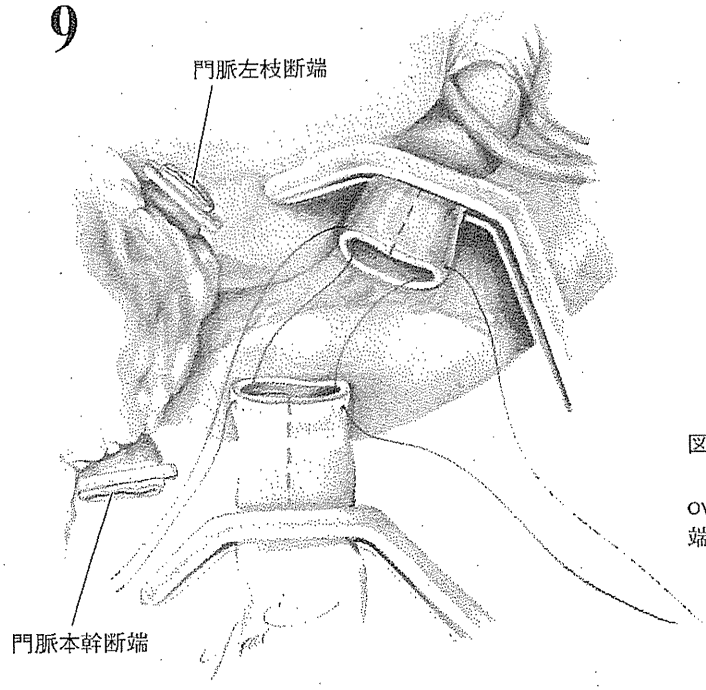


図９　門脈環状切除後端々吻合再建
　縫合は２点支持にて後壁を intraluminal に，前壁を over and over で行う。やや口径差はあるものの直接端々吻合が容易にできる

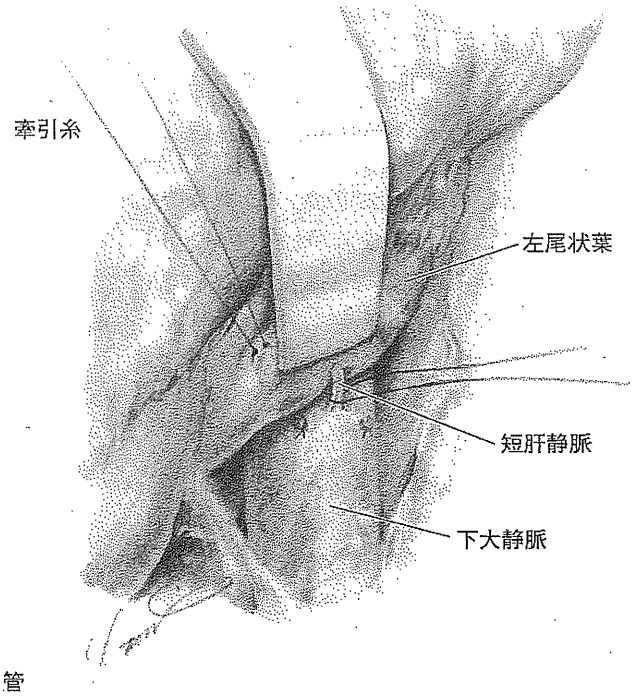


図10a　自在鉤や牽引糸を利用して左尾状葉を右方に脱転，あるいは腹側に挙上しつつ短肝静脈を結紮・切離する

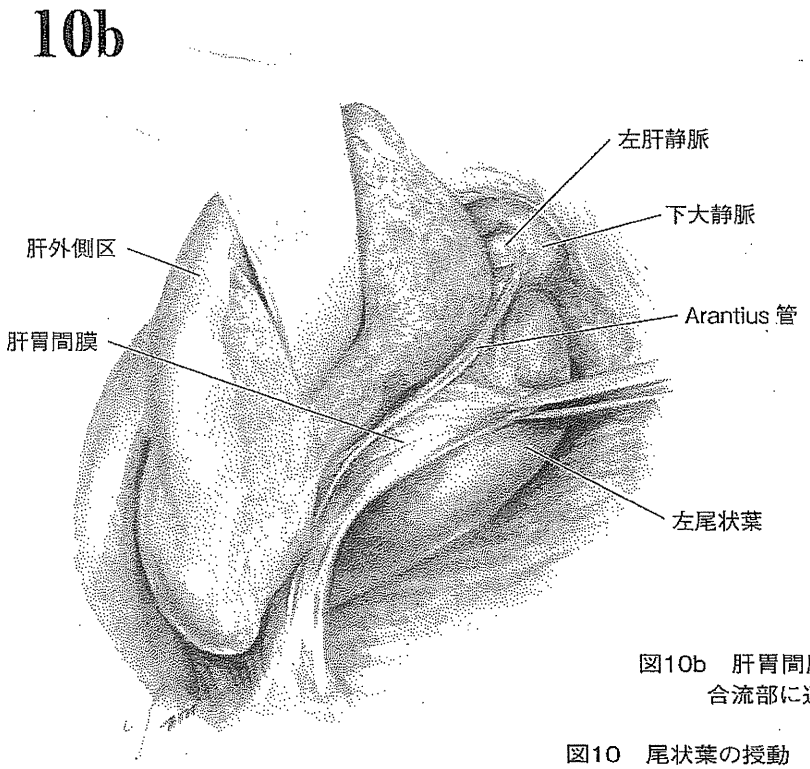


図10b　肝胃間膜を牽引し，Arantius 管が左肝静脈の下大静脈合流部に連続するのを確認し，これを切離する

図10　尾状葉の授動

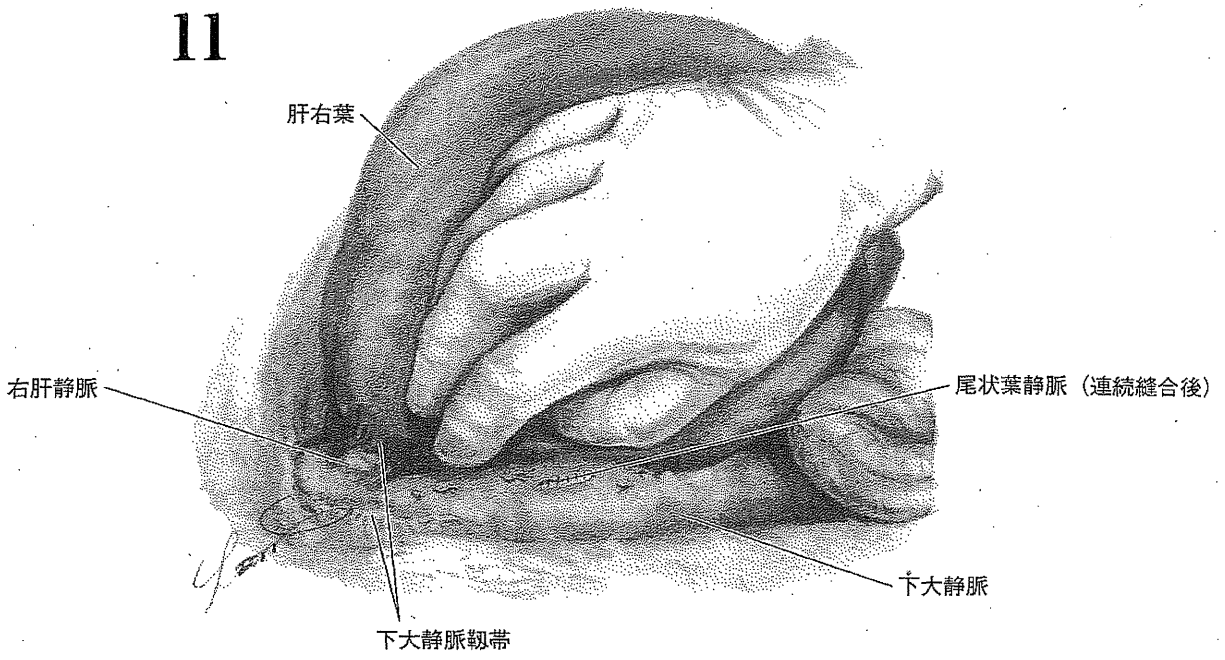


図11　肝右葉の脱転

肝右葉を腹側左側に脱転授動しながら，短肝静脈を順次頭側に向かって結紮・切離を行っていく。頭側で下大静脈靱帯を切離すると右肝静脈が右側から同定可能となるが，靱帯内にも細い静脈枝をしばしば認めるため，切離時には注意が必要である

4.　尾状葉・肝右葉の授動，右肝静脈切離

幅の細い自在鉤や牽引糸を利用して左尾状葉（Spiegel 葉）の視野を確保する。左側および尾側から左尾状葉を右方に脱転，あるいは腹側に挙上しつつ短肝静脈を結紮・切離し，下大静脈面を露出していく（図10a）。尾状葉腹側で肝胃間膜を牽引し，頭側で Arantius 管が左肝静脈の下大静脈合流部に連続するのを確認して，これを切離する。左尾状葉の脱転が困難な場合は無理をせずに肝右葉脱転時に右側からの処理を行う。下大静脈と尾状葉との剝離は静脈壁を正確に露出する層を確保しつつ進めることが重要で，肝被膜や短肝静脈の損傷による出血を避けることができる（図10b）。

続いて肝右葉を腹側左側に脱転授動しながら，短肝静脈を順次頭側に向かって結紮・切離を行っていく。いわゆる尾状葉静脈と呼ばれる太いものは連続縫合によって慎重に閉鎖すべきである。頭側に至って下大静脈靱帯を切離すると右肝静脈を同定可能であるが，靱帯内にも細い静脈枝をしばしば認めるため，切離時には注意が必要である（図11）。右肝静脈は腹側および背側から慎重に剝離を行い，テーピングの後に鏡視下手術用の自動縫合器で切離するか，切離後に連続縫合閉鎖を行う。この時点で肝右葉は完全に授動されるが，脱転操作は温存側である左葉の虚血を招く場合があるため，強い脱転を長時間連続しないように注意が必要である。

5.　肝切離，肝内胆管切離

右肝動脈，門脈右枝の切離で生じた肝表面の変色域に沿って肝実質の切離を開始する。中肝静脈を同定し，その右側を露出しながら頭側に向かいIVCまでの切離を進める。肝表面S4尾側の切離線は臍部の左葉 Glisson の基部で右に分枝する方形葉の Glisson 枝を結紮して新たな変色域を確認し，それに沿って切離を進めることで左葉 Glisson の右縁に至る（図12）。肝切離線の最背側は Arantius 板腹側に向かい，左葉の Glisson 枝（G2+3+4）をテーピングし，そこから動脈・門脈を差し引いた結合織を切離すると左肝管の分枝断端があらわれる（図13）。切除側胆管は必ずブルドッグ鉗子などで閉鎖し，胆汁漏出を起こさないことが必須である。また，それぞれの胆管が切離された直後に支持糸をかけ，これらを見失わないようにする必要がある。

