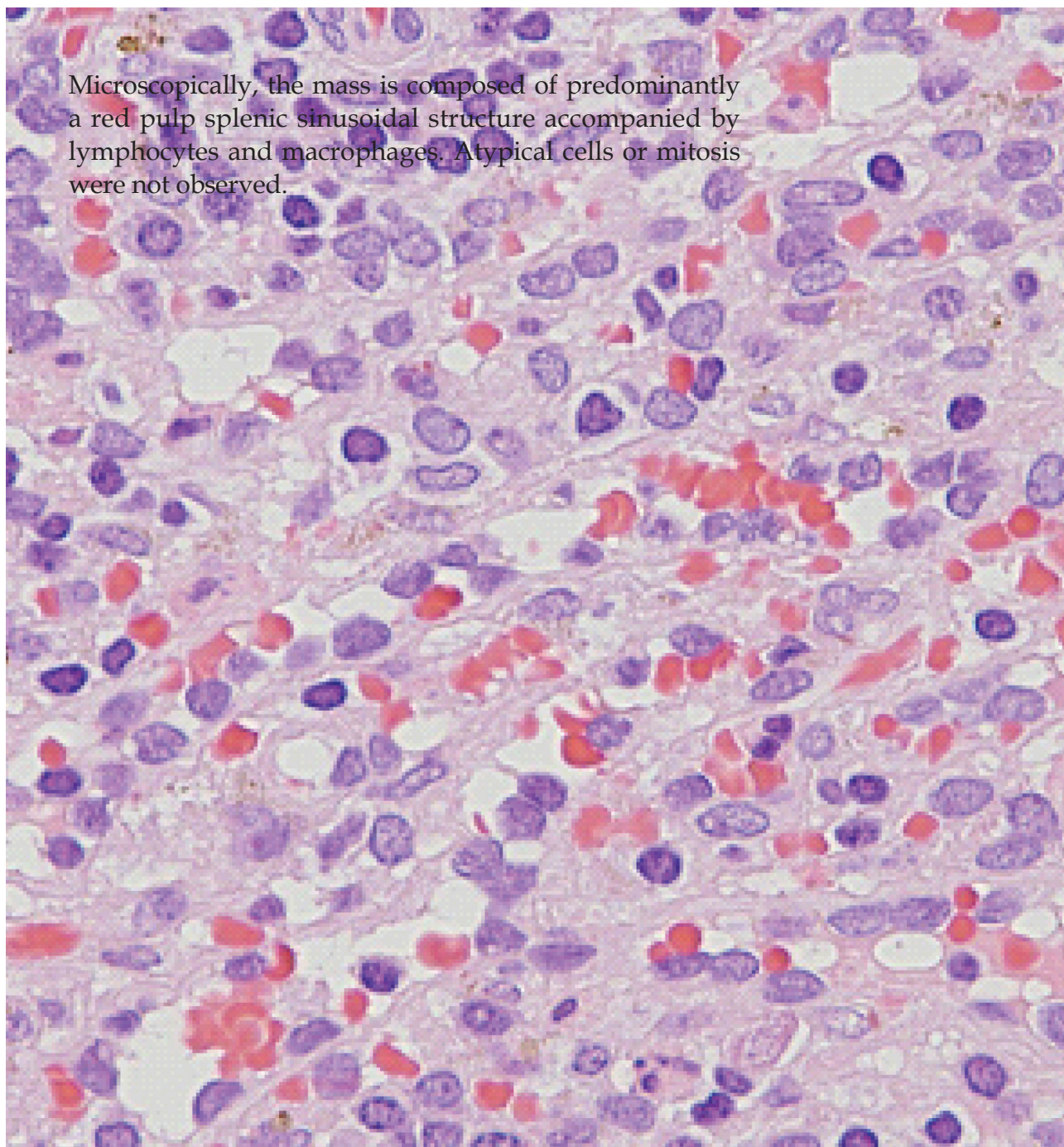




Microscopically, the mass is composed of predominantly a red pulp splenic sinusoidal structure accompanied by lymphocytes and macrophages. Atypical cells or mitosis were not observed.





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Preoperative chemoradiation and extended pelvic lymphadenectomy for rectal cancer: Two distinct principles

Tsuyoshi Konishi, Toshiaki Watanabe, Hirokazu Nagawa, Masatoshi Oya, Masashi Ueno, Hiroya Kuroyanagi, Yoshiya Fujimoto, Takashi Akiyoshi, Toshiharu Yamaguchi, Tetsuichiro Muto

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the presence of metastatic lateral lymph nodes (LLNs), EPL performed by experienced surgeons definitely contributes to decrease local recurrence. On the other hand, a randomized controlled trial in Japan that compared EPL with conventional TME following preoperative RT revealed that EPL is associated with a higher frequency of sexual and urinary dysfunction without oncological benefits in the presence of preoperative RT. On this point, preoperative CRT followed by conventional TME without EPL would be a better therapeutic approach in patients without evident metastatic LLNs. For future treatment, it would be desirable to have a narrower indication for EPL using full advantage of recent improvement in image diagnosis. Although objective comparison of these two principles between Japan and the West is difficult due to differences in patient groups, further studies would lead to the next great step towards future improvement in treating lower rectal cancer.

