.1%)

NA not applicable

[a] All cases showed increase in fibrous tissues

[b] Three cases of focal ideopathetic benign fibrosis as the cause of stricture

[c] Two out of 11 cases showed localized sclerotic tissues; 9 out of 11 cases showed chronic inflammatory infiltrations

[d] All 14 cases showed extensive fibrosis with inflammatory cellular infiltration at stricture

[e] All cases showed fibrosis with nonspecific chronic inflammation

[f] Eight cases of ideopathetic stricture