Table 2. Multivariate analyses of factors affecting overall survival in patients with resected hepatic and pulmonary metastases from colorectal cancer

	Hazard ratio (95% CI)	*P* value
Location of primary tumor		
Rectum	—	0.01
Colon	8.74 (1.53—49.91)	
TNM classification of primary tumor		
I, II, III	—	0.03
IV	11.37 (1.34—96.53)	
Maximum size of tumor at first hepatectomy (cm)		
<3	—	<0.01
≥3	14.47 (2.33–89.85)	

CI, confidence interval; CEA, carcinoembryonic antigen.

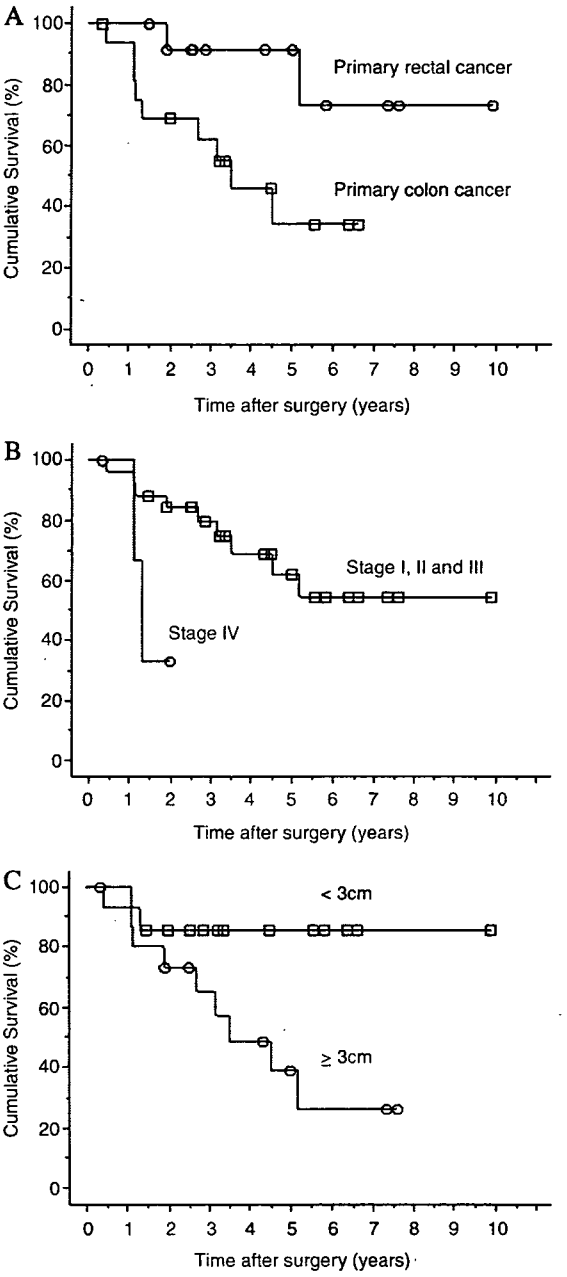

Figure 2. Cumulative survival curves after resections for hepatic and pulmonary metastases of colorectal cancer according to (A) location of primary tumor, (B) stage in TNM classification, and (C) maximum size of hepatic tumor at initial.

disease, several studies have demonstrated the efficacy of resections for both hepatic and pulmonary metastases (2–14). However, because of the frequent recurrences after resections, the best selection criteria for resection have not been established.

Lenhart *et al.* reported a disease-free survival of only 24% at 2 years in patients who underwent sequential hepatic and pulmonary resections for colorectal metastases (9). In the present study, the 2-year disease-free survival rate after the first metastasectomy for the second organ was also 24% with a median disease-free survival of only 13 months. The best treatment strategy for the recurrences after hepatic and pulmonary resections is obscure. However, only surgical removal of metastases offers a chance of cure. Aggressive repeat metastasectomy has been applied for recurrences after hepatic and pulmonary resections in our institution.

For the 30 patients of the present study, 45 hepatectomies and 40 pulmonary resections were performed and 17 patients received three or more resections with a maximum of five resections. Overall survival after the first metastasectomy for the second organ was 58% and nine 5-year survivors were observed. Surprisingly, seven of the nine 5-year survivors had undergone three or more resections. When survival time was calculated from the date of the first metastasectomy for the first metastasized organ, overall survival reached 70% at 5 years with a median survival of 60 months in the present study. Little is available on the result of repeat metastasectomy for recurrences after hepatic and pulmonary resections. Our results of long-term survival after hepatic and pulmonary resections in spite of frequent recurrences support the view that patients who can undergo resections for both hepatic and pulmonary metastases of colorectal cancer are in a selected population but can sometimes survive a long time with multiple metastasectomies. Interestingly, a recent study by Shah *et al.* also reported 74% 5-year survival rate after multidisciplinary surgical metastasectomies for colorectal cancer (19). The strategy and results of Shah *et al.* were similar to ours. However, while a majority of the patients received adjuvant chemotherapy after metastasectomies in Shah's study, no patient underwent adjuvant chemotherapy in the present study. These results indicate that the strategy of aggressive multiple metastasectomies count more than postoperative chemotherapies in the treatment for very restricted population of patients.

We found three factors for poor prognosis: size of hepatic tumor >3 cm at the first hepatectomy, primary colon carcinoma and stage IV tumor.

Maximum size of the hepatic tumor has been reported to be one of the important prognostic factors after hepatic resections for colorectal hepatic metastasis (20,21). This factor could affect prognosis in this population.

The reason for poor prognosis in patients with primary colon cancer is unknown. Patients with primary colon cancer had larger pulmonary tumors, higher CEA levels at the first pulmonary resection and relatively longer intervals from primary resection to the first pulmonary resection than patients with primary rectal cancer. A higher prethoracotomy CEA level was a factor of poor prognosis after hepatic and pulmonary resections in several studies (6,11). However, the reason why patients with primary colon cancer had more advanced pulmonary tumors than those with primary rectal cancer was unclear. A 'cascade' hypothesis based on the anatomy of the draining veins from the colon and rectum suggests that pulmonary metastasis in patients with primary colon carcinoma might come from hepatic metastasis with progressive site-induced change; however, pulmonary metastasis in patients with primary rectal carcinoma might come directly from the primary tumor, which seemed to be compatible with our results (22–24). However, the prognostic power of primary tumor location has not been demonstrated yet in patients with resected colorectal pulmonary metastasis (25–27); further examinations are needed to verify the hypothesis.

Neither the large size of the hepatic tumor nor primary colon carcinoma might influence the selection criteria for hepatic and pulmonary resections, because several long-term survivors were observed, even among patients with those factors.

Patients with stage IV disease had a poorer prognosis and showed no long-term survival. However, stage IV itself should not be considered as a contraindication for resections because the follow-up duration of patients with stage IV was short and the poor prognosis in stage IV was not consistent with the result that the disease-free interval from primary resection showed no correlation with prognosis.

Other factors such as synchronous metastasis (5), bilateral or multiple lung metastases (5,7), multiple liver metastases (8), short disease-free interval (8), simultaneous liver and lung metastases (10), mediastinal nodes involvement (11), primary histology (12) and high levels of both CEA and CA19-9 before metastasectomy (13) have been reported as prognostic factors after hepatic and pulmonary metastasectomy of colorectal cancer. Among those factors, whether the timing of the detection of hepatic and pulmonary metastases influences prognosis after resections has been an issue. In the present study, none of the aforementioned factors, including the timing of the detection of the metastases, showed any prognostic value. Based on our results, no single factor that contraindicated resections for hepatic and pulmonary metastases of colorectal cancer was identified. Thus, surgical resections might be the best option when both hepatic and pulmonary metastases are resectable in colorectal cancer. However, treatment for patients with several poor prognostic factors for multiple resections is still unknown.

The reason for the high survival rate 5 years after resections for hepatic and pulmonary metastases in our study might be partly explained by precise intrathoracic and abdominal examinations using helical computed tomography (28,29). However, it can not be denied that patients who can undergo both hepatic and pulmonary metastasectomy for colon cancer might have unique characteristics in some factors. For example, there may be some unique host-tumor interaction, considering the rare possibility of both hepatic and pulmonary resections for colorectal metastases and the surprisingly high survival rate after the metastasecomies in spite of multiple, multiphase and multi-organ metastases. The aforementioned hypothesis is supported by the fact that excellent survival in the present study was achieved, unexpectedly, without any help of adjuvant chemotherapy, although adjuvant chemotherapy after pulmonary or hepatic metastasectomy is a potential treatment for improving the prognosis of patients with colorectal cancer. Further investigation to clarify the reason for the good prognosis of this population might elucidate the mechanisms of metastases in colorectal cancer.

A limitation of our study is the relatively small population, because patients who can undergo resections for both hepatic and pulmonary metastases of colorectal carcinoma are rare. There is some possibility that correlations between several clinicopathological factors such as positive lymph nodes of the hepatoduodenal ligament, hilus pulmonis, or mediastinum and survival after resections could not be sufficiently validated because of the small cohort. A large multi-institutional study is recommended to verify the correlation.

In conclusion, multiple resections for hepatic and pulmonary metastases of colorectal cancer are safe and effective. Surgical resections could be the best option for resectable hepatic and pulmonary metastases in colorectal cancer.

Acknowledgments

This work was supported in part by grants from Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

References

1. Galandiuk S, Wieand HS, Moertel CG, Cha SS, Fitzgibbons RJ, Jr, Pemberton JH, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. *Surg Gynecol Obstet* 1992;174: 27–32.
2. Smith JW, Fortner JG, Burt M. Resection of hepatic and pulmonary metastases from colorectal cancer. *Surg Oncol* 1992;1:399–404.