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Abstract

Extended pelvic lymphadenectomy (EPL) with total mesorectal excision (TME) has been reported to provide oncological benefit in lower rectal cancer in Japan. In Western countries EPL is not widely accepted because of frequent morbidity but instead preoperative chemoradiation (CRT) followed by TME has been established as a standard treatment for decreasing local recurrence. Recently, several studies have focused on the comparison between these two distinct therapeutic approaches in Western countries and Japan. A study comparing Dutch trial data and Japanese data revealed that EPL and RT are almost equivalent in decreasing local recurrence in lower rectal cancer as compared with TME alone. Considering that almost 45% survival can be achieved by EPL even in

Key words: Rectal cancer; Extended lymphadenectomy; Chemoradiation; Pelvic lymph node; Lateral lymph node

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HISTORICAL BACKGROUND OF SURGICAL APPROACH FOR LOWER RECTAL CANCER IN JAPAN AND WESTERN COUNTRIES

Lateral lymph node (LLN) metastasis is among the strongest causes of local recurrence as well as poor survival in locally advanced lower rectal cancer^[1,2]. Since the late 1970s, Japanese surgeons have carried out extended pelvic lymphadenectomy (EPL) with total mesorectal excision (TME) for lower rectal cancer. Retrospective studies from Japan indicate that EPL decreased local recurrence as well as prolonged survival^[3-5]. During the past 25 years, Japanese surgeons have made remarkable progress in the management of lower rectal cancer with EPL, including imaging modalities for diagnosis of LLN metastasis and nerve-sparing surgical techniques for decreasing sexual and urinary dysfunction^[5-8]. Based on these improved techniques, EPL is still recommended as a standard approach for locally advanced lower rectal cancer in the Japanese Society for Cancer of the Colon, Rectum's guidelines.

In Western countries the literature has been against EPL for rectal cancer^[9-12]. Studies criticized EPL for a low rate of LLN metastasis, poor survival in those with positive LLN, frequent morbidity after surgery and increased operation time as well as blood loss. Instead, Western surgeons have developed preoperative chemoradiation (CRT) as a standard therapeutic approach for locally advanced lower rectal cancer through several randomized controlled trials (RCTs)^[13-15].

Recently, several studies have focused on comparing CRT as the Western standard and EPL as the Japanese standard^[16-20]. Although there are several issues to be discussed in each study, objective comparison of these two standards seems a great step towards future improvement in the treatment of lower rectal cancer.

This review highlights the recent studies on EPL and CRT as two distinct principles for lower rectal cancer.

EPL AS A STANDARD TREATMENT FOR LOWER RECTAL CANCER: EVIDENCE FROM JAPAN

In 1982, Hojo *et al*^[21] in the National Cancer Center reported the outcomes of 160 patients who underwent wide anatomical resection with radical lymphadenectomy (extended surgery) for lower rectal cancer. The authors reported decreased local recurrence of 6.5% for Dukes B and 25% for Dukes C in those undergoing extended surgery as compared with 25% for Dukes B and 45% for Dukes C in conventional surgery. A report from the same group further indicated improved 5-year-survival of 83.2% for Dukes B and 52.5% for Dukes C in those undergoing extended surgery as compared with 63.7% for Dukes B and 30.8% for Dukes C in conventional surgery^[3]. However, Moriya *et al*^[22] also reported that extended surgery is highly associated with longer duration of operation, more blood loss and higher

Table 1 Answers to criticism of extended pelvic lymphadenectomy

Low rate of lateral lymph node metastasis
15.6% for Rb ^a , 12.2% for Rb T3, 25.1% for Rb T4 ^[1]
Poor survival for lateral lymph node positive cases even after dissection
5-year survival of 45.8% in lateral lymph node positive cases ^[1]
Increased Morbidity
Yes, but decreased by autonomic nerve-preservation ^[5,6]
Longer operative time and blood loss
Yes

^aRb: Lower rectal cancer below peritoneal reflection.