6.　胆道再建[9]

胆管切離断端は腹側から $B_4$，$B_3$，$B_2$の3穴，あるいは $B_4$と $B_2$+ $B_3$の2穴になることが多いが，胆管の合

12

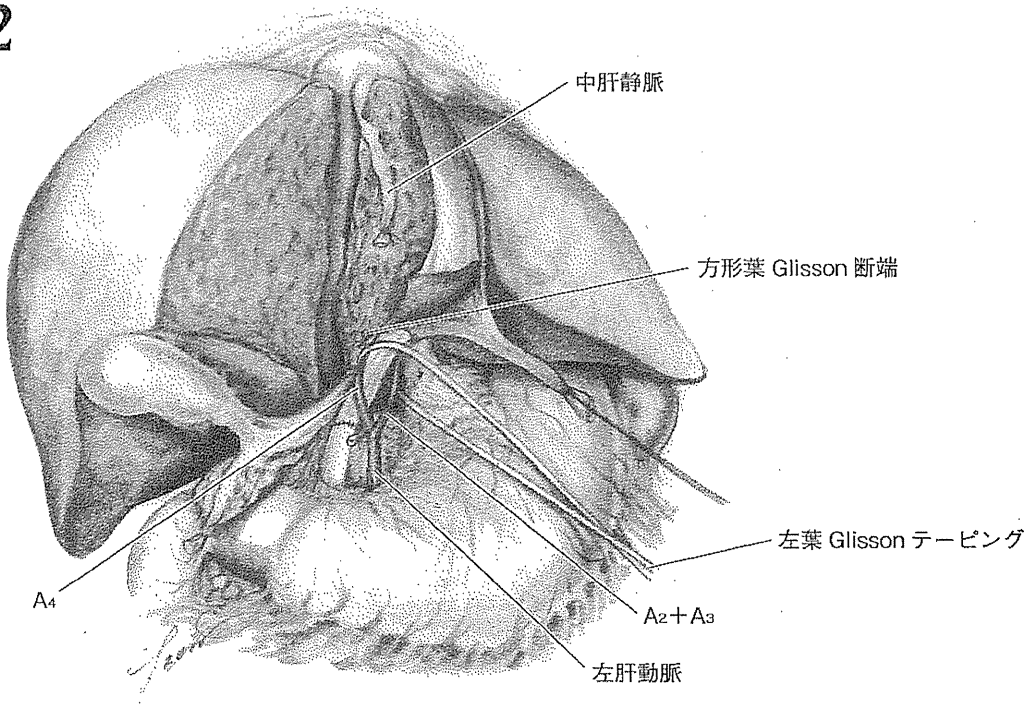


図12　肝切離

肝表面の変色域に沿って肝実質の切離を開始する。中肝静脈を同定し，その右側を露出しながら頭側に向かい下大静脈までの切離を進める。肝表面 S4尾側の切離線は方形葉の Glisson 枝を結紮して新たな変色域を確認し，それに沿って切離を進めることで左葉 Glisson 根部右縁に至る

13

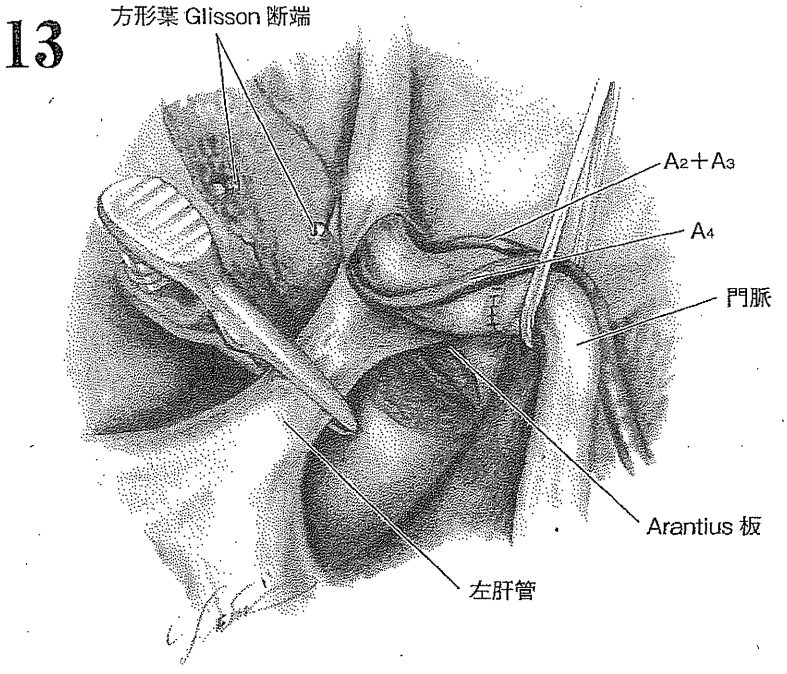


図13　胆管切離

肝切離線の最背側は Arantius 板腹側に向かい，左葉の Glisson 枝（G2＋3＋4）をテーピングし，そこから動脈・門脈を差し引いた結合織を切離すると左肝管の分枝断端があらわれる。切除側胆管は必ずブルドッグ鉗子などで閉鎖し，胆汁漏出を起こさないことが必須である。また，胆管断端は直後に支持糸をかけ，これを見失わないようにする必要がある

流形態によるため術前に予測しておく。複数の分枝を1穴に形成してもよいが，並列するすべての胆管を1つの胆管枝とみなして縫合することも可能である（図14）。空腸脚はRoux-en-Y式に挙上し，線維性組織が多く運針が容易な門脈側を後壁にして吻合を開始する。まず，後壁両側端に外縛りの糸を1針ずつかけ，それ以外は内縛りの結節縫合をかけた後，空腸脚をパラシュート式に一気に寄せて縫合糸の結紮を行う。運針の際には門脈を圧排することになるが，長時間の門脈血流低下は血栓形成の誘引になる可能性があり，注意を要する。

後壁縫合後，節付き5Frの胆管ステントチューブを吻合するすべての胆管に留置し，それぞれの胆管の後壁縫合糸の1本として使用した早期吸収型の縫合糸で固定を行う。チューブの留置・固定はもっとも背側の胆管から開始し，すべてのチューブが固定し終わってから前壁の縫合を開始する。しばしば胆管内腔の確認が困難になることがあるが，ステントチューブをガイドにすることにより，確実に胆管粘膜を縫合することができる。前壁の縫合糸の結紮時には後壁に比較し，胆管壁が裂けやすいため，丁寧で慎重な結紮手技が要求される。

### 7. ドレナージ，閉腹

胆管ステントチューブは挙上空腸脚断端で縫合固定し，さらに空腸断端を腹壁に固定（腹膜化）する。腹腔のドレナージチューブは胆管空腸吻合部背側と肝切離面に閉鎖ドレーンを留置して閉腹を行う（図15）。

14

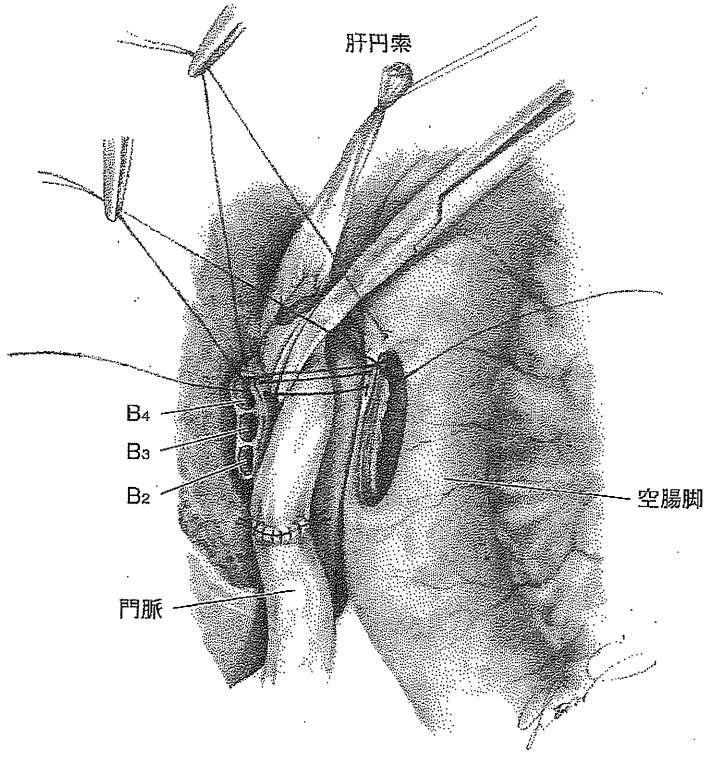


図14　胆道再建

胆管断端は腹側からB4→B3→B2の順に並び，3穴あるいは2穴になることが多い。必ず線維性組織が多く運針が容易な門脈側を後壁にして吻合を開始するが，門脈の過度の圧排に注意が必要である。後壁の縫合後，胆管ステントチューブを後壁縫合糸の1本で固定し，そのチューブをガイドにして前壁の運針を行うと確実に粘膜を縫合できる

15

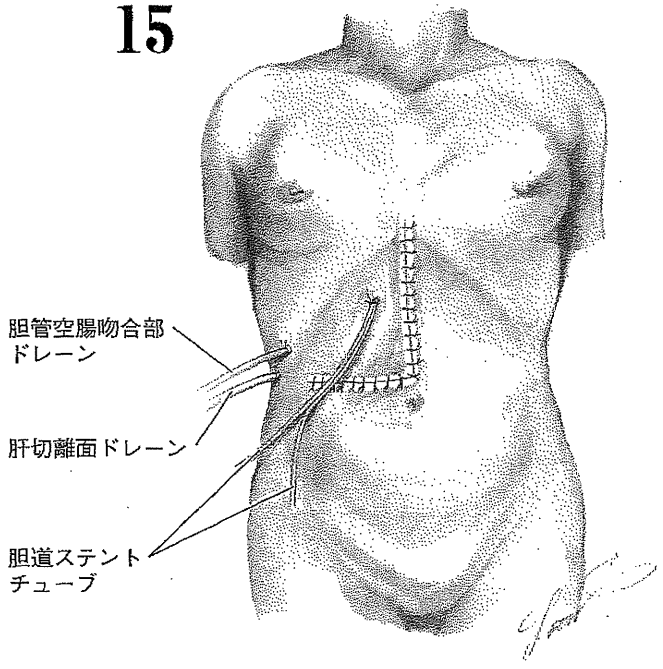


図15　ドレナージ，閉腹

胆管ステントチューブは挙上空腸脚断端で縫合固定し，さらに空腸断端を腹壁に固定（腹膜化）する。腹腔のドレナージチューブは胆管空腸吻合部背側と肝切離面に閉鎖ドレーンを留置して閉腹を行う

## Ⅳ 術後管理

術後は通常の肝葉切除と同様の管理を行う。胆汁瘻を認めた場合でも胆道ドレナージおよび腹腔ドレナージの管理を確実に行うことで保存的に治癒可能である。胆汁漏出量が多い場合はサンプ式ドレナージによる持続吸引を考慮する。術後胆道造影は臨床的に吻合に問題がないと判断されれば必ずしも必要でなく，胆管ステントチューブは術後約2週で抜去する。

門脈合併切除を行った場合，あるいは急激な肝機能増悪を認めた場合，ベッドサイドでのドプラ超音波による門脈血流の評価は重要である。

## □ おわりに

肝門部胆管癌に対する肝右葉・尾状葉・胆管切除術は術前管理の進歩や一定の手術手技が確立されたことにより，比較的安全な手術となった。しかし，高度の侵襲を伴う術式であり，術後成績向上のためには一つひとつの洗練された手技の積み重ねによって，手術時間の短縮や出血量の軽減を図る努力が不可欠である。

### 文　献


1) Kondo, S., Hirano, S., Ambo, Y., Tanak, E., Okushiba, S., Morikawa, T. and Katoh, H. : Forty consecutive resections of hilar cholangiocarcinoma with no postoperative mortality and no positive ductal margins : Results of a prospective study. Ann. Surg., 240 : 95～101, 2004.