3. Gough DB, Donohue JH, Trastek VA, Nagorney DM. Resection of hepatic and pulmonary metastases in patients with colorectal cancer. *Br J Surg* 1994;81:94–6.
4. Ambiru S, Miyazaki M, Ito H, Nakagawa K, Shimizu H, Kato A, et al. Resection of hepatic and pulmonary metastases in patients with colorectal carcinoma. *Cancer* 1998;82:274–8.
5. Murata S, Moriya Y, Akasu T, Fujita S, Sugihara K. Resection of both hepatic and pulmonary metastases in patients with colorectal carcinoma. *Cancer* 1998;83:1086–93.
6. Regnard JF, Grunenwald D, Spaggiari L, Girard P, Elias D, Ducreux M, et al. Surgical treatment of hepatic and pulmonary metastases from colorectal cancers. *Ann Thorac Surg* 1998;66:214–8.
7. Kobayashi K, Kawamura M, Ishihara T. Surgical treatment for both pulmonary and hepatic metastases from colorectal cancer. *J Thorac Cardiovasc Surg* 1999;118:1090–6.
8. Robinson BJ, Rice TW, Strong SA, Rybicki LA, Blackstone EH. Is resection of pulmonary and hepatic metastases warranted in patients with colorectal cancer? *J Thorac Cardiovasc Surg* 1999;117:66–75.
9. Lehnert T, Knaebel HP, Duck M, Bulzebruck H, Herfarth C. Sequential hepatic and pulmonary resections for metastatic colorectal cancer. *Br J Surg* 1999;86:241–3.
10. Nagakura S, Shirai Y, Yamato Y, Yokoyama N, Suda T, Hatakeyama K. Simultaneous detection of colorectal carcinoma liver and lung metastases does not warrant resection. *J Am Coll Surg* 2001;193: 153–60.
11. Headrick JR, Miller DL, Nagorney DM, Allen MS, Deschamps C, Trastek VF, et al. Surgical treatment of hepatic and pulmonary metastases from colon cancer. *Ann Thorac Surg* 2001;71:975–9.
12. Ike H, Shimada H, Togo S, Yamaguchi S, Ichikawa Y, Tanaka K. Sequential resection of lung metastasis following partial hepatectomy for colorectal cancer. *Br J Surg* 2002;89:1164–8.
13. Mineo TC, Ambrogi V, Tonini G, Bollero P, Roselli M, Mineo D, et al. Long-term results after resection of simultaneous and sequential lung and liver metastases from colorectal carcinoma. *J Am Coll Surg* 2003;197:386–91.
14. Reddy RH, Kumar B, Shah R, Mirsadraee S, Papagiannopoulos K, Lodge P, et al. Staged pulmonary and hepatic metastasectomy in colorectal cancer—is it worth it? *Eur J Cardiothorac Surg* 2004;25:151–4.
15. Jass JR, Sobin LH. Histological typing of intestinal tumors. In: Jass JR, Sobin LH, editors. World Health Organization. International Histological Classification of Tumors, 2nd edn, Berlin: Springer 1989.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–81.
17. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B* 1972;34:187–220.
18. Couinaud C. Bases anatomiques des hepatectomies gaucle et droite reglees. *J Chirugie* 1954;70:933–66.
19. Shah SA, Haddad R, Al-Sukhni W, Kim RD, Greig PD, Grant DR, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. *J Am Coll Surg* 2006;202:468–75.
20. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann Surg* 1999;230: 309–18.
21. Nordlinger, B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. *Cancer* 1996;77:1254–62.
22. Weiss L, Ward PM. Effects of metastatic cascades on metastatic patterns: studies on colon-26 carcinomas in mice. *Int J Cancer* 1988;41:450–5.
23. Vidal-Vanaclocha F, Glaves D, Barbera-Guillem E, Weiss L. Quantitative microscopy of mouse colon 26 cells growing in different metastatic sites. *Br J Cancer* 1991;63:748–52.
24. Gregoire M, Blottiere HM, Muleris M, Douillard JY, Meflah K. Karyotypic and phenotypic variations between cell lines established from a primary colorectal tumour and two corresponding metastases from one patient. *Invasion Metastasis* 1993;13:253–66.
25. Saito Y, Omiya H, Kohno K, Kobayashi T, Itoi K, Teramachi M, et al. Pulmonary metastasectomy for 165 patients with colorectal carcinoma: A prognostic assessment. *J Thorac Cardiovasc Surg* 2002;124: 1007–13.
26. Pfannschmidt J, Muley T, Hoffmann H, Dienemann H. Prognostic factors and survival after complete resection of pulmonary metastases from colorectal carcinoma: experiences in 167 patients. *J Thorac Cardiovasc Surg* 2003;126:732–9.
27. Inoue M, Ohta M, Iuchi K, Matsumura A, Ideguchi K, Yasumitsu T, et al. Thoracic Surgery Study Group of Osaka University. Benefits of surgery for patients with pulmonary metastases from colorectal carcinoma. *Ann Thorac Surg* 2004;78:238–44.
28. Takahashi S, Inoue K, Konishi M, Nakagouri T, Kinoshita T. Prognostic factors for poor survival after repeat hepatectomy in patients with colorectal liver metastases. *Surgery* 2003;133:627–34.
29. Watanabe I, Arai T, Ono M, Sugito M, Kawashima K, Ito M, et al. Prognostic factors in resection of pulmonary metastasis from colorectal cancer. *Br J Surg* 2003;90:1436–40.

Surg Endosc (2007) 21: 1466–1468
DOI: 10.1007/s00464-007-9253-5

SURGICAL ENDOSCOPY
and Other Interventional Techniques

Laparoscopy-assisted hepatic lobectomy using hilar Glissonean pedicle transection

A. Cho,[1] T. Asano,[1] H. Yamamoto,[1] M. Nagata,[1] N. Takiguchi,[1] O. Kainuma,[1] H. Souda,[1] H. Gunji,[1] A. Miyazaki,[1] H. Nojima,[1] A. Ikeda,[1] I. Matsumoto,[1] M. Ryu,[1] H. Makino,[2] S. Okazumi[3]

[1] Department of Gastroenterological Surgery, Chiba Cancer Center Hospital, 666-2 Nitonachou, Chuouku, Chiba 260-8717, Japan
[2] Department of Surgery, Shimotsuga General Hospital, Chuouku, Chiba, 260-8717, Japan
[3] Department of Surgery, Chiba University of Medicine, 666-2 Nitonachou, Chuouku, Chiba 260-8717, Japan

Received: 12 October 2006/Accepted: 25 January 2007/Online publication: 14 March 2007

Abstract
Although many reports have described laparoscopic minor liver resections, major hepatic resection, including right or left lobectomy, has not been widely developed because of technical difficulties. This article describes a new technique for performing laparoscopy-assisted right or left hepatic lobectomy using hilar Glissonean pedicle transection. Laparoscopic mobilization of the right or left hepatic lobe is performed, including dissection of the round, faliciform, triangular, and coronary ligaments. The right or left Glissonean pedicle is encircled and divided laparoscopically. A parenchymal dissection is then performed though the upper median or right subcostal incision, through which the resected liver is removed. We successfully performed this procedure in 6 patients without blood transfusion or serious complications. Laparoscopy-assisted hepatic lobectomy using hilar Glissonean pedicle transection can be feasible and safe in highly selected patients.

Key words: Laparoscopy — Hepatic lobectomy — Glissonean pedicle

Laparoscopy for liver resection is a highly specialized field, as laparoscopic liver surgery presents severe technical difficulties. However, the recent rapid development of technological innovations, improvements in surgical skills, and the accumulation of extensive experience by surgeons have improved the feasibility and safety of a laparoscopic approach for properly selected patients. Since the first report of laparoscopic anatomical left lateral segmentectomy in 1996 [1], a limited number of laparoscopic anatomical liver resections have been described [2–6, 9, 12]. During open right or left hepatic lobectomy, the right or left Glissonean pedicle is often ligated and divided en bloc extrahepatically before parenchymal dissection [10, 11]. Herein we describe our experience with laparoscopic encircling and dividing the right or left Glissonean pedicle during laparoscopy-assisted right or left hepatic lobectomy, representing the first description of this laparoscopic technique.

Correspondence to: A. Cho

Surgical procedure

The patient is placed in a supine position when left lobectomy is performed, and in a left semi-lateral decubitus position for right lobectomy. A 12-mm trocar is placed 1 cm below the umbilicus, through which CO_2 gas is delivered. Pneumoperitoneum is controlled electronically at a pressure of 10 mmHg. The other three trocars are located as shown in Figure 1. The round ligament is transected using laparoscopic coagulation shears (LCS; Ethicon Endo Surgery Industries, Cincinnati, OH, USA), and the falciform and coronary ligaments are then dissected to expose the suprahepatic inferior vena cava (IVC). The lesser omentum is sectioned and the hepatoduodenal ligament is encircled by a tape to be used as a tourniquet for complete interruption of blood inflow to the liver only if necessary. For left lobectomy, the left triangular and coronary ligaments are divided to expose the left hepatic vein, so that the left lateral segment can be mobilized. The ligamentum venosum is then divided with LCS while the lateral segment is retracted. Dissection of the porta hepatis is performed with laparoscopic scissors between the hepatic parenchyma and the left Glissonean pedicle, which is then encircled using the Endo Retract Maxi (ERM; United Surgical, a division of Tyco Healthcare group LP; Norwalk, CT, USA) at the hepatic hilum (Fig. 2). The left Glissonean pedicle is divided with a Linear Cutter (Ethicon Endo Surgery Industries, Cincinnati, OH, USA). Next, an upper median incision approximately 6 cm long is made and covered with a Lap Protector (Hakko Shoji, Tokyo, Japan). Parenchymal dissection is performed through the upper median incision to prevent gas embolism, and is continued to the left hepatic vein, which is not meticulously dissected to reduce the risk of tearing. The left hepatic vein is sectioned using a Linear Cutter. The left lobe is then delivered through the upper median incision. For right lobectomy, the right lobe is mobilized by dividing, with laparoscopic scissors and LCS, the hepato-renal, right triangular, and right coronary ligaments, as well as the lateral attachments of the right lobe. The right Glissonean pedicle is encircled using the ERM at the bifurcation in the hepatic hilum (Fig. 3). A little dissection of the hepatic parenchyma covering

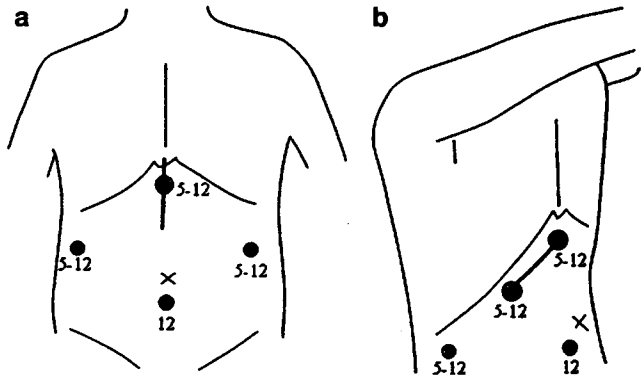

Fig. 1. Diagrams of typical trocar placement for laparoscopy-assisted hepatic lobectomy. **A.** Left lobectomy. Patient is supine with lower limbs apart, and the surgeon stands between the legs. **B.** Right lobectomy. The surgeon is on the left side.