frequency of urinary dysfunction and sexual dysfunction. In 1995, Sugihara *et al*^[5] and Moriya *et al*^[6] reported that autonomic nerve-preserving surgery could reduce urinary and sexual dysfunction without deteriorating oncological outcomes. In this report, patients undergoing preservation of both hypogastric and pelvic nerves achieved 98% excellent or good urinary function, 68% ejaculation and 90% erection. Since this report, EPL with autonomic-nerve preservation has become a standard treatment for locally advanced lower rectal cancer in Japan. Studies from several referral institutions have revealed that the proportion of positive LLN was around 15%, varying from 10.6% to 25.5% in locally advanced lower rectal cancer below peritoneal reflection and the 5-year survival of those undergoing EPL in the presence of metastatic LLNs was around 45%, varying from 37.3% to 49.3%^[1,2,4,5,23-26]. It has been reported that the number of positive LLNs is among the most important predictive factors for survival after EPL. The number of positive LLNs was an independent risk factor for poor survival in patients with metastatic LLNs along with positive mesenteric lymph nodes, female gender, higher age and positive circumferential resection margin^[2,26]. Shirouzu *et al*^[25] also reported that 5-year survival reached over 60% if the involved LLNs were less than three, while the survival decreased to 16.7% with three or more positive LLNs. Risk factors for LLN metastases have been also investigated. Sugihara *et al*^[1] performed multivariate analysis using multi-institutional registry data in Japan and revealed that a short distance from the anal verge to the tumor was independently associated with positive LLNs along with poor histological grade, large tumor size, deeper depth of invasion and female gender. Ueno *et al*^[2] also reported that positive mesenteric lymph node correlated with positive LLNs. Based on the evidence during the past 25 years (Table 1), the present guideline by the Japanese Society for Cancer of the Colon and Rectum clearly states that EPL is indicated for lower rectal cancer with T3 or deeper invasion and the lower edge of the tumor located below the peritoneal reflection.

PREOPERATIVE CRT AS A STANDARD TREATMENT FOR LOWER RECTAL CANCER: EVIDENCE FROM THE WEST

The Dutch Colorectal Cancer Group reported the results

of RCT that randomly assigned 1861 patients with resectable rectal cancer either to preoperative radiation (RT) followed by TME or to TME alone^[13]. The rate of local recurrence at two years was 2.4% in the preoperative RT group and 8.2% in the TME-only group ($P < 0.001$). The German Rectal Cancer Study Group randomly assigned 823 T3/T4 or node-positive rectal cancer to either preoperative CRT followed by TME or TME followed by postoperative CRT^[15]. The overall 5-year survival rates were 76% and 74% for preoperative and postoperative CRT respectively ($P = 0.80$). However, the incidence of local recurrence at five years was 6% in the preoperative CRT and 13% in the postoperative CRT ($P = 0.006$). Grade 3/4 acute toxic effects occurred in 27% of the preoperative CRT group as compared with 40% of the postoperative CRT group ($P = 0.001$), and the rates of long-term toxic effects were 14% and 24% respectively ($P = 0.01$). Importantly, this study further suggested a statistically significant increase in sphincter preservation in preoperative CRT group compared with postoperative CRT group by subanalysis of the 194 patients that required an abdominoperineal excision before randomization as determined by the surgeon ($P = 0.004$). Based on this study, preoperative CRT therapy has become the standard treatment for patients with clinically staged T3/T4 or N1 disease in Western countries^[27]. It has been reported that complete pathologic response rates of 10% to 25% may be achieved with preoperative CRT and benefits of neoadjuvant CRT include tumor regression, downstaging and improvement in respectability and a higher rate of sphincter preservation and local control^[15,28-35]. On the other hand, preoperative CRT is also associated with increased morbidity compared with surgery alone, including increased surgical complications, chronic bowel dysfunction, anorectal sphincter dysfunction (if the sphincter was surgically preserved), and sexual dysfunction^[36-42].

There still remains several unsolved issues regarding preoperative RT and CRT. First, there have been few studies comparing conventional long-course fractionated CRT and short-course RT. Although the Polish trial demonstrated no differences in the oncological outcomes between the two groups, quality control of the study did not seem appropriate as local recurrence in the CRT group exceeded 14%^[39]. Second, there have been no studies that revealed oncological benefit of additional chemotherapy in short-course RT regimen, although its efficacy has been established in conventional long-course fractionated regimen^[14].

COMPARISON BETWEEN EPL AND CRT

There have been two important studies from Japan that investigated oncological and surgical outcomes of EPL and CRT for rectal cancer. Nagawa *et al.*^[19] conducted the first RCT that randomly assigned 45 patients who received neoadjuvant RT for rectal cancer to either TME alone or TME with autonomic nerve-preserving EPL. This trial

showed no difference in survival or local recurrence but more urinary and sexual dysfunction in those undergoing EPL (65% *vs* 27%, $P = 0.02$ and 92% *vs* 45%, $P = 0.02$, respectively). Although this trial included too small a number of cases, these results strongly suggest that EPL does not provide oncological benefit but rather increases autonomic-nerve dysfunctions on condition that patients have received preoperative RT for lower rectal cancer. Another study by Watanabe *et al.*^[20] retrospectively compared outcomes of preoperative RT without EPL and EPL without RT. This study showed no significant difference in survival or local recurrence between the two groups. The authors concluded that preoperative RT can be an alternative therapy in place of EPL for patients with lower rectal cancer. Although there are limitations including the small number of cases, these two studies are important in that they were conducted by the Japanese surgeons who are experienced with EPL for lower rectal cancer. Both studies suggested that EPL would be unnecessary with preoperative RT.