2) Sakuhara, Y., Abo, D., Hasegawa, Y., Shimizu, T., Kamiyama, T., Hirano, S., Fukumori, D., Kawamura, T., Ito, Y. M., Tha, K. K., Shirato, H. and Terae, S. : Preoperative percutaneous transhepatic portal vein embolization with ethanol injection. AJR Am. J. Roentgenol., 198 : 914～922, 2012.

3) Hirano, S., Tanaka, E., Shichinohe, T., Suzuki, O., Hazama, K., Kitagami, H., Okamura, K., Yano, T. and Kondo, S. : Treatment strategy for hilar cholangiocarcinoma, with special reference to the limits of ductal resection in right-sided hepatectomies. J. Hepatobiliary Pancreat. Surg., 14 : 429～433, 2007.

4) Nakanishi, Y., Zen, Y., Kawakami, H., Kubota, K., Itoh, T., Hirano, S., Tanaka, E., Nakanuma, Y. and Kondo, S. : Extrahepatic bile duct carcinoma with extensive intraepithelial spread : A clinicopathological study of 21 cases. Mod. Pathol., 21 : 807～816, 2008.

5) Kawakami, H., Kuwatani, M., Etoh, K., Haba, S., Yamato, H., Shinada, K., Nakanishi, Y., Tanaka, E., Hirano, S., Kondo, S., Kubota, K. and Asaka, M. : Endoscopic retrograde cholangiography versus peroral cholangioscopy to evaluate intraepithelial tumor spread in biliary cancer. Endoscopy, 41 : 959～964, 2009.

6) Ebata, T., Nagino, M., Kamiya, J., Uesaka, K., Nagasaka, T. and Nimura, Y. : Hepatectomy with portal vein resection for hilar cholangiocarcinoma : Audit of 52 consecutive cases. Ann. Surg., 238 : 720～727, 2003.

7) Hirano, S., Kondo, S., Tanaka, E., Shichinohe, T., Tsuchikawa, T. and Kato, K. : No-touch resection of hilar malignancies with right hepatectomy and routine portal reconstruction. J. Hepatobiliary Pancreat. Surg., 16 : 502～507, 2009.

8) Kawakami, H., Kuwatani, M., Onodera, M., Haba, S., Eto, K., Ehira, N., Yamato, H., Kudo, T., Tanaka, E., Hirano, S., Kondo, S. and Asaka, M. : Endoscopic nasobiliary drainage is the most suitable preoperative biliary drainage method in the management of patients with hilar cholangiocarcinoma. J. Gastroenterol., 46 : 242～248, 2011.

# 6 腹腔動脈合併尾側膵切除（DP-CAR）

平野　聡*　田中　栄一*2　土川　貴裕*2
松本　譲*2　中村　透*2　七戸　俊明*3

## はじめに

腹腔動脈合併尾側膵切除術（distal pancreatectomy with *en bloc* celiac axis resection；DP-CAR）は腹腔動脈（CA）や総肝動脈（CHA），脾動脈（SA）根部あるいはそれらの周囲神経叢（plexus：PL）に浸潤した局所進行膵体部癌に対しても癌遺残のない切除を可能にする術式である[1)2)]。

術式の特徴として動脈や消化管の再建が不要で安全性が高く，臓器欠損も少ないことがあげられる。しかし，一方で膵頭部側に張り出す腫瘍では膵断端が広くなり膵液瘻が長期化しやすいことや，虚血性胃症など特有の合併症が起こり得ることを理解しておく必要がある[2)~4)]。また，本術式は上腸間膜動脈（SMA）周囲神経叢（PLsma）の全周郭清など広範な神経叢郭清を行うが，投薬で調整困難な高度の下痢は経験しておらず，癌性疼痛は神経遮断効果で術直後から消失する。すなわち，本術式の急性期以降のQOLは比較的良好であり[5)6)]，補助化学療法へのスムースな導入を目指すことができる。

* Satoshi HIRANO　北海道大学大学院医学研究科消化器外科学分野Ⅱ　教授
*2 Eiichi TANAKA et al.　同外科
*3 Toshiaki SHICHINOHE　同外科　准教授

Keywords
進行膵体部癌，腹腔動脈，拡大切除

## Ⅰ. DP-CARの手術適応と切除範囲

手術適応となるのは①遠隔転移がなく，②CA，CHA，SA根部に近接あるいは浸潤した局所進行膵体部癌のうち，③胃十二指腸動脈に癌浸潤を認めず，下膵十二指腸動脈（IPDA）を含めた膵頭アーケードが確実に温存でき，④PLsmaへの浸潤が腹側半周にとどまる症例である[1)2)]。

切除範囲は尾側膵に加え，CA，CHA，左胃動脈，両側腹腔神経叢，腹腔神経節，SMA周囲神経叢，横隔膜脚の一部，左腎前面のGerota筋膜，左副腎，左腎静脈より頭側の後腹膜脂肪織，横行結腸間膜，下腸間膜静脈を*en bloc*に切除する（図1，2）。リンパ節は膵癌取扱い規約における第2群リンパ節と，大動脈周囲リンパ節のうちNo.16a1，No.16a2を郭清する。また，症例に応じて門脈の合併切除を行う。腹腔動脈切除後にはSMAから膵頭部アーケードを介した側副動脈血流により胃・肝血流が確保されるが，われわれは臓器障害を予防するために術前にIVR（interventional radiology）の手技を用いてCHAおよび左胃動脈の塞栓術を行っている[4)]。

## Ⅱ. DP-CARの手技の実際

### 1. 皮膚切開，開腹（図3）

まず，臍上に至る上腹部正中切開で開腹し，腹

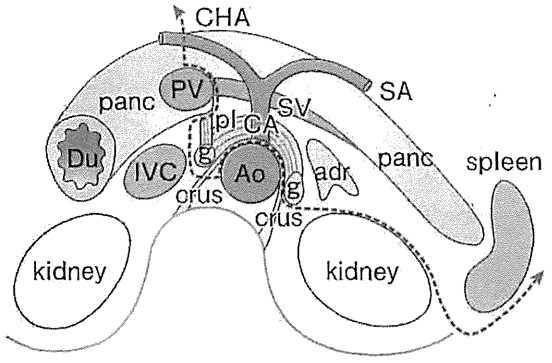


図1　腹腔動脈合併切除を伴う膵尾側切除（DP-CAR）の切除範囲

点線より腹側が切除範囲となる（文献4より引用改変）

Adr：副腎，Ao：大動脈，CA：腹腔動脈，CHA：総肝動脈，crus：横隔膜脚，Du：十二指腸，g：腹腔神経節，IVC：下大静脈，pl：腹腔神経叢，PV：門脈，SA：脾動脈，SV：脾静脈

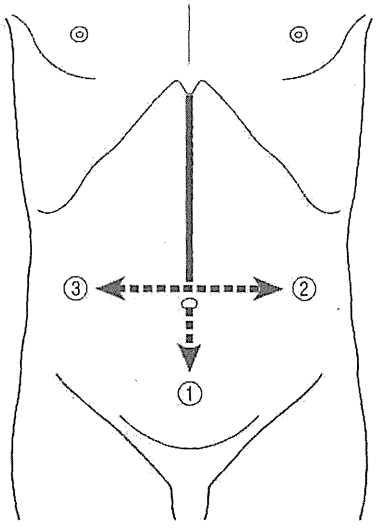


図3　皮膚切開，開腹

臍上に至る上腹部正中切開が基本となる。体格に応じて，この創の下端から臍を縦切する正中切開を追加するか（①），左へ横切開を加えるか（②），②に加えて右へ横切開を加えることで（②+③），十分な術野を得ることができる。

腔内の大まかなinspectionを行う。そのあと，臍を縦切しながら正中切開を尾側に延長するか，左へ横切開を加えるかを体格に応じて決定する。左横切開に加えて右へ横切開を加えることで最大の術野を確保することができる。

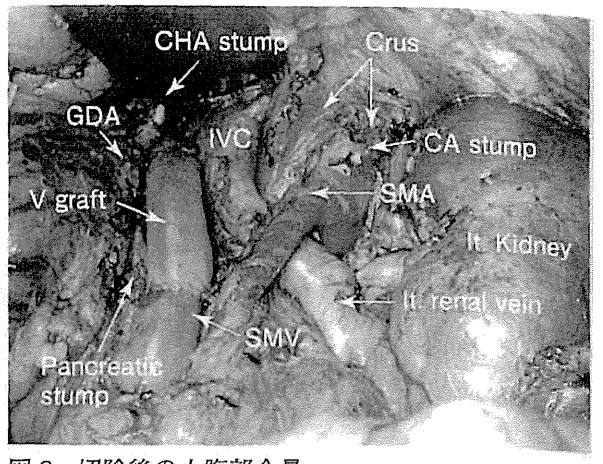


図2　切除後の上腹部全景

門脈合併切除，右外腸骨静脈間置再建例

CHA stump：総肝動脈断端，Crus：横隔膜脚，CA stump：腹腔動脈断端，GDA：胃十二指腸動脈，SMA：上腸間膜動脈，SMV：上腸間膜静脈，Pancreatic stump：膵断端，V graft：右外腸骨静脈グラフト，It. Kidney：左腎，It. renal vein：左腎静脈

## 2. 転移の有無のチェックと結腸の授動

開腹後，肝・腹膜転移がないことを確かめたあと，網嚢を完全に開放してさらに腹膜転移がないことを確認する。その際，切除後に胃大彎側の唯一の供血・脱血路となる左右胃大網動静脈を十分愛護的に扱うべきである。続いて結腸脾彎曲部を十分に足側へ授動しておく。