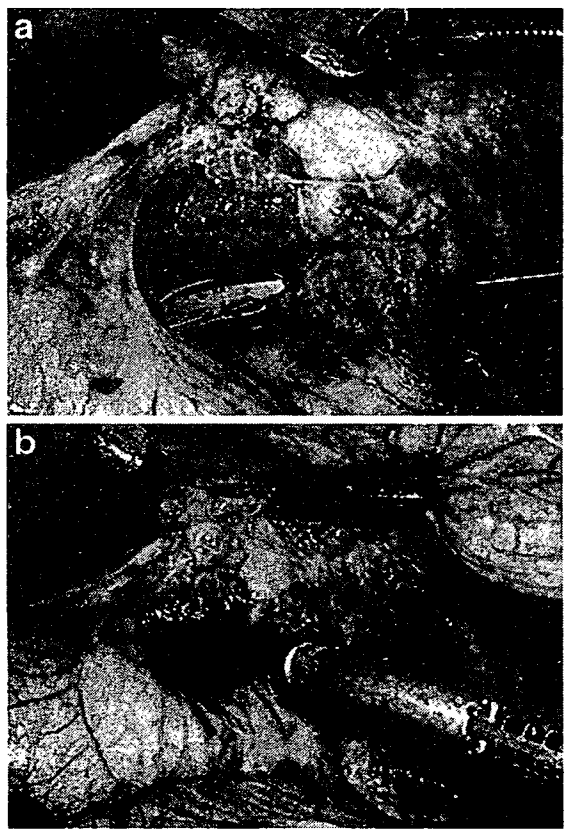

Fig. 2. The left Glissonean pedicle is encircled with the Endo Retract Maxi (ERM) (A) and divided by the Linear Cutter (B).

the bifurcation of the right anterior and posterior Glissonean pedicles facilitates encircling these structures. The right anterior and posterior Glissonean pedicles are encircled with the ERM (Fig. 4) and divided with the Linear Cutter. Next, a right subcostal incision approximately 8 cm long is made and covered with a Lap Protector. A tape is passed between the anterior surface of the IVC and the posterior surface of the caudate lobe for the liver-hanging maneuver through the right subcostal incision, after which parenchymal dissection proceeds from the liver surface to the tape through the right subcostal incision. After liver transaction, the short hepatic veins are divided with endoscopic vascular clips (Ethicon Endo Surgery Industries, Cincinnati, OH, USA), and finally the right hepatic vein is sectioned with the Linear Cutter. The right lobe is then delivered through the right subcostal incision.

Fig. 3. The right Glissonean pedicle is encircled with the ERM.

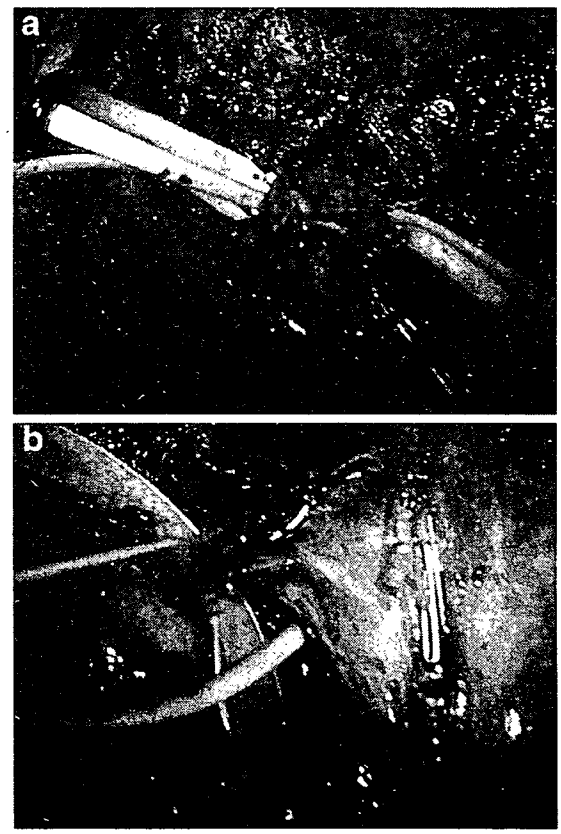

Fig. 4. The right anterior (A) and posterior (B) Glissonean pedicles are encircled with the ERM.

Results

We successfully performed laparoscopy-assisted left lobectomy in 4 patients and laparoscopy-assisted right lobectomy in 2 patients, as planned. No procedures were converted to open hepatectomy. Mean operative time was 175 min (range, 95–330 min). Mean blood loss was 370 mg (range, 80–1250 mg). No patient required blood transfusion and no serious complications were encountered. Mean duration of hospitalization was 9 days (range, 4–14 days). Underlying

pathology was hepatocellular carcinoma (n = 2), intrahepatic stones (n = 2), metastatic liver tumor (n = 1), and benign liver tumor (n = 1). All lesions were well clear of surgical margins.

Discussion

Laparoscopic liver surgery was initially limited for partial resections because of the technical difficulties involved [7, 13]. Recent technological developments and improved endoscopic procedures have spread application of laparoscopic liver resection widely. However, only a few laparoscopic hepatic lobectomies have been reported. The hepatic artery, portal vein, and bile duct, together with connective tissue, are sheathed by the peritoneum to form a fibroid bundle. This portal triad continues from the hepatoduodenal ligament to the intrahepatic portion as the Glissonean pedicle. The entire length of the primary branches of the Glissonean pedicle and the origin of its secondary branches are located outside the liver, and the trunks of the secondary and more peripheral branches run inside the liver [10]. The right or left Glissonean pedicle can thus be ligated and divided en bloc extrahepatically before parenchymal dissection during open hepatic lobectomy [10, 11]. We successfully performed laparoscopic encircling and dividing the right or left Glissonean pedicles extrahepatically before parenchymal dissection in all 6 patients in whom this approach was attempted. Thanks to meticulous and sufficient dissection between hepatic parenchyma and the Glissonean pedicle at the hepatic hilum and encircling the Glissonean pedicle with the ERM, little bleeding was encountered during hilar procedures.

Although a similar laparoscopic technique in which the Glissonean pedicle is encircled has been reported for hemihepatic ischemia, hilar Glissonean pedicle transection and lobectomy were not performed [8]. Previous reports relating to laparoscopic or laparoscopy-assisted right lobectomies have described the right hepatic artery, duct, and portal vein as being dissected and divided separately [9], or the right Glissonean pedicle being transected through the midline incision [5]. We believe that the present procedure can reduce operation time and the size of the additional incision. Although our experience is limited and appropriate indications must await future studies, we believe that laparoscopy-assisted hepatic lobectomy using hilar Glissonean pedicle transwction can be feasible and safe in highly selected patients and offers the usual benefits of laparoscopic surgery, such as reduced invasiveness.

References

1. Azagra JS, Goergen M, Gilbart E, Jacobs D (1996) Laparoscopic anatomical (hepatic) left lateral segmentectomy—technical aspects. Surg Endosc 10: 758–761
2. Belli G, Fantini C, D'Agostino A, Belli A, Cioffi L, Russolillo N (2006) Laparoscopic left lateral hepatic lobectomy: a safer and faster technique. J Hepatobiliary Pancreat Surg 13: 149–154
3. Cadiere GB, Torres R, Dapri G, Capelluto E, Himpens J (2005) Multimedia article: laparoscopic left lateral hepatic lobectomy for metastatic colorectal tumor. Surg Endosc 19: 152
4. Cherqui D, Husson E, Hammoud R, Malassagne B, Stephan F, Bensaid S, Rotman N, Fagniez PL (2000) Laparoscopic liver resections: a feasibility study in 30 patients. Ann Surg 232: 753–762
5. Eguchi D, Nishizaki T, Ohta M, Ishizaki Y, Hanaki N, Okita K, Ohga T, Takahashi I, Ojima Y, Wada H, Tsutsui S (200) Laparoscopy-assisted right hepatic lobectomy using a wall-lifting procedure. Surg Endosc 20:1326–1328
6. Kaneko H (2005) Laparoscopic hepatectomy: indications and outcomes. J Hepatobiliary Pancreat Surg 12: 438–443
7. Kaneko H, Takagi S, Shiba T (1996) Laparoscopic partial hepatectomy and left lateral segmentectomy: technique and results of a clinical series. Surgery 120: 468–475
8. Machado MA, Makdissi FF, Bacchella T, Machado MC (2005) Hemihepatic ischemia for laparoscopic liver resection. Surg Laparosc Endosc Percutan Tech 15: 180–183
9. O'Rourke N, Fielding G (2004) Laparoscopic right hepatectomy: surgical technique. J Gastrointest Surg 8: 213–216
10. Takasaki K (1998) Glissonean pedicle transection method for hepatic resection: a new concept of liver segmentation. J Hepatobiliary Pancreat Surg 5: 286–291
11. Takasaki K, Kobayashi S, Tanaka S, Saito A, Yamamoto M, Hanyu F (1990) Highly anatomically systematized hepatic resection with Glissonean sheath code transection at the hepatic hilus. Int Surg 75: 73–77
12. Vibert E, Perniceni T, Levard H, Denet C, Shahri NK, Gayet B (2006) Laparoscopic liver resection. Br J Surg 93: 67–72
13. Yamanaka N, Tanaka T, Tanaka W, Yamanaka J, Yasui C, Ando T, Takada M, Maeda S, Okamoto E (1998) Laparoscopic partial hepatectomy. Hepatogastroenterology 45: 29–33

The American Journal of Surgery 193 (2007) 1–4
Clinical surgery–International

Relationship between right portal and biliary systems based on reclassification of the liver

Akihiro Cho, M.D.[a,*], Takehide Asano, M.D.[a], Hiroshi Yamamoto, M.D.[a], Matsuo Nagata, M.D.[a], Nobuhiro Takiguchi, M.D.[a], Osamu Kainuma, M.D.[a], Hiroaki Soda, M.D.[a], Mikito Mori, M.D.[a], Souichi Narumoto, M.D.[a], Shinichi Okazumi, M.D.[b], Harufumi Makino, M.D.[c], Takenori Ochiai, M.D., Ph.D., F.A.C.S.[b], Munemasa Ryu, M.D.[a]

[a]*Department of Surgery, Chiba Cancer Center Hospital, 666-2 Nitonachou, Chuouku, Chiba 260-8717, Japan*
[b]*Department of Academic Surgery, Graduate School of Medicine, Chiba University, Chuouku, Chiba, Japan*
[c]*Research Center for Medical Engineering, Chiba University, Chuouku, Chiba, Japan*

Manuscript received January 9, 2006; revised manuscript April 23, 2006

Abstract

Background: Although the anatomy of the right portal and biliary systems and their interrelationships must be understood to safely and satisfactorily perform left-sided resection of hilar cholangiocarcinoma or right-lobe living donor liver transplantation, the anatomies of the right portal and biliary systems are extremely difficult to understand.
Methods: A total of 60 patients with normal liver underwent computed tomography during both portography and cholangiography to evaluate relationships between the right biliary and portal systems based on reclassification of the liver to divide the right liver into 3 segments.
Results: All ventral and posterior ducts constantly join medially to the anterior portal trunk. In contrast, some dorsal ducts join the ventral duct medially and others join the posterior duct lateral to the anterior trunk.
Conclusions: Reclassification of the liver to divide the right liver into 3 segments facilitates an understanding of relationships between the right portal and biliary systems. © 2007 Excerpta Medica Inc. All rights reserved.