Recently, several studies have been published that compared oncological outcomes of EPL in Japan with that of CRT outside of Japan. Kim *et al.*^[17] compared the outcomes of 309 patients in Korea who received conventional TME plus postoperative CRT and 176 patients in Japan who underwent EPL without CRT for stage II/III lower rectal cancer. There were no significant differences in overall or disease-free survival. However, local recurrence in stage III lower rectal cancer occurred 2.2 times more frequently in the EPL group than the CRT group (16.7% *vs* 7.5%, $P = 0.044$). Accordingly, the authors concluded that adjuvant CRT is needed after EPL to reduce local recurrence. Although this study is important in shedding light on the international comparison between EPL and CRT, there are major issues to be discussed as pointed out by Watanabe *et al.*^[43], including different proportions of patients receiving adjuvant chemotherapy between the two groups and selection bias due to the different definition of lower rectal cancer between Korea and Japan.

Kusters *et al.*^[18] conducted a comparison between 324 patients undergoing EPL plus TME at National Cancer Center in Japan, 379 patients undergoing preoperative RT plus TME in the Dutch trial and 376 patients undergoing TME alone in the same trial. Rates of local recurrence were 6.9%, 5.8% and 12.1% for the Japanese, Dutch RT+TME and Dutch TME groups respectively. Notably, recurrence in the lateral pelvis was 2.2%, 0.8% and 2.7% in the Japanese, Dutch RT+TME and Dutch TME groups respectively, while presacral recurrence was 0.6%, 3.7% and 3.2% in each group. Based on these results, the authors concluded that both EPL and preoperative RT result in good local control as compared with TME alone. Furthermore, they speculated that preoperative RT can sterilize micrometastases in the lateral pelvis while extended surgery results in less presacral recurrence. In this study, tumor height from the anal verge was matched between the groups and the majority of the three groups did not receive adjuvant chemotherapy. However, it is still

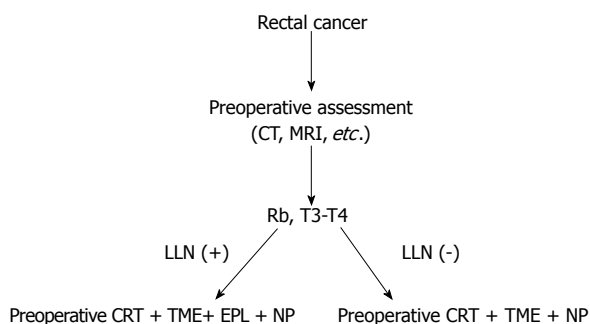


Figure 1 Proposal of rectal cancer management. Rb: Lower rectal cancer below peritoneal reflection; LLN: Lateral lymph node; CRT: Chemoradiation; TME: Total mesorectal excision; EPL: Extended pelvic lymphadenectomy; NP: Nerve preservation.

difficult to compare the Japanese patients with the Dutch patients and there could be potential bias including non-randomization and upstaging. Nevertheless, this study provides useful information on the therapeutic approaches to prevent local recurrence from the two representative referral centers in Japan and Europe.

Most recently, a meta-analysis of 20 studies was published that compared the perioperative outcomes, survival and recurrence between 2577 patients undergoing EPL and 2925 patients undergoing conventional surgery without EPL^[16]. The EPL group showed longer operating time and greater intra-operative blood loss than the non-EPL group. However, there was no difference in 5-year survival, 5-year disease-free survival and local or distant recurrence. Notably, in patients with Dukes C cancer, the EPL group had better survival as well as local recurrence than the non-EPL group, while there was no significant difference in patients with Dukes B. Regarding urinary function, data from three studies including 139 patients showed higher prevalence of urinary dysfunction in the EPL group. Individual studies showed higher frequency of male sexual dysfunction in the EPL group and therefore this outcome was not meta-analyzed. The authors concluded that EPL does not seem to provide oncological benefit but seems to be associated with increased urinary and sexual dysfunctions. This paper includes several issues to be discussed. First, most studies involved in this meta-analysis are retrospective, non-randomized trials. Second, seven out of the twenty studies included upper rectal cancer although LLN metastasis do not occur in the tumors at this level^[1] and furthermore, most studies did not include tumor height from the anal verge as matching criteria. Third, there was no information regarding the addition of adjuvant chemotherapy in each group. Fourth, there was only one study that all patients in each group underwent CRT and six studies had some patients who underwent CRT. Accordingly, there could be bias regarding the tumor height and proportion of those receiving adjuvant chemotherapy or CRT between the groups. Nevertheless, this study is the first meta-analysis that assessed the value of EPL. Although the authors' conclusion was unfavorable for EPL, an important implication of this study was that EPL provided better survival and local recurrence than non-EPL

in Dukes C cancers. Considering the incidence of metastatic LLNs in advanced lower rectal cancer is no more than 15%^[1,2,4,5,23-26], it is not surprising that statistical difference was not observed in this analysis as the majority of the patients undergoing EPL did not actually need EPL. Recently, Yano *et al*^[8] reported that LLNs metastasis can be diagnosed with high accuracy (sensitivity 95%, specificity 94%) in marked contrast to mesorectal node metastasis. It would be more practical to apply EPL to a narrower indication, i.e. patients with positive LLNs diagnosed by preoperative image or intraoperative findings and those carrying high risk for LLN metastasis such as Dukes C lower rectal cancer (Figure 1).