## 3. SMA周囲神経叢（PLsma）切開から腹腔動脈遮断まで（図4）

Kocher授動を行い，下大静脈前面につづいて左腎静脈を露出する。左腎静脈をテーピングし，左側に剝離を進めると上縁に流入する左副腎静脈を同定できる。これが大動脈に近い場合はこの時点で結紮・切離することで大動脈前面を露出しやすくなる。腎静脈の頭側の大動脈前面でSMAを確認し，その背側で神経叢を4〜5 cm遠位側に向かって縦割りし，SMA外膜を露出したら慎重に全周を剝離後，テーピングを行う。PLsmaのすぐ頭側には腫瘍があり，剝離には細心の注意を要する。背側膵動脈がSMAから分岐する場合にはその処理を行う。

つづいて下大静脈を右側に圧排し，右横隔膜脚を露出するように頭側に剝離を行うと右腹腔神経節，No.16a2 precaval, retrocaval, interaortico-

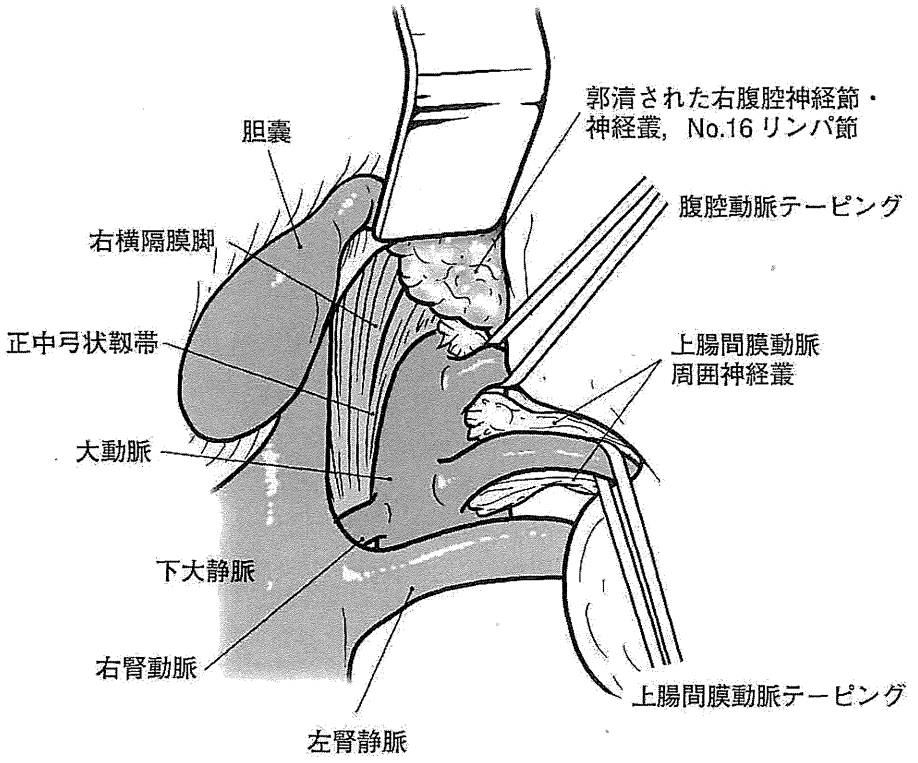


**図 4　上腸間膜動脈神経叢郭清から腹腔動脈遮断まで**

上腸間膜動脈根部背側で神経叢を縦割りにし，全周性に 4〜5 cm 遠位側に向かって剝離を行う。右横隔膜脚を露出する層で右腹腔神経節，No.16a2 inter リンパ節を *en bloc* に郭清する。正中弓状靱帯脚を切離して腹腔動脈根部に至り，これを結紮するかブルドック鉗子でクランプしておく。

caval リンパ節を *en bloc* に切除郭清できる。さらに横隔膜脚の尾側端を形成する正中弓状靱帯脚を切離すると容易に腹腔動脈（CA）根部に至ることができる。CA は最小限の剝離でテーピングを行い，結紮するかブルドック鉗子でクランプしておく。

## 4. 後腹膜郭清（図 5）

Treitz 靱帯の切離によって空腸起始部を授動し後腹膜腔に達すると，すでに剝離・テーピングを済ませた左腎静脈に到達する。そのすぐ頭側で SMA にかけたテープを求め，両者を引き出しておく。横行結腸間膜の膵体部を被う部分を下腸間膜静脈とともに合併切除し，左腎静脈と SMA のテープを結腸間膜の頭側に引き出す。つぎに，左腎動脈を確認し，動静脈を尾側縁として後腹膜組織を *en bloc* に切除する。左外側では左腎被膜に達してそのまま上極の被膜を露出しながら背側に向かって腎筋膜，腎周囲脂肪織を切離すると左副腎が切除側に含まれる。後腹膜組織の切離を内側に進めると左横隔膜脚に至り，脚前面を露出しながら頭側に向かうと左腹腔神経節，No.16a2 laterocaval リンパ節が郭清できる。

## 5. 総肝動脈切離から膵切離（門脈合併切除再建）まで

膵前面に戻り，胃十二指腸動脈（GDA）・総肝動脈（CHA）・固有肝動脈（PHA）を最小限の範囲で剝離・同定する。膵頭アーケードを経由する血流を確認し CHA を結紮切離するが，TAE の影響で剝離がやや困難なことがある。腫瘍が膵頭側に張り出している場合には GDA を膵への小分枝を処理しつつ右側へ授動し，膵切離が腫瘍から十分離れて行えるように準備する（図 6）。

門脈の前面あるいは右側よりで腫瘍から離れてトンネリングを行ったのち，十分なマージンを確保して膵切離を行う。膵頸部で離断が可能な場合はエンド GIA™ トライステイプル™ が膵液瘻予

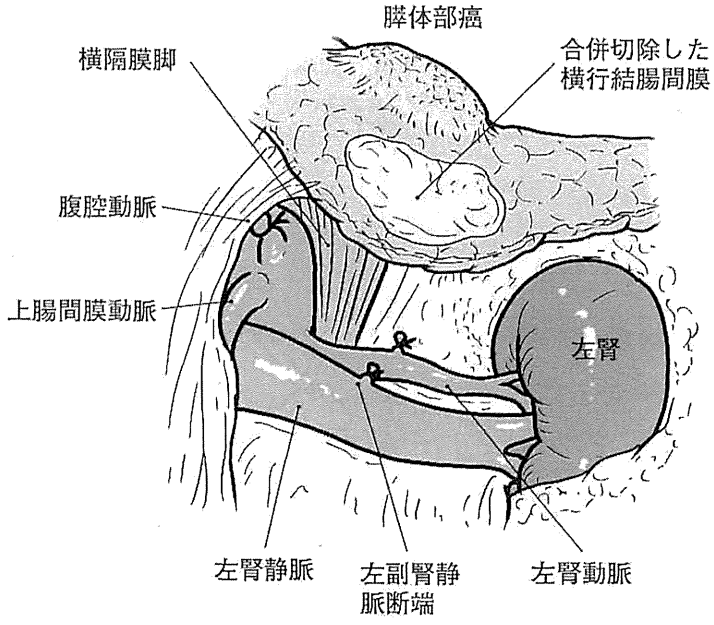


図5　後腹膜郭清

左腎動脈より頭側の後腹膜組織の切離を行う。左外側では左腎上極の被膜を露出しながら腎筋膜，腎周囲脂肪織を切離すると左副腎が切除側に含まれる。内側では左横隔膜脚前面を露出しながら頭側に向かうと，左腹腔神経節，No.16a2 latero リンパ節が郭清できる。

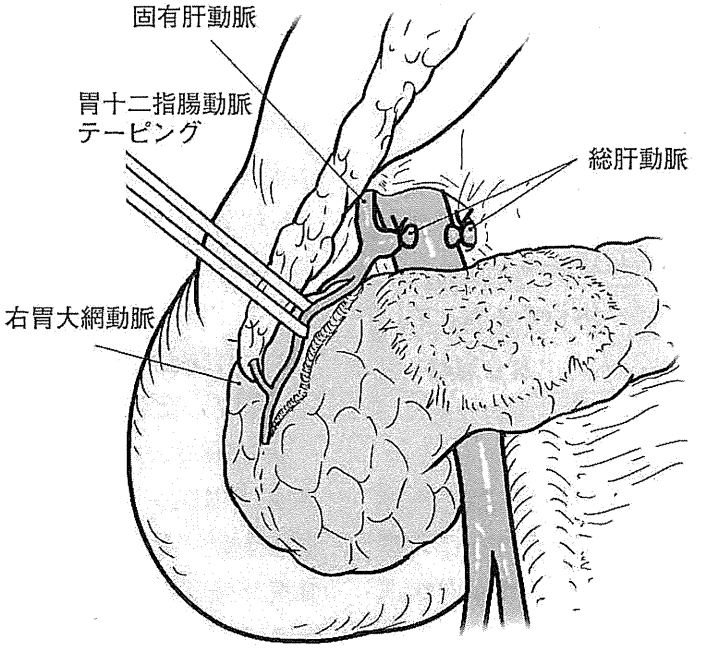


図6　総肝動脈切離と胃十二指腸動脈の授動

胃十二指腸動脈を確認し，慎重に温存しながら総肝動脈および固有肝動脈を露出する。膵頭アーケードを経由する血流を確認して総肝動脈を結紮切離する。腫瘍が膵頭側に張り出している場合には胃十二指腸動脈を右側へ授動して，膵切離が腫瘍から十分離れて行えるように準備する。

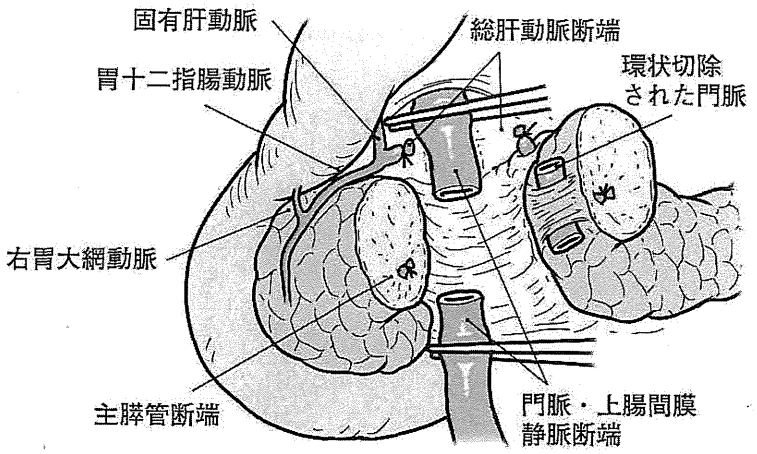


図7　膵切離，門脈合併切除再建

膵のトンネリングは腫瘍の位置に応じて門脈前面または右面で行い，腫瘍との間に十分なマージンを確保して膵切離を行う。腫瘍が膵頭側に張り出している場合，膵頭部は門脈右背側に向かって斜めに切離されるが，主膵管は必ず結紮し，膵断端は4-0モノフィラメント糸による連続縫合で緩く縫縮する。腫瘍の部位によって脾静脈切離が可能な場合と，門脈の楔状あるいは環状の門脈合併切除を伴う場合とに分けられる。