Keywords: Hilar cholangiocarcinoma; Living donor liver transplantation; Reclassification of the liver; 3D portocholangiography

Although en bloc resection has contributed to improved long-term survival in patients with hilar cholangiocarcinoma, a formidable challenge remains for surgeons in the complex anatomy of the portal and biliary systems, particularly involving the hepatic hilum [1–4]. In addition, biliary complications such as biliary stricture and anastomotic leakage reportedly remain as serious problems in living donor liver transplantation, and are caused by ischemia of the biliary tract or incomplete understanding of the surgical anatomy of the bile duct system [5–8]. Relationships between the left biliary duct and left portal vein systems have been analyzed using ex vivo cadaveric liver corrosion casts [8–10] and in vivo radiologic analysis [11,12]. In contrast, understanding the segmental anatomy of the right liver is more difficult than that of the left liver because many variations exist and anatomic relationships between the right biliary duct and the right portal vein system have not been established thoroughly. Reclassification of the liver to divide the right liver into 3 vertical segments has been proposed, to simplify the segmental anatomy of the right liver [13–15]. The present study aimed to re-evaluate relationships between the right biliary duct and right portal vein systems based on this reclassification.

Patients and Methods

Between April 2001 and May 2005, a total of 36 patients underwent percutaneous transhepatic biliary drainage as a result of obstructive jaundice, and 46 patients underwent drip-infusion cholangiography–computed tomography (CT) for preoperative evaluation of laparoscopic cholecystectomy. Of these patients, 71 met the following inclusion criteria: no lesions in the liver, no cirrhosis, no extrahepatic lesions distorting the intrahepatic venous anatomy, and no previous liver surgery. Another 11 patients in whom the right portal vein was

* Corresponding author. Tel.: +81-43-264-5431; fax: +81-43-262-8680.
E-mail address: acho@chiba-cc.jp

0002-9610/07/$ – see front matter
doi:10.1016/j.amjsurg.2006.10.007

absent were excluded. Our study group thus comprised the remaining 60 patients, with a mean age of 62.3 years (range, 16–74 y). The underlying pathology was cholecystolithiasis (n = 31), pancreatic cancer (n = 12), gallbladder polyp (n = 8), bile duct cancer (n = 5), and choledocholithiasis (n = 4). All study protocols were approved by the institutional review board, and informed consent was obtained from all patients before the procedure was performed. All studies were performed using a LightSpeed Ultra 16-slice multidetector CT scanner (GE Medical Systems, Milwaukee, WI). The 25 patients undergoing percutaneous transhepatic biliary drainage underwent CT after injection of iohexol (Omnipaque, 300 mg/mL of iodine; Daiichi, Tokyo, Japan) diluted 1:10 with saline through biliary catheters. In addition, CT during arterial portography was performed during biliary opacification of contrast medium [14]. In 35 patients, 100 mL of iohexol was injected at 3 mL/s through a 20-gauge intravenous catheter into a medially located antecubital vein using a Dual Shot power injector (Nemoto-kyorindo, Tokyo, Japan) after drip-infusion cholangiography. Neither serious nor minor complications occurred during or after procedures in all patients. CT data were downloaded to an independent workstation equipped with software for perspective volume rendering (Virtual Place; Office Azemoto, Tokyo, Japan). By using this software, 3-dimensional (3D) images were reconstructed. We have previously reported that the right anterior portal vein does not bifurcate into the anterosuperior branch (P8) and anteroinferior branch (P5), instead it bifurcates into the right ventral portal vein and the right dorsal portal vein. Reclassification of the liver to divide the right liver into anterior, middle, and posterior vertical segments has been proposed (Fig. 1) [13–15]. Based on this reclassification of the liver, we assessed the confluence pattern of the right ventral, dorsal, and posterior biliary branches, and the relationship between the right portal and biliary systems. Original consecutive axial CT images and 3D images were interpreted independently in a blinded fashion by 2 of the authors (A.C., H.Y.) who were very familiar with CT features and the anatomy of the liver. Any discrepancies that occurred were resolved by consensus.

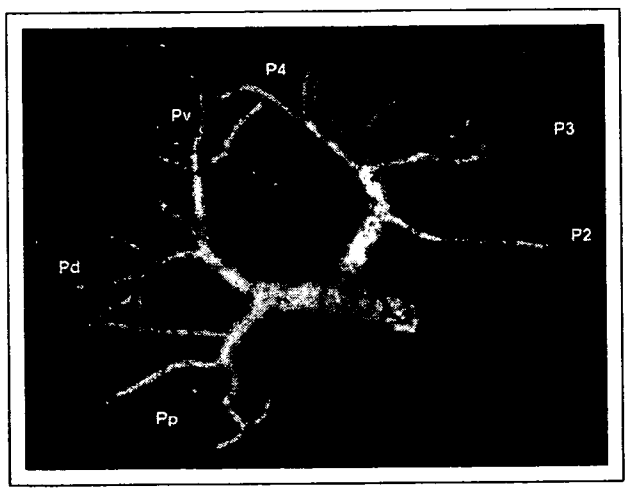

Fig. 1. Computer-generated 3D images of the caudo-cranial view showing ventral portal branches (PV) and dorsal portal branches (PD). PP, right posterior portal vein; P2, left laterosuperior portal branch; P3, left lateroinferior portal branch; P4, medial portal branch. Portal branching pattern seems symmetric.

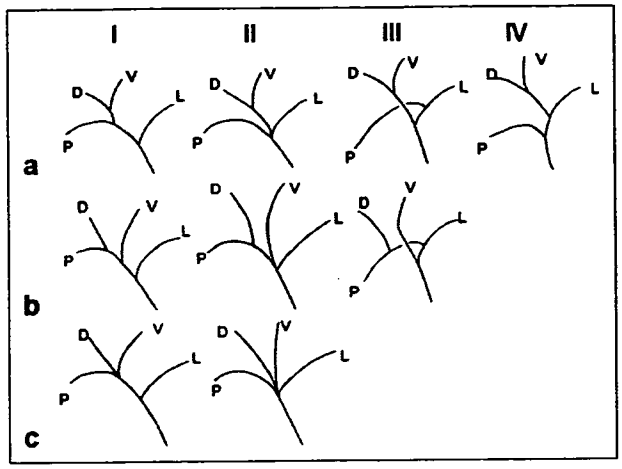

Fig. 2. Confluence patterns of right ventral, dorsal, posterior, and left hepatic ducts. V, ventral duct; D, dorsal duct; P, posterior duct; L, left hepatic duct.

Results

Confluence patterns of left, anterior, and posterior ducts

Confluence patterns were classified as type I (38 patients; 63%), normal configuration; type II (14 patients; 23%), triad confluence; type III (7 patients; 12%), posterior segmental duct joining left hepatic duct; or type IV (1 patient; 2%), distal confluence of the right posterior segmental duct. In type I, the anterior and posterior ducts unite to form the right duct, then the right and left ducts unite. In type II, the anterior, posterior, and left ducts unite immediately. In type III, the posterior and left ducts unite to form the common duct, then the anterior duct joins. In type IV, the anterior and left ducts unite to form the common duct, then the posterior duct joins distally.

Confluence patterns of right ventral, dorsal, and posterior ducts

Three distinct subtypes were detected with regard to confluence patterns of the right ventral, dorsal, and posterior ducts (Fig. 2). Subtype a was characterized by union of the ventral and dorsal ducts to form the anterior duct. Subtype b was characterized by a common trunk of the dorsal and posterior ducts. Subtype c was characterized by immediate union of the ventral, dorsal, and posterior ducts. Types Ia, Ib, and Ic were seen in 30 (50%), 6 (10%), and 2 (3%) of the 60 patients, respectively. Types IIa, IIb, and IIc were seen in 9 (15%), 4 (7%), and 1 (2%) of the 60 patients, respectively. Types IIIa and IIIb were seen in 5 (8%) and 2 (3%) of the 60 patients, respectively. Type IVa was seen 1 of the 60 patients (2%) (Table 1). Type IIIc and IVc did not exist

Table 1
Confluence patterns of the ventral, dorsal, posterior, and left hepatic ducts

Subtypes of confluence pattern	Confluence patterns of hilar bile ducts			
	I	II	III	IV
a	30 (50)	9 (15)	5 (8)	1 (2)
b	6 (10)	4 (7)	2 (3)	0 (0)
c	2 (3)	1 (2)	—	—
Total	38 (63)	14 (23)	7 (12)	1 (2)

Data in parentheses are percentages.

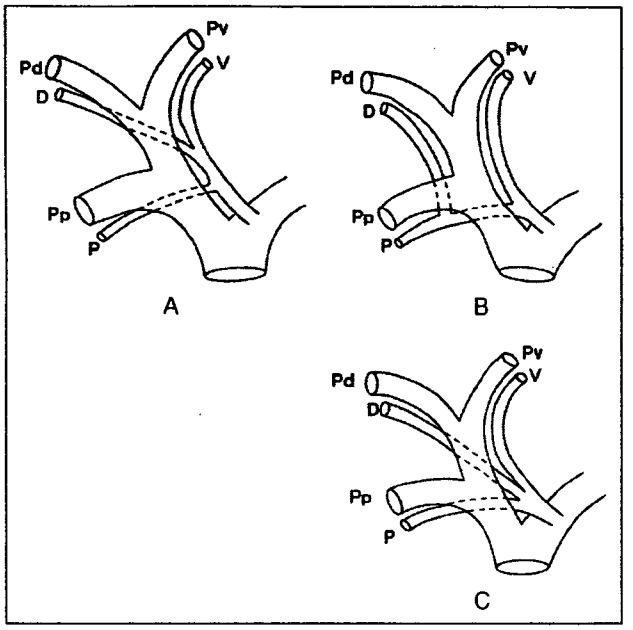

Fig. 3. Variants of right biliary and portal systems. (A) Ventral and dorsal ducts unite medial to the right anterior portal trunk, then the posterior duct also joins medial to the right anterior portal trunk. (B) Posterior and dorsal ducts unite lateral to the right anterior portal trunk, then the ventral duct joins medial to the right anterior portal trunk. (C) Ventral, dorsal, and posterior ducts unite medial to the right anterior portal trunk. PV = ventral portal branch; Pd = dorsal portal branch; Pp = right posterior portal vein; V = ventral duct; D = dorsal duct; P = posterior duct.

theoretically. Type IV b was not detected in the present study.

Relationship between right portal and biliary systems

The orientations in which the right posterior ducts crossed the right portal vein cranially, and in which the right biliary ducts ran superior to the right portal vein were constant (Fig. 3). In all 45 type Ia, IIa, IIIa, and IVa patients, the ventral and dorsal ducts united medial to the right anterior portal trunk, then the posterior duct also joined medial to the right anterior portal trunk (Figs. 3A and 4). In all 12 type Ib, IIb, and IIIb patients, the posterior and dorsal ducts united lateral to the right anterior portal trunk, then the ventral duct joined medial to the right anterior portal trunk (Figs. 3B and 5). In all 3 type Ic and IIc patients, the ventral, dorsal, and posterior ducts united medial to the right anterior portal trunk (Figs. 3C and 6).