CONCLUSION

There still exists a great controversy regarding the oncological benefit of EPL. However, as suggested by Kusters *et al*^[18], EPL performed by experienced surgeons provides better local control than TME alone. Furthermore, almost 45% survival is achieved by EPL in the presence of metastatic LLNs even without RT or CRT^[1,2,4,5,23-26]. In the light of these findings, EPL definitely contributes to decrease local recurrence in lower rectal cancer. On the other hand, it is true that EPL is associated with high frequency of sexual and urinary dysfunction^[16,19]. On this point, preoperative CRT without EPL would be a better alternative to reduce local recurrence in patients without evident metastatic LLNs^[19,20]. For future treatment, it would be desirable to have a narrower indication for EPL using full advantage of recent improvement in image diagnosis. In patients with evident metastatic LLNs, preoperative CRT plus EPL plus perioperative chemotherapy would be the next promising challenge. Further objective comparison of the two principles between Japan and the West would lead to the next great step towards future improvement in treating lower rectal cancer.

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Is laparoscopic colorectal cancer surgery equal to open surgery? An evidence based perspective

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Abstract

Laparoscopic colorectal surgery (LCS) is an evolving subject. Recent studies show that LCS can not only offer safe surgery but evidence is growing that this new technique can be superior to classical open procedures. Fewer perioperative complications and faster postoperative recovery are regularly mentioned when studies of LCS are presented. Even though the learning curve of LCS is frequently debated when limitations of laparoscopic surgeries are reviewed, studies show that in experienced hands LCS can be a safe procedure for colorectal cancer treatment. The learning curve however, is associated with high conversion rates and economical aspects such as higher costs and prolonged hospital stay. Nevertheless, laparoscopic colorectal cancer surgery (LCCR) offers several advantages such as less co-morbidity and less postoperative pain in comparison with open procedures. Furthermore, the good exposure of the pelvic cavity by laparoscopy and the magnification of anatomical structures seem to facilitate pelvic dissection laparoscopically. Moreover, recent studies describe no difference in safety and oncological radicalness in LCCR compared to the open total mesorectal excision (TME).

The oncological adequacy of LCCR still remains unproven today, because long-term results do not yet exist. To date, only a few studies have described the results of laparoscopic TME combined with preoperative adjuvant treatment for colorectal cancer. The aim of this review is to examine the various areas of development and controversy of LCCR in comparison to the conventional open approach.

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Key words: Anterior resection; Total mesorectal excision; Rectal cancer; Laparoscopy; Colorectal cancer; Surgery
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INTRODUCTION

Throughout the past decade, evidence is growing that laparoscopic colorectal surgery (LCS) can be superior to classical open procedures^[1]. Fewer perioperative complications and a faster postoperative recovery resulting in shorter duration of hospital stay appear to be the main advantages^[1]. The wide implementation of LCS in clinical practice made the limitations of these technically demanding procedures more clear. The learning curve in LCS is frequently debated when limitations of

laparoscopy are reviewed^[2-4]. An estimated 50 segmental procedures are necessary to gain sufficient proficiency in LCS^[5]. Potential reasons for this prolonged learning curve in comparison to open surgery are exposure difficulties of the colonic anatomy and lack of tactile sense. The learning curve overall in laparoscopic techniques is associated with higher conversion rate, prolonged hospital stay, increased costs and higher morbidity^[6]. In the early 1990s, an attempt was started to facilitate the transition from open surgeries to minimally invasive/minimal access surgery by introducing the hand-assisted laparoscopic surgical technique (HALS)^[7]. The loss of pneumoperitoneum and impaired hand movements were the main obstacles encountered. For these specific reasons, hand-access ports were introduced^[8,9].

The laparoscopic approach for colon resection is widely accepted but its definitive role in rectal tumors is still controversially debated due to technical difficulties and missing long-term results. Tumor size and volume and pelvic dimensions may influence intraoperative and/or immediate outcome^[10,11]. Laparoscopic colorectal cancer surgery (LCCR) nevertheless offers several advantages in comparison to open procedures, including less postoperative pain, shorter duration of postoperative paralytic ileus, shorter hospital stay and less co-morbidity^[12,13]. Furthermore, the good exposure of the pelvic cavity by laparoscopy and the magnification of anatomical structures seem to facilitate pelvic dissection laparoscopically^[10]. Moreover, as advocated by Heald and Ryall, there is no compromise on the surgical radicality and safety while performing an adequate total mesorectal excision (TME)^[14,15]. The oncological adequacy of LCCR still remains unproven today because long-term results over a time span of at least 10 years of LCCR do not yet exist. Potential concerns have arisen including port site recurrence and abdominal wall metastases when the suitability of LCCR is considered for colorectal cancer^[16]. To date, only a few studies have described the results of laparoscopic TME (LTME) combined with preoperative adjuvant treatment for colorectal cancer^[17,18].