防効果もあり，有用な可能性が高い。

GDAの授動を要した場合，膵は門脈の背側面に向かって電気メスで斜めに切離するが，主膵管は必ず同定して結紮する。広い断面を縫縮することは困難であるため，切離時に牽引に用いた4-0モノフィラメント非吸収糸で断面を若干縮小させる程度に連続縫合を行い，微細な分枝膵管からの膵液漏れを予防する。

腫瘍が体部側にあり脾静脈に十分な“縛りしろ”が確保できる場合以外，上腸間膜静脈は脾静脈との合流部で楔状切除が必要になる。門脈切離前には膵頭部から門脈への全分枝を結紮あるいはクランプする必要がある。さらに強い門脈浸潤を疑う場合は環状切除が必要となるが，切除長が2～3 cm以上になるときは左腎静脈グラフトによる間置再建を考慮する（図7）。

## 6. SMA周囲神経叢（PLsma）の切離および膵頭神経叢（PLphII）と膵鉤部間の切離

術野を左側に転じ，すでに根部から切離されているPLsma切開線を背側のまま末梢側に向かって延長させ，動脈からの剝離を進める。腫瘍が尾側に大きく張り出している場合，下膵十二指腸動脈（IPDA）の損傷を防ぐため，あらかじめ第一空腸動脈をテーピングし，IPDAの走行を確認して神経叢を右側に向かって横断する。神経叢を横断し，動脈を乗り越えると上腸間膜静脈背側で膵鉤部に達することができる（図8）。つぎに鉤状

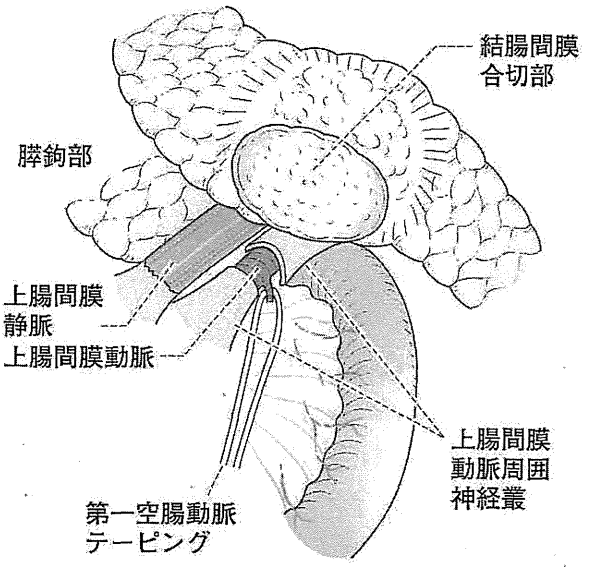


図8　上腸間膜動脈神経叢切離

すでに根部背側で切開されている上腸間膜動脈周囲神経叢をさらに背側で末梢に向かって切開を延長する。腫瘍が尾側に大きく張り出している場合は，下膵十二指腸動脈（IPDA）の損傷を防ぐため，あらかじめ第一空腸動脈をテーピングし，IPDAの走行を確認して神経叢を横断する。膵頭神経叢を右側に向かって横断し，動脈を乗り越えると上腸間膜静脈背側で膵鉤部に達することができる。

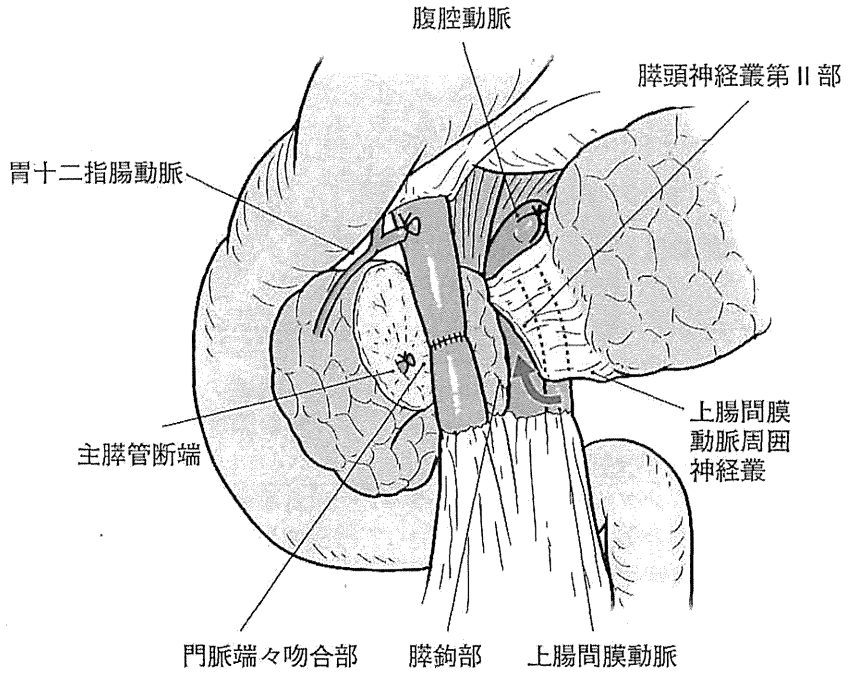


図9　膵頭神経叢と膵鉤部の切離
鉤状突起に沿って膵頭神経叢第II部との間を頭側に切離していく（矢印）と大動脈前面に到達し，すでに血流遮断してある腹腔動脈根部が確認できる。

突起に沿って膵頭神経叢第II部（PLphII）との間を頭側に切離していくと大動脈前面に到達し，すでに血流遮断してある腹腔動脈根部が確認できる（図9）。

### 7．腹腔動脈（CA）・左胃動脈切離（図10）

腹腔動脈（CA）を結紮切離し，横隔膜脚の露出を正中から左側に向かい，左側からの横隔膜脚剝離層と連続させる。左胃動静脈を処理しながら胃小彎との間を切離し，さらに胃脾間膜を脾に沿って切離すると胃との連続は絶たれる。

### 8．後腹膜脂肪組織の切離，切除検体摘出から閉腹まで

切除側の膵体部は後腹膜のみと連続している状態となる。切除膵の断端を腹側左側に脱転しながら先に行っていた左側後腹膜の剝離面を左背側に連続させ，脾周囲の後腹膜に至ると切除が終了する。

固有肝動脈，右胃大網動脈の血流を確認後，膵切離断端近傍と左横隔膜下にドレーンを確実に留置し，閉腹する（図11）。

## おわりに

本術式によって，これまで非切除とされてきた局所進行癌であっても高いR0切除率と局所制御効果が得られる。しかし，実際の手技は大動脈やCA，SMAなどの大血管を扱うため，難度の高い術式であることを十分念頭において手術に臨むべきである。

## 文献

1) Kondo S et al : Results of radical distal pancreatectomy with en bloc resection of the celiac artery for locally advanced cancer of the pancreatic body. Langenbecks Arch Surg 388 : 101-106, 2003
2) Hirano S et al : Distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer : long-term results. Ann Surg 246 : 46-51, 2007
3) Kondo S et al : Ischemic gastropathy after distal pancreatectomy with celiac axis resection. Surg Today 34 : 337-340, 2004
4) Abo D et al : Feasibility of a dual microcatheter-dual interlocking detachable coil technique in preoperative embolization in preparation for distal pancreatectomy with en bloc celiac axis resection for locally advanced pancreatic body cancer. J Hepatobiliary Pancreat Sci 19 : 431-437, 2012

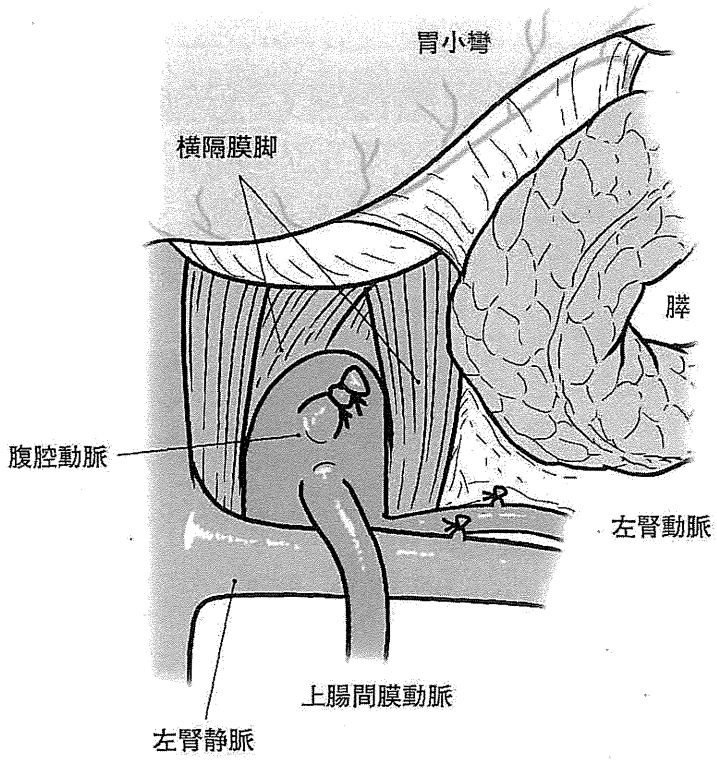


**図 10　腹腔動脈・左胃動脈切離**

腹腔動脈を結紮切離し，横隔膜脚の露出を正中から左側に進み，左側からの横隔膜脚剝離層と連続させる。左胃動静脈を切離しながら胃小彎との間を切離する。

5) Kondo S et al : Radical distal pancreatectomy with en bloc resection of the celiac artery, plexus, and ganglions for advanced cancer of the pancreatic body : a preliminary report on perfect pain relief. JOP 2 : 93-97, 2001
6) Hirano S et al : Postoperative bowel function and nutritional status following distal pancreatectomy with en-bloc celiac axis resection. Dig Surg 22 : 212-216, 2010

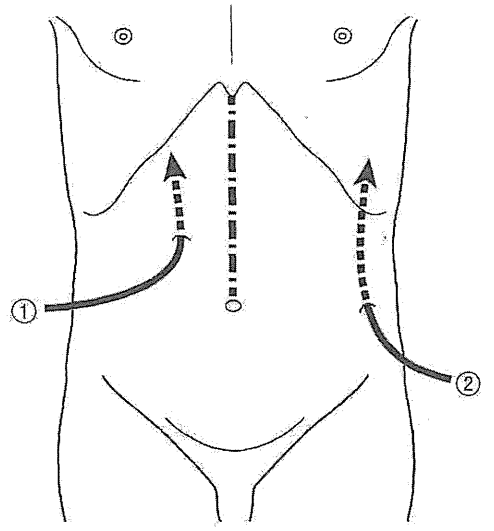


**図 11　ドレーン挿入，閉腹**

膵断端（①）および左横隔膜下（②）に閉鎖ドレーンを留置して閉腹する。

J Gastroenterol (2015) 50:119–120
DOI 10.1007/s00535-014-0967-6

The Japanese Society of Gastroenterology

EDITORIAL

# Is "liquid biopsy" useful for assessing HER2 status in gastric cancer?

**Hideaki Shimada**

Received: 24 April 2014 / Accepted: 28 April 2014 / Published online: 14 May 2014
© Springer Japan 2014

After a delay of several years from its introduction to treat breast cancer, anti-HER2 monoclonal antibody (trastuzumab) combined with chemotherapy was proposed as a standard option for HER2-positive patients with advanced and/or recurrent gastric cancer [1]. Although immunohistochemical analysis of tumor tissues takes first priority for selecting patients, the "heterogeneity" of HER2 expression and/or difficulties in biopsy are frequent limitations, particularly for recurrent gastric cancer. Therefore, multiple biopsies are required to evaluate the precise status of HER2 expression [2, 3].