Comments

Relationships between the left portal and biliary systems have been analyzed thoroughly using ex vivo corrosion casts [8] and in vivo radiologic examination [11], and is not so difficult to understand. The left biliary ducts are located cranial to the transverse and umbilical portions. Three distinct types can be identified: the segment 2 duct (B2) and segment 3 duct (B3) unite lateral to the umbilical portion, which lies on the umbilical fissure, then the segment 4 duct (B4) joins medial to the umbilical fissure; B3 and B4 unite medial to the umbilical fissure, then B2 joins medial to the umbilical fissure; or B2, B3, and B4 unite medial to the umbilical fissure [8,11]. In contrast, few reports have described relationships between the

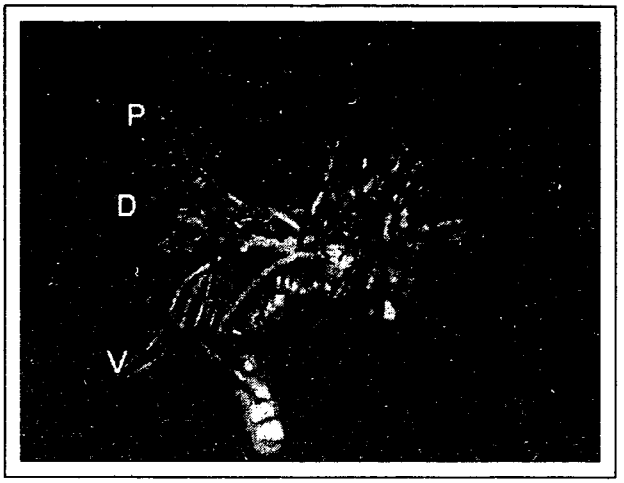

Fig. 4. Three-dimensional portocholangiography showing a craniocaudal view of the portobiliary system. The ventral and dorsal ducts unite to form the anterior duct, then the posterior duct joins (subtype a). V = ventral duct; D = dorsal duct; P = posterior duct.

right portal and biliary systems and understanding based on Couinaud's [9] numbering system is difficult because of the many variations. Recent studies have described the right anterior portal vein as bifurcating into the ventral and dorsal branches [13–17]. Because the right anterior portal vein bifurcated into the ventral and dorsal branches and most posterior portal veins did not bifurcate, we proposed reclassification of the liver to divide the right liver into anterior, middle, and posterior segments, supplied by the ventral, dorsal, and posterior portal branches, respectively [14,15]. The anterior and middle segments proposed by us correspond to the ventral and dorsal regions of Couinaud's [9] segment 8 and 5 (right paramedian sector), respectively, and the posterior segment is equivalent to Couinaud's [9] segment 7 and 6 (right lateral sector). Couinaud [9] divided the left liver into 3 segments, designated as segment 2 (S2), segment 3 (S3), and segment 4 (S4). S2 is supplied by the

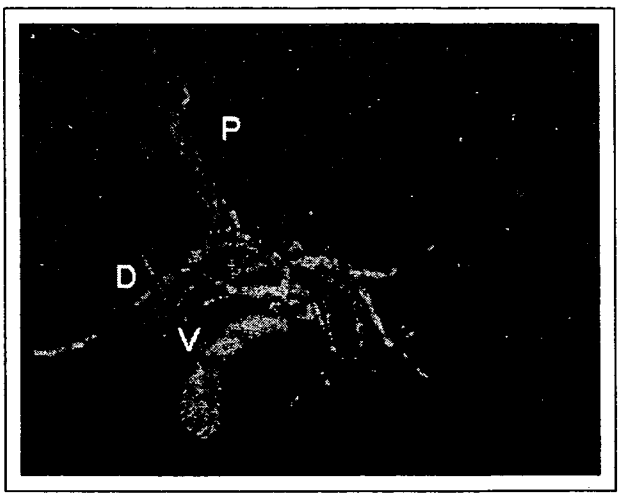

Fig. 5. Three-dimensional portocholangiography showing a craniocaudal view of the portobiliary system. The dorsal and posterior ducts unite, then the ventral duct joins (subtype b). V = ventral duct; D = dorsal duct; P = posterior duct.

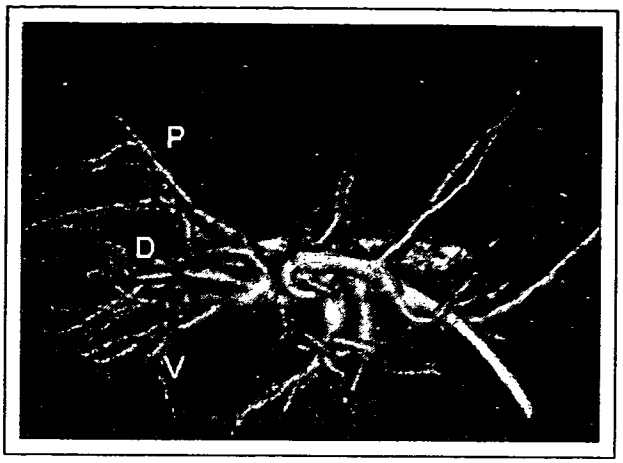

Fig. 6. Three-dimensional portocholangiography showing a craniocaudal view of the portobiliary system. The ventral, dorsal, and posterior ducts unite immediately (subtype c). V = ventral duct; D = dorsal duct; P = posterior duct.

second-order portal vein (P2), and S3 and S4 are each supplied by third-order portal branches (P3 and P4). Portal ramifications thus seem to be symmetric under our new classification because the posterior segment is supplied by the second-order posterior portal vein, and the anterior and middle segments are each supplied by third-order portal branches (ventral and dorsal branches) [14,15]. Thus, the right anterior segment may correspond to segment 4, the right middle segment to segment 3, and the posterior segment to segment 2 [15]. In addition, we proposed the anterior fissure by which the anterior and middle segments were divided [14]. We practically performed segmental hepatic resections along with the anterior fissure [14,15,18,19]. This new anatomic classification may facilitate an understanding of the relationships between the right portal and biliary systems. In the present study, the right portal vein constantly bifurcated into the posterior portal vein and the anterior portal vein, which then bifurcated into the ventral and dorsal branches. In contrast, biliary confluence patterns were classified as type I, normal configuration; type II, triad confluence; type III, posterior segmental duct joining the left hepatic duct; or type IV, distal confluence of the right posterior segmental duct as reported previously [9,10,20]. In addition, 3 distinct relationships exist between the right portal and biliary systems: the ventral and dorsal ducts unite medial to the anterior portal trunk, then the posterior duct joins close to the hepatic hilum; the dorsal and posterior ducts unite lateral to the anterior portal trunk, then the ventral duct joins medial to the anterior portal trunk; or the ventral, dorsal, and posterior ducts unite medial to the anterior portal trunk. Kamiya et al [21], in a review of 107 resected livers, also described the dorsal duct joining the posterior duct in 16.8%. In the left liver, B4 and B2 constantly join medial to the umbilical fissure, and B3 joins either B2 lateral to the umbilical fissure or B4 medial to the umbilical fissure. According to the present study, the ventral duct and posterior duct constantly join medial to the anterior portal trunk, which lies on the anterior fissure [13,14], and the dorsal duct joins either the ventral duct medial to the anterior fissure or the posterior duct lateral to the anterior fissure. We believe that recognition of this relationship between the right portal and biliary systems is useful to divide the bile duct during the donation of a right liver graft. In addition, the middle segment may be able to be preserved during left-sided resection of hilar cholangiocarcinoma if the dorsal duct joins the posterior duct lateral to the anterior fissure (subtype b). In conclusion, although our study was limited in that no actual gold standard existed for the findings, and comparisons of radiologic and surgical findings must await a future study, we consider that the right liver contains 3, not 4, segments as proposed by Couinaud [9].

References

[1] Nimura Y, Hayakawa N, Kamiya J, et al. Hepatic segmentectomy with caudate lobe resection for bile duct carcinoma of the hepatic hilus. World J Surg 1990;14:535–44.
[2] Nimura Y, Hayakawa N, Kamiya J, et al. Hilar cholangiocarcinoma—surgical anatomy and curative resection. J Hepatobiliary Pancreat Surg 1995;2:239–48.
[3] Hemming AW, Reed AI, Fujita S, et al. Surgical management of hilar cholangiocarcinoma. Ann Surg 2005;241:693–702.
[4] Otto G, Romaneehsen B, Hoppe-Lotichius M, et al. Hilar cholangiocarcinoma: resectability and radicality after routine diagnostic imaging. J Hepatobiliary Pancreat Surg 2004;11:310–8.
[5] Fan ST, Lo CM, Liu CL, et al. Biliary reconstruction and complications of right lobe live donor liver transplantation. Ann Surg 2002; 236:676–83.
[6] Lee KW, Joh JW, Kim SJ, et al. High hilar dissection: new technique to reduce biliary complication in living donor liver transplantation. Liver Transpl 2004;10:1158–62.
[7] Fulcher AS, Turner MA, Ham JM. Late biliary complications in right lobe living donor transplantation recipients: imaging findings and therapeutic interventions. J Comput Assist Tomogr 2002;26:422–7.
[8] Reichert PR, Renz JF, D'Albuquerque LA, et al. Surgical anatomy of the left lateral segment as applied to living-donor and split-liver transplantation: a clinicopathologic study. Ann Surg 2000;232:658–64.
[9] Couinaud C. Surgical anatomy of the liver revisited. Paris: Couinaud C, 1989.
[10] Healey JE, Schroy PC. Anatomy of the biliary ducts within the human liver. Arch Surg 1953;66:599–616.
[11] Cho A, Okazumi S, Yoshinaga Y, et al. Relationship between left biliary duct system and left portal vein: evaluation with three-dimensional portocholangiography. Radiology 2003;228:246–50.
[12] Cho A, Ryu M, Kinoshita T, et al. Radiological anatomy of the medial segmental bile duct of the liver assessed by CT cholangiography. Hepatogastroenterology 2003;50:945–8.
[13] Cho A, Okazumi S, Makino H, et al. Relation between hepatic and portal veins in the right paramedian sector: proposal for anatomical reclassification of the liver. World J Surg 2004;28:8–12.
[14] Cho A, Okazumi S, Makino H, et al. Anterior fissure of the right liver—the third door of the liver. J Hepatobiliary Pancreat Surg 2004;11:390–6.
[15] Cho A, Okazumi S, Miyazawa Y, et al. Proposal for a reclassification of liver based anatomy on portal ramifications. Am J Surg 2005;189:195–9.
[16] Cho A, Okazumi S, Takayama W, et al. Anatomy of the right anterosuperior area (segment 8) of the liver: evaluation with helical CT during arterial portography. Radiology 2000;214:491–5.
[17] Kogure K, Kuwano H, Fujimaki N, et al. Reproposal for Hjortsjo's segmental anatomy on the anterior segment in human liver. Arch Surg 2002;137:1118–24.
[18] Cho A, Okazumi S, Miyazawa Y, et al. Limited resection based on reclassification of segment 8 of the liver. Hepatogastroenterology 2004;51:575–6.
[19] Cho A, Okazumi S, Miyazawa Y, et al. Limited resection of the right hemiliver based on reclassification of the right anterior segment of the liver. Hepatogastroenterology 2004;51:820–1.
[20] Kitagawa Y, Nimura Y, Hayakawa N, et al. Intrahepatic segmental bile duct patterns in hepatolithiasis: a comparative cholangiographic study between Taiwan and Japan. J Hepatobiliary Pancreat Surg 2003;10:377–81.
[21] Kamiya J, Nagino M, Uesaka K, et al. Clinicoanatomical studies on the dorsal subsegmental bile duct of the right anterior superior segment of the human liver. Langenbecks Arch Surg 2003;388: 107–11.