Cost benefits of LCS is another area that is difficult to assess simply because total costs of a surgical procedure can be relatively easy to assess but the total economic costs are very difficult to measure because the earlier reintegration in the patient's normal life cannot be "financially" measured by simple figures.

This review examines the various areas of development and controversy of LCCR in comparison to the conventional open approach.

ROLE OF LTME

Since the early 1970s, low anterior resection (LAR) has been the main surgical procedure to surgically treat rectal cancers^[19]. Even in experienced hands the local recurrence has averaged about 30% and 5-year survival rates ranged from 27% to 42%^[20,21]. Furthermore, the risk of damaging the autonomous pelvic nerve plexus resulting in a high incidence of sexual and bladder dysfunction was regularly

encountered in LAR^[22]. Local control and survival has been dramatically improved by the introduction of the TME first described by Heald *et al*^[14] in 1982. TME includes the routine excision of the intact mesorectum by precise dissection in the tissue plane between the visceral and parietal layers of the pelvic fascia. Importantly, pathological studies by Reynolds *et al*^[23] emphasized the widespread distribution of metastases within the boundaries of the mesorectal fascia. This was a strong argument for the complete resection of the mesorectum that includes uninvolved circumferential margins. Nevertheless, TME yields a considerably lower local recurrence rate^[24], better function of the sphincter^[25], longer survival^[26] and reduction in the need for abdominoperineal amputation^[27] (Miles procedure). A recent study of open TME has described local recurrence rates of 4% to 8% and cancer-specific survival rates of 70% to 80% at 5 years^[28]. A prospectively randomized study of 622 patients with rectal cancer by Law *et al*^[29] demonstrated the outcomes of the TME and of partial mesorectal excision (PME). The reported local recurrence rate in the study group undergoing anterior resection with mesorectal excision was reported as 9.7% and the cancer specific survival was 74.5%^[29]. They performed TME in mid and distal rectal cancer and PME for proximal rectal cancer when a 4 to 5 cm mesorectal margin could be achieved. They reported a comparable mortality and morbidity rate whereas a significantly longer median operating time with more blood loss and a prolonged hospital stay occurred in the TME group due to the higher complexity of the TME itself compared to PME. They concluded that local control and survival of patients requiring TME is comparable to those with proximal rectal cancers where adequate clearance can be achieved by PME^[29].

A major problem that limits the broad acceptance of laparoscopic cancer surgeries is the significant skepticism about LCS for cancer although laparoscopy is very popular in the treatment of many intra-abdominal disorders. The potential benefits of the laparoscopic technique must in fact be weighed against the potential for limited oncological outcomes due to inadequate resection, potential occurrence of port site metastases or metastatic spread^[30-32]. Moreover, surgeons are fearful that laparoscopic surgery could be more harmful to cancer patients than open procedures^[33]. To address certain important issues of laparoscopic surgeries in rectal cancer surgery, Leroy *et al*^[19] described the application of LTME following the principles of open TME in an unselected population of patients. This study demonstrated not only that LTME is feasible and safe, but also achieved a level of cancer control at least comparable to that reported in open TME. Interestingly, they did not report a single port site metastasis of the entire study population of 98 individuals^[19]. Several limitations nevertheless have been discussed by the authors. First, the study did not include a group of patients operated on by conventional surgical methods in the same period of time. Second, all surgeries were performed by only one surgeon which makes overall interpretation of data difficult because the results might not be reproducible in other hands.

Laparoscopy is relatively new and recent studies reporting randomized trials comparing open *vs* laparoscopic surgeries^[34] have been criticized because of the high risk of bias due to surgeons operating within the early phase of the learning curve^[35] and the associated effect on the treatment group.

Morbidity of the laparoscopic approach

The reported anastomotic leakage rate after LTME was 17% but only 65%^[19] of these patients required a reoperation for drainage or diversion. These numbers are according to leakage rates that are reported to be as high as 10%-20% in open TME^[36,37] although some series have reported rates as low as 5% after TME^[38]. To prevent the risk of anastomotic leakage, some authors suggested temporary protective colostomies or ileostomies in analogy to open surgery, side-to-end anastomoses or pouches to prevent clinically apparent leakage.