A "liquid biopsy" using blood is useful for characterizing circulating tumor cells instead of biopsies of tumor tissues [4], and serum biomarkers of gastrointestinal tumors provide convenient tools to assess tumor phenotypes [5]. For example, a recent extensive survey of the literature suggests that serum markers such as CEA, CA19-9, and CA72-4 facilitate staging of gastric cancers before surgery or chemotherapy and for assessing response to therapy and the risk of recurrence [6]. Moreover, serum biomarkers such as HER2 ECD may overcome the problem of heterogeneity of HER2 expression in tumor tissues. A systematic review of 63 studies of breast cancer conducted by Leyland-Jones et al. [7] revealed that HER2 ECD expression was significantly associated with the HER2 status of tumors. However, the serum HER2 ECD levels were not consistently related to patients' outcomes. Furthermore, the authors noted that 13 different assay techniques using 15 different cut-off values may explain the discrepant results. The results of four studies of gastric cancer are inconsistent regarding the associations among serum HER2 ECD levels, tissue HER2 expression status, and patients' responses to treatment and their outcomes [8–11]. Similar to the results of these breast cancer studies, different cut-off values were used to define positive rates [11]. Because there is only limited data on the serum HER2 ECD levels in gastric cancer patients, it will be necessary to conduct more studies. Moreover, chemiluminescent immunoassays (CLIAs) [12] show promise as alternatives to enzyme-linked immunosorbent assays (ELISAs) for accurately assessing the HER2 status of tumors.

In recent issues of the *Journal of Gastroenterology*, Oyama et al. [13], using a highly sensitive CLIA, reported their evaluation of the clinical utility of using serum HER2 ECD levels in a study of 150 gastric cancer patients. Analysis of 36 patients before and after chemotherapy revealed significant associations between serum HER2 ECD and tissue HER2 expression levels, leading them to conclude that serum HER2 ECD levels predict tissue HER2 expression and therefore show promise for monitoring patients' response to treatment. Although the low sensitivity (36.0 %) of serum HER2 ECD levels for detecting tissue HER2 expression may limit its use, it is excellent for monitoring the response to treatment. Because treatment with trastuzumab may interfere with the conventional ELISA [12], CLIA shows promise as an alternative. Thus, Oyama et al. established for the first time that a "liquid biopsy" to detect HER2 expression in tumors shows promise for monitoring the response to treatment of advanced/recurrent gastric cancer patients.

Zhang et al. [14] reported that an assay based on linear ribonucleic acid (RNA) fluorescent amplification catalyzed

This comment refers to the article available at doi:10.1007/s00535-014-0941-3.

H. Shimada (✉)
Department of Surgery and Clinical Oncology, Toho University School of Medicine, Tokyo, Japan
e-mail: hideaki.shimada@med.toho-u.ac.jp

by T7 RNA polymerase technology is more sensitive compared with other methods. The studies described here lead one to the reasonable conclusion that a liquid biopsy to detect gastric carcinoma could be developed to improve the quality of monitoring of this disease and predicting its treatment response. What will be the next target of a liquid biopsy for gastric cancer? The malignant potential of gastric cancer is frequently attributed to high levels of angiogenic factors and/or growth factor expression rather than those of HER2 expression. Examples include vascular endothelial growth factor, fibroblast growth factor, and thymidine phosphorylase [15]. These molecules, as well as their receptors, may serve as potential targets of liquid biopsy assays for selecting the most appropriate treatment for gastric cancer patients.

**Conflict of interest** There is no conflict of interest regarding this manuscript.

## References


1. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomized controlled trial. Lancet. 2010;376:687–97.
2. Aizawa M, Nagatsuma AK, Kitada K, et al. Evaluation of HER2-based biology in 1,006 cases of gastric cancer in a Japanese population. Gastric Cancer. 2014;17:34–42.
3. Boku N. HER2-positive gastric cancer. Gastric Cancer. 2014;17:1–12.
4. Turner N, Pestrin M, Galardi F, et al. Can biomarker assessment on circulating tumor cells help direct therapy in metastatic breast cancer? Cancers (Basel). 2014;6:684–707.
5. Shimada H, Yajima S, Oshima Y, et al. Impact of serum biomarkers on esophageal squamous cell carcinoma. Esophagus. 2012;9:131–40.
6. Shimada H, Noie T, Ohashi M, et al. Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. Gastric Cancer. 2014;17:26–33.
7. Leyland-Jones B, Smith BR. Serum HER2 testing in patients with HER2-positive breast cancer: the death knell tolls. Lancet Oncol. 2011;12:286–95.
8. Kono K, Naganuma H, Sekikawa T, et al. Serum level of HER-2/neu in patients with gastric cancer: correlation with HER-2/neu overexpression in gastric carcinoma tissue. Tumour Biol. 2000;21:139–44.
9. Takehana T, Kunitomo K, Kono K, et al. Status of c-erbB-2 in gastric adenocarcinoma: a comparative study of immunohistochemistry, fluorescence in situ hybridization and enzyme-linked immuno-sorbent assay. Int J Cancer. 2002;98:833–7.
10. Narita T, Seshimo A, Suzuki M, et al. Status of tissue expression and serum levels of HER2 in gastric cancer patients in Japan. Hepatogastroenterology. 2013;60:1083–8.
11. Dai SQ, An X, Wang F, Shao Q, et al. Serum HER 2 extracellular domain level is correlated with tissue HER 2 status in metastatic gastric or gastro-oesophageal junction adenocarcinoma. PLoS One. 2013;8:e63458.
12. Lam L, McAndrew N, Yee M, et al. Challenges in the clinical utility of the serum test for HER2 ECD. Biochim Biophys Acta. 2012;1826:199–208.
13. Oyama K, Fushida S, Tsukada T, et al. Evaluation of serum HER2-ECD levels in patients with gastric cancer. J Gastroenterol. 2014;. doi:10.1007/s00535-014-0941-3.
14. Zhang H, Cheng X, Richter M, Greene MI. A sensitive and high-throughput assay to detect low abundance proteins in serum. Nat Med. 2006;12:473–7.
15. Oshima T, Masuda M. Molecular targeted agents for gastric and gastroesophageal junction cancer. Surg Today. 2012;42:313–27.

Surg Today (2014) 44:1957–1961
DOI 10.1007/s00595-013-0787-y

CASE REPORT

# Long-term monitoring of serum p53 antibody after neoadjuvant chemotherapy and surgery for esophageal adenocarcinoma: report of a case

**Hideaki Shimada · Matsuo Nagata · Akihiro Cho · Nobuhiro Takiguchi · Osamu Kainuma · Hiroaki Soda · Atsushi Ikeda · Yoshihiro Nabeya · Satoshi Yajima · Hiroshi Yamamoto · Takahiro Sugiyama · Makiko Itami**

Received: 25 February 2013 / Accepted: 13 May 2013 / Published online: 17 November 2013
© Springer Japan 2013

**Abstract** We monitored serum p53 antibody (s-p53-Ab) titers in a 76-year-old man with esophageal adenocarcinoma, clinical stage III (T2N2M0), for over 4 years, including during the perioperative period and throughout follow-up after surgery. Screening tests for CA19-9 (205 IU/ml) and s-p53-Abs (381 U/ml) were positive before treatment. After neoadjuvant chemotherapy with 5-FU and cisplatin, CA19-9 decreased to the normal range, but the s-p53-Ab titer remained positive (224 U/ml). Pathological findings of surgically resected specimens showed stage T1b disease and no lymph node metastases. After surgery, s-p53-Ab titers consistently decreased, with no disease recurrence. Although the s-p53-Ab titer remained positive even after 4 years, it decreased to 8.66, 3.59, 2.38, and 1.92 U/ml, 1, 2, 3, and 4 years after surgery, respectively. Thus, monitoring perioperative changes in s-p53-Ab titers proved useful for detecting the presence of residual cancer cells in a patient with superficial esophageal adenocarcinoma.

**Keywords** Serum p53 antibody · Esophageal adenocarcinoma · Surgery · Monitoring

H. Shimada (✉) · S. Yajima
Department of Surgery, School of Medicine, Toho University, 6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-8541, Japan
e-mail: hideaki.shimada@med.toho-u.ac.jp

M. Nagata · A. Cho · N. Takiguchi · O. Kainuma · H. Soda · A. Ikeda · Y. Nabeya · H. Yamamoto
Department of Gastroenterological Surgery, Chiba Cancer Center, 666-2 Nitona-cho, Chuou-ku, Chiba, Japan

T. Sugiyama · M. Itami
Department of Pathology, Chiba Cancer Center, 666-2 Nitona-cho, Chuou-ku, Chiba, Japan

## Introduction

Overexpression of mutant p53 protein has been found to induce serum p53 IgG antibodies (s-p53-Abs) in patients with esophageal squamous cell carcinoma (SCC) [1, 2] including stage I cancer [3]. Our previous report showed that monitoring s-p53-Abs was useful for predicting tumor recurrence in patients with esophageal SCC, possibly because the antibody response is caused by the presence of residual cancer cells [4]. Although several studies have demonstrated the clinicopathological significance of s-p53-Abs in patients with esophageal SCC [5–8] or gastric/colon adenocarcinoma [9–12], there is little information about the clinicopathological significance of the perioperative s-p53-Ab titer in patients with esophageal adenocarcinoma [13]. This case report follows the perioperative and long-term changes in s-p53-Ab titers in a patient with esophageal adenocarcinoma treated with neoadjuvant chemotherapy followed by radical surgery. To our knowledge, this is the first case report to document the long-term monitoring of s-p53-Ab titers for more than 4 years after surgery in a patient with esophageal adenocarcinoma.