特集 Stage IV 大腸癌と診断したらどうするか

Stage IV 大腸癌の治療方針はどう変わったか

Trend of treatment strategy for stage IV colorectal cancer

杉原 健一
SUGIHARA Kenichi

大腸癌遠隔転移の診断技術や肝切除・肺切除技術の改善により，最近の20年間でStage IV大腸癌の治療方針が変わってきた．遠隔転移巣が切除可能であれば，原発巣とともに遠隔転移巣も切除することが奨められる．遠隔転移巣が切除不能であっても，原発転移巣は切除したほうが，改善されてきている全身化学療法の治療効果により，予後の改善が期待できる．

はじめに

2006年3月に刊行された大腸癌取扱い規約第7版[1]ではStage IVの定義が変更され，従来の肝転移，肺転移，腹膜播種，それ以外の遠隔転移(骨，脳，副腎，脾など)に加え，領域リンパ節以外のリンパ節転移をも加えている．したがって，大腸脈周囲リンパ節への転移があればStage IVとなる．大腸癌研究会の全国登録のデータからStage IVは大腸癌全体の18.2%であり，肝転移が10.7%，肺転移が1.6%，腹膜播種が5.0%，その他が0.9%であった[2]．

大腸癌が診断された時点ですでに遠隔転移があれば，局所治療である手術治療では治癒が期待できないと以前は判断されており，肉眼的にすべて取りきれたとしても治癒切除として扱われなかった．そのため，大腸癌取扱い規約では初版以来第4版までは相対的非治癒切除として分類されていた．しかし，同時性肝転移や腹膜播種がすべて切除された場合には治癒が得られる症例も出てきたことから，1994年4月に出版された第5版以降は根治度Bとして分類されるようになった．

2005年に大腸癌研究会から出版された「大腸癌治療ガイドライン　医師用2005年版」[2]に記載されているStage IV大腸癌の治療方針では，まず，遠隔転移巣切除が可能か否かで，分類されている(図1)．遠隔転移巣が切除可能であれば原発巣を根治的切除し，遠隔転移巣切除を行う．不可能であれば，原発巣に起因する症状により，原発巣を切除するか否かを決めている．

本特集では遠隔転移臓器別に治療方針が独立して論じられていることから，本稿では各遠隔転移に関し概説するとともに，遠隔転移巣が切除不可能な場合の原発巣切除に関し考察する．

東京医科歯科大学大学院医歯学総合研究科消化機能再建学講座 教授
Key words : Stage IV 大腸癌／肝転移／腹膜播種／遠隔リンパ節転移

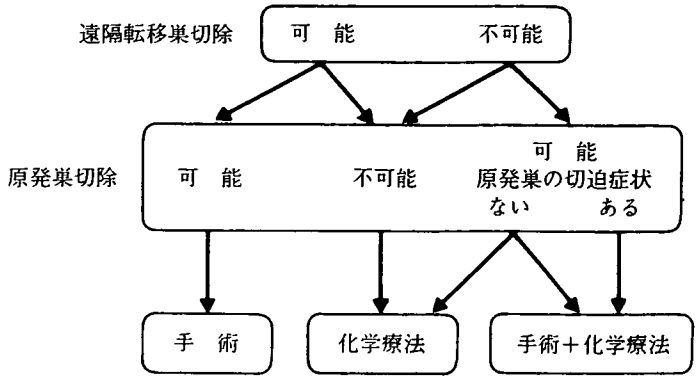

図1 Stage IV の治療方針

I. 遠隔転移の治療方針

1．肝 転 移

1）カスケード理論

血行性転移ではその広がりに関してカスケード理論がある．Weiss ら[3]は結腸癌1,541例の剖検を行い，大腸癌血行性転移の機序を検討した．その結果，「大腸癌の大部分の症例では，まず，肝に血行性転移が成立し，ある程度の大きさになるとそこから肺に転移する．さらに，肺から全身に癌細胞が散布される」にしたがっていると結論した．肝転移がなければ他の血行性転移がない率は85%，また，肝転移症例で肺転移がなく他の血行性転移を有する率は27%であった．したがって，カスケード理論に当てはまらない血行性転移は14%であった．ちなみに，肝転移がなく肺転移を伴う率は4%であり，肝転移がない症例での他の血行性転移臓器は骨髄，副腎，腎であり，肝転移があって肺転移がない症例での他の血行性転移臓器は副腎，脾，骨髄であった．したがって，血行性転移では肝に限局している時期がある．その段階で肝転移巣をすべて切除できれば根治が可能となる．

2）肝切除の適応

大腸癌肝転移に対する肝切除の適応は，肝画像診断や肝切除手技，周術期管理の進歩とともに変化してきた．1980年以前は単発例のみが手術の対象であったが，1980年代には転移個数が3個以下が切除の適応となっていた[4]．1990年代に入り，積極的に肝切除を行っている施設からの多数例の分析で，4個以上であっても長期生存を得る症例が少なからずあることが報告されるようになった．また，1986年に3個までが切除適応であると報告したIwatuki ら[5]は8年後に新たに分析し，4個以上でも長期生存例があり，切除の対象となる症例があると結論している．

3）同時性肝転移の予後は悪い

Stage IV である同時性肝転移は，異時性肝転移と比べ予後は不良である[6]．大腸癌研究会での同時肝転移446症例のアンケート調査では，肝切除が36.3%に，肝動注が23.8%に，全身化学療法が24.7%に行われ，無治療は12.6%であった[7]．当科では1990年から2004年までに同時性肝転移129例を経験し，同時性が異時性に比べ有意に予後不良であった(5年生存率は同時性40.7%，異時性18.0%)．その原因の一つには肝切除率が低いことがあげられ，同時性肝転移の肝切除率は24.8%で(異時性では60%)であった．しかし切除例の5年生存率には差がなく，同時性50.5%，異時性51.5%であった．

4）同時切除か異時切除か

同時性肝転移で肝切除が適応になった場合，原発巣との同時切除か異時切除かが問題になる．1980年代後半から1990年代半ばまでは，同時切除では侵襲が大きくなることによる合併症の増加が懸念されていた．しかし，同時切除でも合併症は増加しないとの報告が相次いだ[8)-10)]．これとは

別に，腫瘍学的問題として，転移巣が2 cm 以下の小さな場合，2～3ヵ月観察期間をおいてから再度肝切除の適応を検討したほうが良いとの意見がある[11]．肝画像診断の質的問題から，小さな転移巣がある場合，画像に描出されないより小さな転移巣が潜んでいる可能性がある．それらを顕在化させるために，一定期間観察して，適応を再検討するとの考えである．どちらの考えのも利点と欠点があり，症例ごとに判断すべきと考える．

5）ネオアジュバント

大腸癌に対する化学療法の進歩が著しく，奏効率や生存期間が有意に改善してきている．その効果的な化学療法を切除不能大腸癌肝転移に用いて転移巣を縮小させて切除可能にし，予後を改善することが試みられている[12)-14)]．確かに最近の大腸癌化学療法の進歩には目を見張るものがあり，大腸癌肝転移に対するネオアジュバントとして用いられる可能性がある．ただ，ここで問題なのは肝切除不能の判断である．欧米での肝切除手技はmajor hepatectomy であるため，転移巣が両葉存在する場合は切除の対象にならないことが多い．また，大腸癌治癒切除後のフォローアップでは画像診断が定期的に行われていないため，肝転移が進行した状態で発見されることが多い．肝転移の切除率は，フランスでは同時性肝転移で6.3%，異時性肝転移で16.9%と報告されている[15]．同時性と異時性を合わせての切除率は，米国では12%，ドイツでは24%であった[16)17)]．

一方，本邦では肝部分切除が中心であるため，両葉に転移があっても切除が可能である．大腸癌研究会のデータでは同時性肝転移の肝切除率は36.3%であり[7]，異時性の切除率は46.1%であった[18]．これからただちに本邦ではネオアジュバントの意味がないとは考えない．肝切除できたとしても同時性肝転移，Grade B ないしは H2 では再発率が高いことから，術前に微小転移を抑えたり，また，ダウンステージにより安全で癌を露出させない手術をめざしてのネオアジュバントには意味があると思う．

2．肺 転 移

肺転移に関しては，大腸癌取扱い規約第7版[1]や大腸癌治療ガイドライン[2]に分類や治療方針が記載されているが，肝転移ほど明確にはなっていない．切除ができれば30%～60%の5年生存が報告されている．しかし，いずれも単一施設からの少ない症例数の報告であり，また，手術適応にもコンセンサスが得られていない．多施設共同研究により，staging を定め，手術適応や治療効果を明らかにする必要がある．

3．腹膜播種

欧米の一部では，大腸癌腹膜播種に対して積極的な治療を行う考えがある．これは腹膜切除(peritonectomy)と温熱化学療法を組み合わせた方法であり[19]，2007年3月に開催された米国の第60回 Cancer Symposium of the Society of Surgical Oncology でも2時間の発表と討論が組まれていた．しかし，この治療法の対象は主に虫垂偽粘液腫による腹膜播種である．この疾患は本邦には少なく，通常の大腸癌の腹膜播種がこの治療法の対象になることはまれと考える．本邦では，腹膜播種に関する多数例の報告はないが，大腸癌取扱い規約(第7版)[1]では腹膜播種があっても肉眼的に取りきれればR0で，根治度Bである．大腸癌治療ガイドライン[2]では，「P_1 の場合は完全切除が望ましい」「P_2 で容易に切除可能なものは完全切除を考慮する」と記載されている．望月[20]は，腹膜播種が取りきれれば予後は切除しない場合より良好であり，P_1 の5年生存率は30%と報告している．

4．遠隔リンパ節転移

大腸癌取扱い規約(第7版)[1]では，それまで N_4 として扱われていた大動脈周囲リンパ節が，遠隔リンパ節(M)として分類された．これまでは郭清範囲の対象であった大動脈周囲リンパ節に関する研究は少ない．第44回大腸癌研究会で行われたアンケート調査[21]では，84施設のうち75%の施設で適応を決めて予防的大腸脈周囲郭清を行ってい

た．53施設からの症例では大動脈周囲リンパ節陽性率はS状結腸癌で2.1%，直腸癌で1.9%であった．大動脈周囲リンパ節陽性例では肝転移(31%)や腹膜播種(21%)の頻度が高く，57%が根治度Cであった．アンケート調査のため，大動脈周囲リンパ節郭清の効果は明らかではないが，転移頻度と根治性から見て，少なくとも予防的大動脈周囲リンパ節郭清の意義はほとんどないと思われる．