Modern concepts in pouch formation

In recent years improved functional results were achieved while introducing modern concepts for rectal replacements after LAR. The colon J-pouch-anal and -low rectal anastomosis was developed by Parc *et al*^[39] and Lazorthes *et al*^[40]. The superiority of J-pouches over straight coloanal anastomosis has been demonstrated in multiple randomized trials and is rarely contested^[41-43]. Complications of large colon J-pouches (8-10 cm) can occur by manifestations of defecatory dysfunctions with further medical necessities of suppositories, medication and enemas in about 25% to 37% of patients^[44,45]. Therefore surgeons tend to construct shorter pouches with a limb length of about 5 to 6 cm^[46]. Shorter J-pouch formations have improved functional results which have been confirmed in randomized controlled studies^[47,48]. A modern concept of a transverse coloplasty pouch was explored by Z'graggen *et al*^[49] where 37 patients underwent low anterior rectal resection with TME for rectal cancer and 4 for benign pathology. Total intraoperative complications occurred in 7% of patients and all were unrelated to the transverse coloplasty pouch. Furthermore, apart from nonexistent hospital mortality, the total complication rate was 27%. An anastomotic leakage rate was recorded as 7%. Furthermore, dysfunction such as stool urgency, fragmentation and incontinence grade 1 and 2 were regularly observed within the initial 6 mo; thereafter the incidence decreased significantly. None of the patients had difficulties in pouch evacuation. The authors concluded that the transverse coloplasty pouch can be safely used for reconstruction after sphincter-preserving rectal resection^[49]. The early function of this small-volume reservoir is favorable and can be compared to other colonic reservoirs. Furthermore, long-term problems of pouch evacuation can be avoided with this concept of a transverse coloplasty^[49]. Whether there is a clinical significant difference in pouch formation performed in open *vs* laparoscopic surgery, or long term function of these pouches is not compared today and potentially assumed to be equal.

Oncological outcomes and adequacy of lymph node dissection

One aspect of great concern is whether laparoscopy provides a radicality of resection equivalent to that of the open procedure in terms of oncological outcomes. For a successful cancer operation several objectives must be achieved: adequate tumor margin, adequate lymph node dissection and prevention of the spillage of cancer cells into the peritoneal cavity or the adjacent lumen of the bowel^[19]. Only two recent studies reported superior recovery of distal margins during open right colectomy^[50], whereas Lord *et al*^[51] similarly reported superior recovery of distal margins during laparoscopic-assisted anterior resection for colorectal cancer. Leroy *et al*^[19] demonstrated that all laparoscopically operated patients had negative margins although these results were not prospectively assessed. The mean tumor free margin was 3.46 cm^[19]. However, a limitation of this study was that the impact on local recurrence as well as on overall survival could not be determined. With regard to lymph node dissection, two randomized trials^[52,53] compared the outcomes of LCCR with the standard open procedure. In terms of recovered lymph nodes, none of the mentioned studies found a significant difference between the laparoscopic or the standard open procedure^[52,53]. Despite these results, Leroy *et al*^[19] debate whether the harvest of lymph nodes per se is an appropriate measure of the adequacy of a technique because the number of lymph nodes identified in a specimen is not only dependent on the surgeon but also on the diligence of the pathologist. The relevance of lymph node assessment as an outcome measure is probably not adequate because the pathologic result is often not included as a primary endpoint of the study.

Local recurrence and port side metastases

The local recurrence rates reported by Enker *et al*^[54] of 6% are comparable with a published series of open TME. In a long-term study by Heald *et al*^[55] an overall 6% rate of local recurrences at 5 years post surgery and 8% after 10 years was found. Another study by Hainsworth *et al*^[56] reported an overall recurrence rate of 11% that was stage dependent i.e. 0% for Duke's A stage, 8% for Dukes B and 30% for Dukes C. Advanced lymph node disease (N2) as well as perineural invasion and positive lateral margins were reported as risk factors for local recurrence^[56,57]. Because of the relatively low number of local recurrence after either open or LCS, future prospective randomized trials have to be adequately powered to gain further information about this crucial issue.

Even though port side metastases occur, they seem to be only a minor obstacle that occurs during laparoscopic colectomy. A recent review of 20 laparoscopic colectomy studies performed between 1994 and 1998 found 30 port site metastases of about 1% after a mean follow-up of 10-33 mo^[58].

Long-term survival in LTME

The overall 5-year survival rate published by Leroy *et al*^[19]

was 65% and the overall cancer specific 5-year survival rate was 75%. These numbers are potentially in favor with previously reported results of open surgery. A multicenter study by Havenga *et al.*^[59] found 5-year survival rates of overall survival and cancer-specific survival of 62%-75% and 75%-80% respectively^[59]. Variations in survival rates between studies can be related to differences in the makeup of the study population. In this regard, important factors such as the inclusion of patients undergoing palliative resection, acceptance of screening colonoscopies in the population, differing definitions of curative surgery and a mix of different stages makes it almost impossible to judge common outcomes objectively and this can impact on the study results. Multicentric studies with clearly defined inclusion and treatment criteria may contribute to a better comparison of study results and also potentially influence further study groups to maintain certain “gold” standards. Therefore, the comparability of studies might become more transparent and the interpretation of their results more obvious.

COST EFFECTIVENESS

In times of financial restrictions when health insurance rates are increasing every year, the cost effectiveness of a new medical procedure needs to be addressed carefully. Today there is no doubt that laparoscopic procedures are more costly compared to open surgeries if only direct medical costs such as materials, salaries and infrastructure are considered. What remains unclear is whether laparoscopy is as cost effective in terms of overall costs compared to open surgery. This assessment includes non-hospital related economic costs including cost reduction to the social health care system where patients are perhaps re-integrated earlier in their normal social and professional lives.