## Case report

A 76-year-old man was referred to our hospital for investigation of dysphagia. Endoscopic examination showed a circumferential tumor located in the lower esophagus (Fig. 1a). A biopsy identified the tumor as a moderately differentiated adenocarcinoma that was overexpressing p53 protein (Fig. 1b). Upper gastrointestinal radiography and computed tomography (CT) showed an 8-cm-long semi-circumferential tumor (Fig. 1c). Positron emission tomography (PET) and CT showed enlargement of the

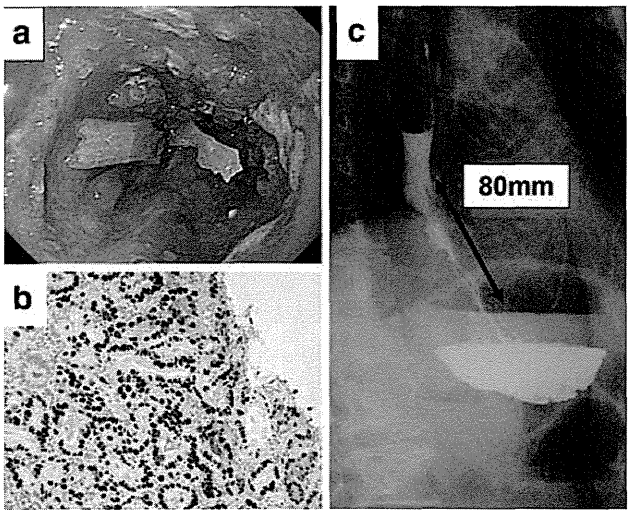


**Fig. 1** **a** Endoscopic view, **b** p53 immunoreactivity in the biopsy specimen, and **c** esophagography showed lower thoracic esophageal adenocarcinoma with p53 overexpression

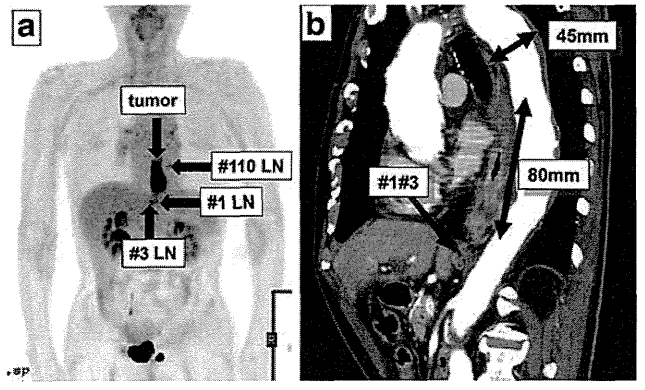


**Fig. 2** **a** Positron emission tomography and **b** computed tomography showed lower thoracic esophageal cancer with #1 and #3 lymph node metastases

peri-gastric lymph nodes (#1 and/or #3 according to the Japanese Classification of Esophageal Cancer [14]) that were positive according to the standard uptake values for PET (Fig. 2a, b). The disease was diagnosed as clinical stage III (T3N2M0).

Tests for serum tumor markers before treatment revealed positivity for CA19-9 (205 IU/ml) and s-p53-Abs (381 U/ml), and negativity for CEA, SCC-antigen, and CYFRA21-1 (Fig. 3). The s-p53-Ab titers were assessed by ELISA using a highly specific and quantitative p53 Abs ELISA kit (MESACUP anti-p53 Test; Medical & Biological Laboratories Co. Ltd.; Nagoya, Japan) with a cut-off value of 1.3 U/ml [15]. He received three courses of neoadjuvant chemotherapy comprising 5 FU (800 mg/m$^2$/day, given for 5 days) and cisplatin (80 mg/m$^2$/day, given on day 1). After chemotherapy, both the main tumor and the metastatic lymph node had decreased in size (Fig. 2).

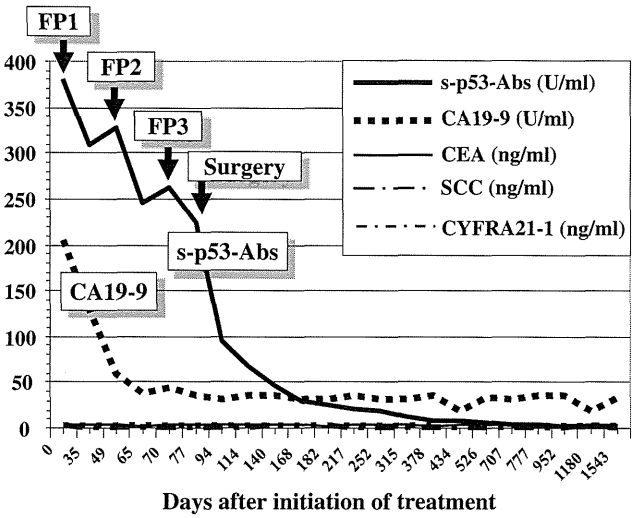


**Fig. 3** Changes in serum p53 antibody titers during chemotherapy followed by surgery. The CA19-9 concentration decreased to within the normal range after two courses of chemotherapy

Although the serum concentration of CA19-9 decreased to within the normal range, the s-p53-Ab titer remained positive at 224 U/ml (Fig. 3). We then performed subtotal esophagectomy and two-field dissection of the mediastinal and abdominal lymph nodes through a right thoracotomy. This procedure was followed by reconstruction with a gastric tube via the retrosternal route.

Examination of the surgically resected specimen revealed viable adenocarcinoma located in Barrett's mucosa (Fig. 4). The pathological diagnosis was moderately differentiated adenocarcinoma, CT-pT1b, SM3, ly0, v1, pIM0, pN0 ($n$ = 0/29), according to the Japanese Classification of Esophageal Cancer [14]. The histological assessment was grade 1a. Because Barrett's mucosa with neither atypia nor dysplasia was present in the middle to lower esophagus, this adenocarcinoma appeared to be associated with Barrett's esophagus. Two of five #3 lymph nodes showed fibrosis with foamy macrophages, but no cancer cells were found in the dissected lymph nodes. This finding indicated that the metastatic cancer cells had completely disappeared following chemotherapy (Fig. 5).

After surgery, the patient's s-p53-Ab titer decreased consistently, with no transient increases, during the follow-up period of 4 years, as follows: 8.66 U/ml after 1 year, 3.59 U/ml after 2 years, 2.38 U/ml after 3 years, and 1.92 U/ml after 4 years. The CA19-9 value was consistently negative after chemotherapy throughout the follow-up period (Fig. 3). Although the s-p53-Ab titers remained slightly positive even 4 years after radical treatment, no sign of recurrence has been observed on CT or PET to date.

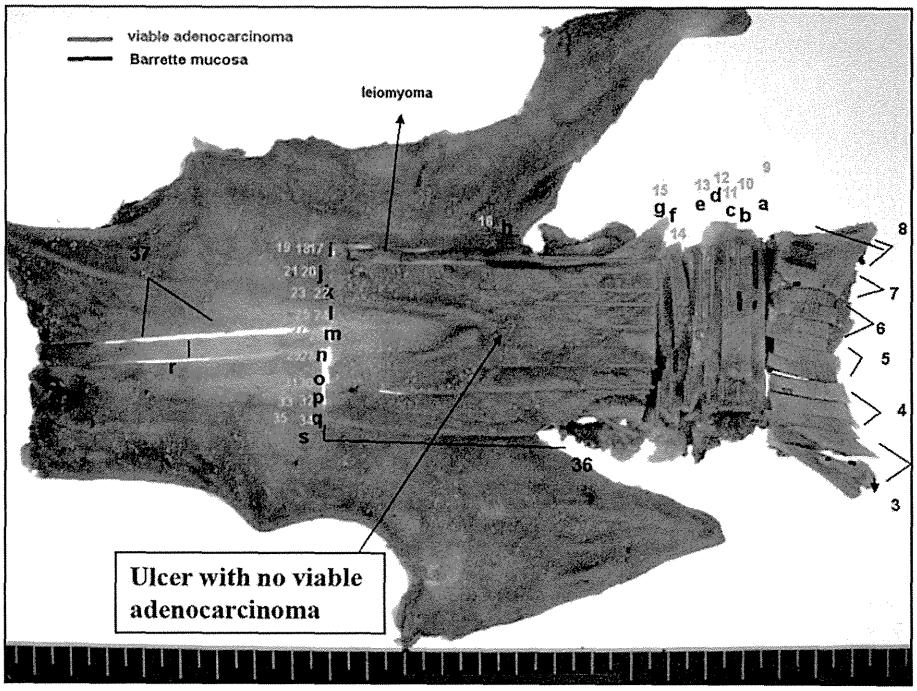


**Fig. 4** Resected specimen showing viable adenocarcinoma (*red line*) located in Barrett's mucosa (*blue line*) (color figure online)

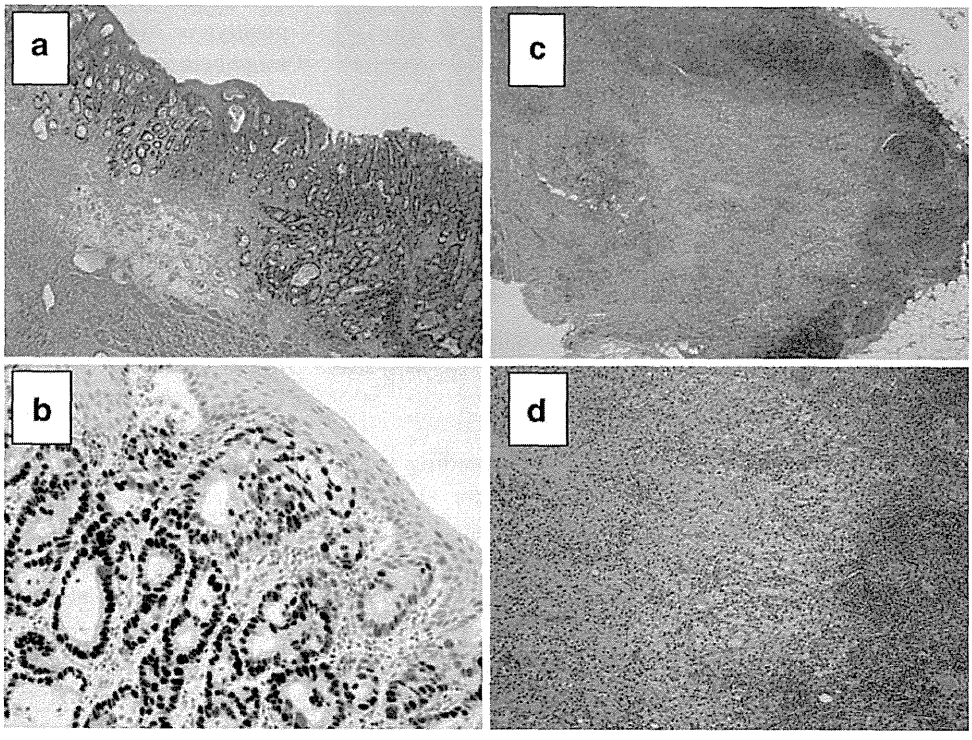


**Fig. 5** **a** Viable cancer cells in the submucosal layer and **b** strongly expressed p53 protein. **c**, **d** The dissected #3 lymph node was replaced by fibrosis, with accumulation of foam cells; no remaining carcinoma was observed

## Discussion

Serum tumor markers in cancer patients assist with establishing diagnosis, estimating prognosis, monitoring treatment, and detecting tumor recurrence [6]. In the present case, viable adenocarcinoma cells limited to the esophageal submucosal layer were detected through surveillance of s-p53-Abs. Because the specificity of this marker is greater than 95 % [15], we believe that monitoring s-p53-Abs will help to detect residual cancer cells and identify patients who require further treatment. In our previous study, patients whose s-p53-Ab titers did not decrease after treatment had a significantly worse survival than those with decreasing s-p53-Ab titers [4]. In the present case, the

s-p53-Ab titer was consistently positive, even after conversion to negativity for CA19-9. The most likely reason that the CA19-9 level decreased to within the normal range was because CA19-9 expression in adenocarcinoma is associated with tumor load and nodal involvement [16].