II. 遠隔転移巣が切除不可能の場合，原発巣を切除するか

遠隔転移巣が切除不能である場合，原発巣による症状(腸閉塞，出血・貧血)があれば原発巣の切除が奨められる．しかし，癌が広範転移しているに直腸癌では，原発巣切除の侵襲が大きいと判断した場合は人工肛門造設を選択することが多い．

切除不能な遠隔転移を伴うStage IV大腸癌の治療では，原発巣を切除したほうが予後の改善が期待できるが，切除の頻度は右側結腸癌では高く，直腸癌では低いと報告されている．Cookら[22]は，Stage IV大腸癌26,754例のうち原発巣切除は66%に行われ，切除率は右側結腸癌と左側結腸癌でそれぞれ75.3%，73.0%であったが，直腸癌では45.6%であり，原発巣切除例と非切除例での50%生存期間はそれぞれ結腸では11ヵ月と2ヵ月，直腸癌では16ヵ月と6ヵ月と報告している．Templeら[23]はSEERのデータを用いて65歳以上のStage IV大腸癌9,011例を検討した．原発巣切除率は72%で，遠隔転移巣も切除された症例は3.9%であり，直腸癌では切除＋吻合されたのは31%で，切除+人工肛門造設が69%であった．診断から原発巣切除まで4ヵ月以内の症例では，非切除例ないしは4ヵ月以上たって切除された症例に比べ明らかに生存期間が長かった．これらの報告では，手術が行える症例選択にバイアスがかかっているので，原発巣切除例と非切除例の生存期間を比較することには意味がないが，切除が行われれば12ヵ月以上の生存が期待できることを示している．また，これらの報告の症例集積期間ではまだFOLFOXやFOLFIRI，分子標的薬が使われていない時代であったことから，現在ではより長期間の生存が期待できる．Ruoら[24]はStage IV大腸癌422症例のうち，無症状で原発巣切除を受けた127例と非切除例103例を比較検討した．切除例の術後30日以内の死亡率は1.6%，合併症率は20.5%であった．切除例には，右側結腸癌が多く，遠隔転移臓器数が少なく(1ないし2臓器)，肝転移例では癌の肝占拠率が小さく，また，50%生存期間は16ヵ月(非切除例では9ヵ月)であった．この結果から，遠隔転移切除不能Stage IV大腸癌症例が無症状であっても，全身への転移が広範ではなく，肝転移が高度でなければ，原発巣切除を推奨している．

一方，切除不能遠隔転移を伴ったStage IV大腸癌で，原発巣は切除可能であるが症状がないためまず全身化学療法を行って経過を見た報告がある[25]．24例のうち，経過中に大腸閉塞が合併した症例が4例あり，2例には切除を行い，2例にはステントを留置した．また，3例では腹痛のため切除が行われた．肝転移が縮小した1例には根治的手術がなされた．24例の50%生存期間は10.3ヵ月であった．

以上の研究結果からは，切除不能遠隔転移を伴うStage IV大腸癌では，無症状であっても，肝転移が広範でなければ原発巣を切除し，残存病巣には最近成績の向上した全身化学療法に期待することが推奨される．

文　献

1) 大腸癌研究会編：大腸癌研究会大腸癌取扱い規約　第7版，金原出版，東京，2006.
2) 大腸癌研究会編：大腸癌研究会大腸癌治療ガイドライン，金原出版，東京，2005.
3) Weiss L, Grundmann E, Hartveit F, et al: Hematogenous metastatic patterns in colonic carcinoma: an analysis of 1541 necropsies. J Pathol 150: 195-203, 1986.
4) Iwatsuki S, Esquivel CO, Gordon RD, et al: Liver resection for metastatic colorectal cancer. Surgery 182: 804-810, 1986.

5) Gayowski TJ, Iwatsuki S, Madariaga JR, et al : Experience in hepatic resection for metastatic colorectal cancer : analysis of clinical and pathological factors Surgery 116 : 703-711, 1994.
6) Scheele J, Stang R, Altendorf-Hofmann A, et al : Resection of colorectal liver metastasis. World J Surg 19 : 59-71, 1995.
7) 河原正樹，加藤智之，森　武生ほか：本邦における大腸癌同時性肝転移に対する治療の現況(第2報)．日本大腸肛門病会誌　56：55-61，2003.
8) de Santibanes E, Lassalle FB, McCormack L, et al : Simultaneous colorectal and hepatic resections for colorectal cancer ; prospective and long term outcomes. J Am Coll Surg 195 : 196-202, 2002.
9) Chua HK, Sondenaa K, Tsiotos GT, et al : Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastasis. Dis Colon Rectum 47 : 1310-1316, 2004.
10) Capussotti L, Ferrero A, Vigano L, et al : Major liver resection synchronous with colorectal surgery. Ann Surg Oncol 14 : 195-201, 2007.
11) Scheele J : Hepatectomy for liver metastases. Br J Surg 80 : 274-276, 1993.
12) Bismuth H, Adam R, LeviF, et al : Resection of nonresectable liver metastasis colorectal cancer after neoadjuvant chemotherapy. Ann Surg 224 : 509-522, 1996.
13) Alberts SR, Horvath WL, Sternfeld WC, et al : Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer : a north central cancer treatment group phase II study. J Clin Oncol 23 : 9243-9249, 2005.
14) Masi G, Cupini S, Marcucci L, et al : Treatment with 5-fluorouracil/folic acid, Oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. Ann Surg Oncol 13 : 58-65, 2006.
15) Manfredi S, Lepage C, Hatem C, et al : Epidemiology and management of liver metastases from colorectal cancer. Ann Surg 244 : 254-259, 2006.
16) Cady B, Stone MD : The role of surgical resection of liver metastases in colorectal carcinoma. Semin. Oncol 18 : 399-406, 1991.
17) Scheele J, Stangl R, Altendorf-Hofmann A : Hepatic metastases from colorectal carcinoma : impact of surgical resection on the natural history. Br J Surg 77 : 1241-1246, 1990.
18) Kobayashi H, Mochizuki H, Sugihara K, et al : Characteristics of recurrence and surveillance tools after curative resection for colorectal cancer : a multicenter study. Surgery 141 : 67-75, 2007.
19) Sugarbaker PH : Peritonectomy procedures. Ann Surg 231 : 29-42, 1995.
20) 望月英隆：腹膜播種を伴う大腸癌．上西紀夫，田中雅夫(編)消化器癌の外科治療，pp100-102，中外医学社，東京，2001.
21) 正木忠彦，武藤徹一郎，安富正幸：大動脈周囲リンパ節転移の実態：第44回大腸癌研究会アンケート調査報告．大腸肛門病会誌　50：318-330，1997.
22) Cook AD, Single R, McCahill LE : Surgical resection of primary tumors in patients who present with Stage IV colorectal cancer : an analysis of surveillance, epidemiology, and end results data, 1988 to 2000. Ann Surg Oncol 12 : 637-645.
23) Temple LKF, Hsiel L, Wong D et al : Use of surgery among elderly patients with Stage IV colorectal cancer. J Clon Oncol 22 : 3475-3484, 2004.
24) Ruo L, Gougoutas C, Paty PB, et al : Elective bowel resection for incurable stage IV colorectal cancer : prognostic variables for asymptomatic patients. J Am Coll Surg 196 : 722-728, 2003.
25) Sarela AI, Duthrie JA, Seymour MT, et al : Non-operative management of the primary tumor in patients with incurable stage IV colorectal cancer. Br J Surg 88 : 1352-1356, 2001.

大腸癌の化学療法の進歩と限界

植竹　宏之　　石川　敏昭　杉原　健一

別　刷
日本医師会雑誌
第136巻・第3号
平成19（2007）年6月

大腸癌の化学療法の進歩と限界

植竹宏之[*1]　石川敏昭[*2]　杉原健一[*3]

キーワード　多剤併用療法　個別化治療　医療費

Ⅰ．はじめに

近年，新規薬剤や多剤併用療法が導入され大腸癌化学療法は急激に変化している．また，患者のQOLに配慮して外来化学療法が重視され，利便性から経口抗癌剤も注目されている．一方で，高価な薬剤の開発により治療費が高騰するなどの問題点も指摘されており，抗癌剤への感受性因子や予後因子の解析による個別化治療の検討がさらに重視されると考える．

本稿では，最近の大腸癌化学療法の進歩や注目すべき話題を，特に①多剤併用療法および新規抗癌剤，②術後補助化学療法，③個別化治療の面から検討し，④医療費の高騰などの問題点についても概説する．

Ⅱ．大腸癌化学療法の進歩

1．多剤併用療法および新規抗癌剤

(1) 多剤併用療法

わが国における進行再発大腸癌に対する治療法の変遷と予後の改善を**図1**に示した．近年はファーストラインとして多剤併用療法が普及した．抗癌剤を2剤以上併用する場合，その組み合わせとしては，①単剤でも抗腫瘍効果があるもの同士の組み合わせ［5-FU系薬剤＋イリノテカン（CPT-11）など］，②単剤では効果が薄いが，併用するとbiochemical modulationや薬剤の腫瘍への移行率の上昇などにより高い抗腫瘍効果が発揮される組み合わせ［5-FU＋ロイコボリン（LV），オキサリプラチンを含むレジメン，分子標的治療薬を含むレジメンなど］がある．代表的なレジメンは5-FU＋LV＋オキサリプラチン（FOLFOX，FLOX）と，5-FU＋LV＋CPT-11（FOLFIRI，IFL）である．しかし，多剤併用療法は抗腫瘍効果が高いと同時に有害事象も起こりやすい．

図1　進行再発大腸癌化学療法の変遷と予後の改善

米国National Comprehensive Cancer Network（NCCN）がインターネット上に示している治療ガイドライン[1]においても，切除不能大腸癌に対する治療方針は，まず「患者が強力な治療に耐えうるか」を判断し，耐えうる患者に対しては分子標的治療薬を含む多剤併用療法を行うことが推奨されるが，耐えられない患者に対しては5-FU＋LVなどの治療が推奨されて

[*1] **うえたけ・ひろゆき**：東京医科歯科大学大学院医歯学総合研究科准教授（応用腫瘍学）．平成元年東京医科歯科大学医学部卒業．主研究領域：大腸癌化学療法．
[*2] **いしかわ・としあき**：東京医科歯科大学大学院医歯学総合研究科応用腫瘍学，[*3] **すぎはら・けんいち**：同教授（腫瘍外科学）．

いる.