Patients with advanced stage tumors frequently have very high p53 antibody titers [7]. Because the present case suggests that p53 antibody concentrations decrease gradually, patients with extremely high antibody titers will tend to have detectable antibody concentrations for a long period. As the half-life of IgG antibodies is approximately 30 days, 1 month would not be sufficient for them to become negative in patients with extremely high titers [4]. However, noting changes in s-p53-Ab titers 1 month after surgery could still be helpful for predicting long-term disease-free survival. In the present case, the rapid reduction in s-p53-Ab titers after surgery might have indicated complete clearance of residual cancer cells.

A significant association between s-p53-Abs and molecular alterations in the p53 protein is evident [1–3]. Therefore, patients with extremely high s-p53-Ab titers are more likely to have tumors resistant to chemotherapy and/or radiation therapy [17–19]. In the present case, chemotherapy seemed to be effective, particularly on the metastatic lymph nodes, and the changes in s-p53-Ab titers precisely reflected the tumor response. A similar treatment response was reported in patients who received chemotherapy for colon adenocarcinoma [20]. Another study revealed that 47 % of tumors had p53 mutations and 34 % had p53 protein overexpression in esophageal adenocarcinoma [21]. As ELISA is quick and easy to use to detect p53 alteration in cancer cells, perioperative monitoring of s-p53-Ab titers may prove useful for identifying the presence of residual cancer cells and predicting long-term surgical outcomes. Even after chemotherapy or chemoradiotherapy, sero-positive patients may be good candidates for treatment with adjuvant surgery. While further studies are required to gain a more precise understanding of the clinical implications of s-p53-Ab titers in esophageal adenocarcinoma, this case shows that monitoring changes in s-p53-Ab titers during chemotherapy and/or surgery may be a useful tool for detecting residual cancer cells.

**Conflict of interest** Hideaki Shimada and his co-authors have no conflict of interest.

## References


1. von Brevern MC, Hollstein MC, Cawley HM, De Benedetti VM, Bennett WP, Liang L, et al. Circulating anti-p53 antibodies in esophageal cancer patients are found predominantly in individuals with p53 core domain mutations in their tumors. Cancer Res. 1996;56:4917–21.
2. Hagiwara N, Onda M, Miyashita M, Sasajima K. Detection of circulating anti-p53 antibodies in esophageal cancer patients. J Nippon Med Sch. 2000;67:110–7.
3. Shimada H, Takeda A, Arima M, Okazumi S, Matsubara H, Nabeya Y, et al. Serum p53 antibody is a useful tumor marker in superficial esophageal squamous cell carcinoma. Cancer. 2000;89:1677–83.
4. Shimada H, Shiratori T, Takeda A, Matsushita K, Okazumi S, Akutsu Y, et al. Perioperative changes of serum p53 antibody titer is a predictor for survival in patients with esophageal squamous cell carcinoma. World J Surg. 2009;33:272–7.
5. Shimada H, Ochiai T. Molecular diagnosis and treatment for esophageal carcinoma with p53. Esophagus. 2007;4:165–8.
6. Shimada H, Yajima S, Oshima Y, Hiwasa T, Tagawa M, Matsushita K, et al. Impact of serum biomarkers on esophageal squamous cell carcinoma. Esophagus. 2012;9:131–40.
7. Shimada H, Nabeya Y, Okazumi S, Matsubara H, Funami Y, Shiratori T, et al. Prognostic significance of serum p53 antibody in patients with esophageal squamous cell carcinoma. Surgery. 2000;132:41–7.
8. Takahashi K, Miyashita M, Nomura T, Makino H, Futami R, Kashiwabara M, et al. Serum p53 antibody as a predictor of early recurrence in patients with postoperative esophageal squamous cell carcinoma. Dis Esophagus. 2007;20:117–22.
9. Shimizu K, Ueda Y, Yamagishi H. Titration of serum p53 antibodies in patients with gastric cancer: a single-institute study of 40 patients. Gastric Cancer. 2005;8:214–9.
10. Nakajima K, Suzuki T, Shimada H, Hayashi H, Takeda A, Ochiai T. Detection of preoperative serum anti-p53 antibodies in gastric cancer. Tumour Biol. 1999;20:147–52.
11. Maehara Y, Kakeji Y, Watanabe A, Baba H, Kusumoto H, Kohnoe S, et al. Clinical implications of serum anti-p53 antibodies for patients with gastric carcinoma. Cancer. 1999;85:302–8.
12. Ochiai H, Ohishi T, Osumi K, Tokuyama J, Urakami H, Seki S, et al. Reevaluation of serum p53 antibody as a tumor marker in colorectal cancer patients. Surg Today. 2012;42:164–8.
13. Cawley HM, Meltzer SJ, De Benedetti VM, Hollstein MC, Muehlbauer KR, Liang L, et al. Anti-p53 antibodies in patients with Barrett's esophagus or esophageal carcinoma can predate cancer diagnosis. Gastroenterology. 1998;115:19–27.
14. Japanese Society for Esophageal Diseases. Guidelines for clinical and pathological studies on carcinoma of the esophagus. 10th ed. Tokyo: Kanehara; 2007.
15. Shimada H, Ochiai T, Nomura F, Japan p53 Antibody Research Group. Titration of serum p53 antibodies in 1,085 patients with various types of malignant tumors: a multiinstitutional analysis by the Japan p53 Antibody Research Group. Cancer. 2003;97:682–9.
16. Shimada H, Noie T, Ohashi M, Oba K, Takahashi Y. Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association. Gastric Cancer. 2013. doi:10.1007/s10120-013-0259-5.
17. Shimada H, Okazumi S, Takeda A, Nabeya Y, Matsubara H, Funami Y, et al. Presence of serum p53 antibodies is associated with decreased in vitro chemosensitivity in patients with esophageal cancer. Surg Today. 2001;31:591–6.
18. Shimada H, Kitabayashi H, Nabeya Y, Okazumi S, Matsubara H, Funami Y, et al. Treatment response and prognosis of patients after recurrence of esophageal cancer. Surgery. 2003;133:24–31.
19. Cai HY, Wang XH, Tian Y, Gao LY, Zhang LJ, Zhang ZY. Changes of serum p53 antibodies and clinical significance of radiotherapy for esophageal squamous cell carcinoma. World J Gastroenterol. 2008;14:4082–6.

20. Lechpammer M, Lukac J, Lechpammer S, Kovacević D, Loda M, Kusić Z. Humoral immune response to p53 correlates with clinical course in colorectal cancer patients during adjuvant chemotherapy. Int J Colorectal Dis. 2004;19:114–20.

21. Madani K, Zhao R, Lim HJ, Casson AG. Prognostic value of p53 mutations in oesophageal adenocarcinoma: final results of a 15-year prospective study. Eur J Cardiothorac Surg. 2010;37:1427–32.

Gastric Cancer (2014) 17:26–33
DOI 10.1007/s10120-013-0259-5

REVIEW ARTICLE

# Clinical significance of serum tumor markers for gastric cancer: a systematic review of literature by the Task Force of the Japanese Gastric Cancer Association

**Hideaki Shimada · Tamaki Noie · Manabu Ohashi · Koji Oba · Yutaka Takahashi**

Received: 25 December 2012 / Accepted: 24 March 2013 / Published online: 10 April 2013
© The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2013

**Abstract** The aim of this review was to evaluate the clinical significance of serum tumor markers, particularly CEA, CA19-9, and CA72-4, in patients with gastric cancer. A systematic literature search was performed using PubMed/MEDLINE with the keywords "gastric cancer" and "tumor marker," to select 4,925 relevant reports published before the end of November 2012. A total of 187 publications contained data for CEA and CA19-9, and 19 publications contained data related to all three tumor markers. The positive rates were 21.1 % for CEA, 27.8 % for CA19-9, and 30.0 % for CA72-4. These three markers were significantly associated with tumor stage and patient survival. Serum markers are not useful for early cancer, but they are useful for detecting recurrence and distant metastasis, predicting patient survival, and monitoring after surgery. Tumor marker monitoring may be useful for patients after surgery because the positive conversion of tumor markers usually occurs 2–3 months before imaging abnormalities. Among other tumor markers, alpha-fetoprotein (AFP) is useful for detecting and predicting liver metastases. Moreover, CA125 and sialyl Tn antigens (STN) are useful for detecting peritoneal metastases. Although no prospective trial has yet been completed to evaluate the clinical significance of these serum markers, this literature survey suggests that combinations of CEA, CA19-9, and CA72-4 are the most effective ways for staging before surgery or chemotherapy. In particular, monitoring tumor markers that were elevated before surgery or chemotherapy could be useful for detection of recurrence or evaluation of the response.

**Keywords** CA19-9 · CA72-4 · CEA · Gastric cancer · Serum tumor marker · Systematic review

H. Shimada (✉)
Department of Surgery, School of Medicine, Toho University, 6-11-1 Omori-Nishi, Ota-ku, Tokyo 143-8541, Japan
e-mail: hideaki.shimada@med.toho-u.ac.jp

H. Shimada
Japanese Gastric Cancer Association Task Force for Research Promotion, Tokyo, Japan

T. Noie
Department of Surgery, Kanto Medical Center NTT East, Tokyo 141-8625, Japan

M. Ohashi
Department of Surgery, Tokyo Metropolitan Komagome Hospital, Tokyo 113-8677, Japan

K. Oba
Translational Research and Clinical Trial Center, Hokkaido University Hospital, Hokkaido University, Hokkaido 060-8648, Japan

Y. Takahashi
Cancer Chemotherapy, KAKEN Hospital, International University of Health and Welfare, Ichikawa 272-0827, Japan

## Introduction

The Japanese Public Health Insurance System covers the costs of monitoring patients with gastric cancer using serum tumor markers. Nine types of serum markers are officially certified for use in disease monitoring: carcinoembryonic antigen (CEA) in the sialyl Lewis A group; CA19-9 and CA50 in the sialyl Lewis Tn group; STN and CA72-4 in the mucin antigen group; and CA125, alpha-fetoprotein (AFP), IAP, and TPA. Many studies have demonstrated the clinical significance of each marker; however, appropriate indications for serum tumor marker monitoring remain unclear. The serum levels of CEA,