多剤併用療法がファーストラインで行われた場合，セカンドライン治療に用いるレジメンの選択も,「違う系統の薬剤に変更する」といった単純な選択ではなくなる．すなわち，腫瘍が多剤併用療法に対して抵抗性になった場合（あるいは有害事象が tolerable でない場合），いずれの薬剤に対して腫瘍が抵抗性になったかは必ずしも明らかでなく，薬剤に特異的な有害事象（オキサリプラチンの神経毒性のように）でない限り，有害事象を引き起こした薬剤は特定されないからである．

Tournigand らはファーストライン→セカンドラインとして，FOLFOX→FOLFIRI，あるいは FOLFIRI→FOLFOX が望ましいと報告している[2]．すなわち，ベースとなる 5-FU＋LV の投与レジメンは変更せずに，オキサリプラチンと CPT-11 がファーストラインかセカンドラインのいずれかに投与される方法により，生存期間の延長が得られると報告した．

(2) 分子標的治療薬

これまでの抗癌剤は癌細胞および核酸，微小管などをターゲットとし，癌細胞の分裂・増殖を抑制するものであった．一方，近年は分子生物学的手法が急速に発達し，癌細胞の特異的な分子を標的として抗腫瘍効果を発現する低分子化合物や抗体が開発されている．大腸癌治療において現在，わが国で最も注目されている分子標的治療薬はベバシズマブである．ベバシズマブは癌細胞の増殖にかかわる血管新生因子 VEGF（vascular endothelial growth factor）に対する中和抗体であり，欧米における進行再発大腸癌に対するランダム化比較試験においては，抗癌剤との併用により優れた治療効果を示した．

ベバシズマブの作用機序は，生体内において VEGF 活性阻害による血管新生の抑制（「兵糧攻め」）というよりは，むしろ腫瘍血管の構造や機能の正常化をもたらして抗癌剤の腫瘍細胞への移行を促進していることである[3]．ベバシズマブの主な有害事象を表1に示した．予測が困難であった副作用が欧米の臨床試験において報告された．これは，VEGF のような増殖因子が生体内において多彩な副次的生理活性を有しているためと考えられる．

表1　ベバシズマブ療法の特徴的有害事象と発生頻度

	発生頻度（%）	
	すべての grade	grade 3，4
高血圧症	6～32	0～25
蛋白尿	19～38	0.8～1
動脈血栓症	8.6～13	1.2～9
創傷治癒遅延	2～5	—
腫瘍関連出血	29～69	0～15.6
消化管穿孔	*	1.0～4.2

＊消化管穿孔は grade 3 以上

(3) 経口抗癌剤への注目

わが国では利便性の面から消化器癌などの治療において経口フッ化ピリミジン製剤が広く使用されてきた．簡便さ以外の経口薬の有利な点は有効血中濃度の維持であり，細胞周期依存性に抗腫瘍効果を発揮する薬剤は経口投与も理にかなっている[4]．経口抗癌剤で特に注目されるのはテガフール・ウラシル配合剤（UFT®）＋経口 LV とテガフール・ギメラシル・オテラシルカリウム配合剤（TS-1®），加えてわが国では未承認であるが欧米の標準的経口薬であるカペシタビンである．多剤併用療法において，5-FU＋LV 静注の部分を経口薬に置き換える治療法について，多くの臨床試験が行われている．

2. 術後補助化学療法

大腸癌において，進行再発例に対する化学療法の治療効果は飛躍的に上昇しているものの，化学療法のみで治癒する症例はほとんどみられない．一方，治癒切除後であっても術後には一定頻度に再発が起こることから，術後補助化学療法は重要である．大腸癌における術後補助化学療法の対象は stage III 症例である．術後補助化学療法は手術単独に比して，stage III 症例の

再発のリスクを約10%減じる.

術後補助化学療法においては，通常，進行再発症例に対し有効であることが示された新規薬剤レジメンを用いた臨床試験が行われる．欧米では大腸癌補助化学療法において，5-FU＋LVにCPT-11やオキサリプラチンを併用投与するレジメンを用いた比較臨床試験が行われた．これらの結果では，オキサリプラチン併用群の3年無再発生存は5FU＋LVのみの群に比し有意に優れており，FOLFOXやFLOXの有効性が確認されたが，CPT-11併用の有効性は示されなかった.

一方，欧米での標準治療を日本に導入するにあたり，以下のような問題点がある．①大腸癌において日本における手術単独での治療成績は欧米に比して良好である．したがって，毒性の強いレジメンで補助化学療法を行う必要があるのかは疑問の余地がある．②日本の補助化学療法は外科医によって行われることが多いので，複雑で毒性の強いレジメンは治療効果のうえで大きなメリットがない限り普及しにくい．③日本におけるランダム化比較試験においては，5-FU系経口薬単剤投与の有用性が示されている(特に直腸癌).

大腸癌における補助化学療法の対象はstage III症例であることにはコンセンサスが得られているが，stage II症例の10～15%に再発が起こる．この再発リスクの高い群に対しては補助化学療法の必要性を明らかにする必要がある．臨床病理学的にはT4N0M0．穿孔例．腸閉塞例．脈管侵襲陽性例などが，分子生物学的マーカーではmicrosatellite instabilityや18qのloss of heterozygosityなどがハイリスク群と報告されている[5]が，定まった見解はない.

3. 個別化治療

既述のように，抗癌剤治療によって根治する切除不能固形癌症例はきわめてまれである．したがって，癌化学療法は開始の時点からすでに延命治療であり，緩和的要素を含む．この点からも，消化器癌化学療法における薬剤感受性研究の意義は大きい．つまり，治療効果が高く副作用の少ない化学療法を選択すること，あるいは無益な治療を避けることは，患者側にも医療側にも大きな利益となるからである.

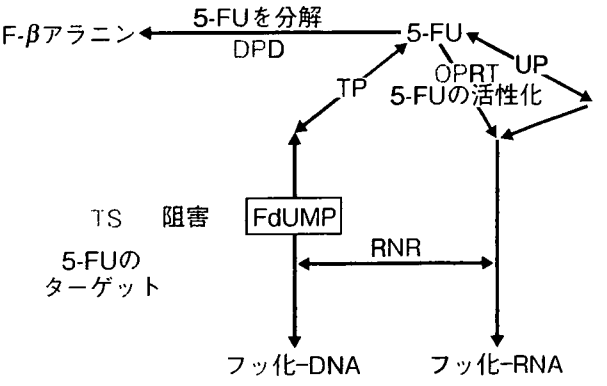

図2　5-FUの代謝経路

TP；thymidine phosphorylase，UP；uridine phosphorylase，FdUMP；5-fluoro-deoxyuridine monophosphate，RNR；ribonucleotide reductase

われわれはフッ化ピリミジン代謝酵素および抗癌剤標的酵素の発現に着目して，5-FU系薬剤の治療効果予測を目指してきた(**図2**)．進行再発大腸癌や乳癌においては原発巣のTS(thymidylate synthase，5-FUのターゲット)，DPD(dihydropyrimidine dehydrogenase．5-FUの分解経路の律速酵素)，OPRT(orotate phosphoribosyl transferase．5-FUの活性化酵素)のmRNA発現量を組み合わせて，5-FU系薬剤の効果予測がある程度可能となった[6~8].

多剤併用療法の時代においても，抗癌剤感受性因子，抵抗性因子の研究が重要なことはいうまでもないが，候補となる遺伝子や蛋白もより多くなる．したがって，研究手法としては前述のような抗癌剤のターゲットや代謝関連酵素の遺伝子・蛋白発現を詳細に研究するcandidate approachのみでなく，数千～数万の遺伝子発現を網羅的に検索するマイクロアレイを用いたglobal approachの有用性が検討されている.

4. 医療費の高騰

固形癌の化学療法においては新規薬剤の導入

と多剤併用療法の普及，および適切な支持療法で予後の改善が得られたことは明らかであるが，これらはいずれも医療費の高騰をもたらす．LVとオキサリプラチンを使用するレジメンは，月に約45万円の医療費となる．保険の種類によりこの何割かを（一定限度以上は還付されるとはいえ）患者が支払う．新規薬剤の価格には平均10年の研究開発費が反映するとされており，分子標的治療薬はさらに高額である．

医療費と患者の予後は正の相関を示すという報告がある．また，「現在の大腸癌化学療法のdose limiting toxicityは治療費である」と述べる研究者もいる．医療費および患者負担の高騰に対する対策として，われわれ研究者が貢献できることは「無益な治療を避ける」ことであろう．患者に有益な治療，エビデンスのある治療は積極的に行い，逆に無益な薬剤投与を長期間行うことなどは厳に慎む．また，治験への参加も患者負担を減らす．

将来の理想像としては個別化治療であろう．前述の個別化治療が確立し，治療効果が高く副作用が少ない治療法が患者個々に選択されることが，「無益な治療を避ける」ことに直結する．

Ⅲ．おわりに

以上，最近の大腸癌化学療法の動向を概説した．近年，長足の進歩を遂げ治療効果が高くなった大腸癌化学療法のさらなる発展性を期待する方法として，化学療法と手術を効率的に組み合わせて治癒切除率の向上を目指す試みが行われている．また，欧米で使用されエビデンスの確立した新規薬剤やレジメンの導入は重要であるが，それらがわが国の現状に即しているか，あるいは実臨床の場での普及が可能であるかを十分検討しなければならない．医療費の高騰など現在の問題点を明らかにし，解決法を議論することも重要である．治療の個別化治療を含め，大腸癌化学療法のさらなる進化が期待される．

文　献

1) http://www.nccn.org/
2) Tournigand C, André T, Achille E, *et al* : FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer : a randomized GERCOR study. *J Clin Oncol* 2004 ; 22 (2) : 229–237.
3) Kerr DJ : Targeting angiogenesis in cancer : clinical development of bevacizumab. *Nat Clin Pract Oncol* 2004 ; 1 (1) : 39–43.
4) 佐々木康綱：経口抗癌剤の臨床薬理学—経口フッ化ピリミジン製剤を中心として．*Mebio Oncol* 2006 ; 3(1) : 9–15.
5) 植竹宏之，石川敏昭，杉原健一：大腸癌における Adjuvant Chemotherapy の動向．*Focus on Oncology* 2006 ; 5 : 11–12.
6) Ichikawa W, Uetake H, Shirota Y, *et al* : Both gene expression for orotate phosphoribosyltransferase and its ratio to dihydropyrimidine dehydrogenase influence outcome following fluoropyrimidine — based chemotherapy for metastatic colorectal cancer. *Br J Cancer* 2003 ; 89 (8) : 1486–1492.
7) Ichikawa W, Uetake H, Shirota Y, *et al* : Combination of dihydropyrimidine dehydrogenase and thymidylate synthase gene expressions in primary tumors as predictive parameters for the efficacy of fluoropyrimidine—based chemotherapy for metastatic colorectal cancer. *Clin Cancer Res* 2003 ; 9 (2) : 786–791.
8) Kakimoto M, Uetake H, Osanai T, *et al* : Thymidylate synthase and dihydropyrimidine dehydrogenase gene expression in breast cancer predicts 5-FU sensitivity by a histocultural drug sensitivity test. *Cancer Lett* 2005 ; 223 (1) : 103–111.