There are however, studies that compared the cost effectiveness of HALS and LCS. Targarona *et al.*^[60] described the total costs for HALS and laparoscopic-assisted colectomies (LAC) surgery including operating room costs, salaries of personnel and costs of disposable and non-disposable materials. They did not find a significant difference in total costs for surgery between LAC and HALS group.

Polle *et al.*^[61] on the other hand described costs for surgery and hospital admission. In their study, overall costs for surgery were significantly higher in the LAC group^[61] due to the higher costs of disposable materials such as trocars and the longer operating time required for LAC. However, the total costs for LAC were lower (by € 1864) compared to the HALS group. This reduction in total costs was not statistically significant and was explained by the earlier discharge of patients that underwent LAC.

POTENTIAL ADVANTAGES OF THE LTME

Every new surgical technique faces hurdles, initial weaknesses and limitations. The development of refined

instrumentation combined with a set of specific surgical skills has tremendously aided the implementation of advanced laparoscopy in colorectal surgery. Whereas laparoscopy is considered as the method of choice for cholecystectomies, laparoscopic approaches are still under debate for colorectal surgeries. Multiple studies and centers have proven that advanced surgical procedures such as laparoscopic pancreaticoduodenectomy^[62], laparoscopic-assisted esophageal cancer operations^[63], laparoscopic subtotal gastric cancer operations^[64] and others are technically feasible though not necessarily beneficial even when practiced in specialized centers.

While many considerations have been placed on the potential negative impact of LCS on patient outcomes, little attention has been paid to discovering the potential of laparoscopy in helping to improve those outcomes. Greater patient comfort and earlier hospital discharge while ensuring the oncological radicality as detailed in recent studies, display potential benefits of laparoscopic procedures in colorectal surgery.

A major advantage of laparoscopic surgery lies in the magnification that is offered by the endoscopic camera which enables greater surgical precision and better identification of tissue structures such as the presacral nerve plexus. Preservation of this plexus is an important quality measurement of every rectal cancer operation independent of the approach. The dissection of this plexus may be particularly demanding in a narrow deep pelvis. Furthermore, to perform deep pelvic dissection with full preservation of the presacral nerves in full view and magnification offered by the laparoscope will undoubtedly improve and accelerate the teaching of colorectal cancer surgery. This important step may potentially lead to greater standardization of the surgical approach and technique.

To address the importance of a standardized procedure, it is pertinent to note that a major problem of published studies on adjuvant therapy in the treatment of rectal carcinoma is that the surgical procedures have not been strictly standardized in these studies. Therefore, the unbiased effect of adjuvant therapies in rectal cancer is difficult to assess. The only way to study the effect of neoadjuvant treatment in colorectal surgery would be when strictly standardized and quality-controlled procedures are performed^[65]. In this type of approach lies another important advantage of LCS. Laparoscopy per se enables the operation to be recorded and differences in operative technique to be documented. Standardization processes become easier to manage and may improve the quality of studies significantly. Documented videos can be used to prove that adherence to the strict oncological criteria was maintained.

The possibility that laparoscopy will lead to an improved platform for expanded opportunities for instructions have a particular relevance in rectal surgery. Despite the improvements gained through the implementation of adjuvant and neoadjuvant treatments, the individual skills of the surgeon remains an important factor in tumor control and the reduction of disease and morbidity^[66,67].

Local recurrence rates after rectal surgeries can be decreased by over 50%; this impressive improvement was achieved by a surgical teaching initiative in the county of Stockholm^[68] and shows the effectiveness of adequate teaching and standardization in surgical techniques. Calculations have demonstrated that if optimal TME surgery could be widely implemented, the outcome improvement in terms of decreased local recurrence rates and better survival would be about four times greater than that achieved by adjuvant therapy - and at a fraction of the cost^[69]. More refined computer simulations of surgical procedures and virtual reality training systems may further improve the practice of laparoscopic surgery for various fields such as rectal cancer^[70-72].

Improved future technology will make laparoscopic instruments even more suitable for robotic control and video images are well suited for transmission. This will make it possible to perform laparoscopic surgeries even from remote distances^[73]. This enables an expert surgeon to teach or monitor the performance of an advanced or new technical approach by real-time intervention. Such long-distance communication and teaching has the potential to blunt the learning curve and improve teaching and training. Finally, this could lead to an improvement in greater (and perhaps global) standardization of surgical procedures.

In times of financial restrictions, the overall costs of surgical procedures are of great importance. Although the overall costs are considered to be generally higher for laparoscopic procedures than open surgeries, the benefits of an early return to work and a reduction in intra-abdominal adhesions could offset these higher costs in the long run. Certain studies, including randomized controlled trials^[13], have documented a number of advantages of laparoscopy in the short term including earlier hospital discharge, less pain and use of narcotics, improved and earlier bowel function and earlier resumption of a normal diet^[52,53]. In terms of quality of life (QoL) outcomes, a recent multicenter study showed a significant reduction in the postoperative requirement for analgesia and a shorter hospital stay was reported in laparoscopic surgery. But despite these facts, the short-term QoL benefits for laparoscopic procedures were only minimal compared to open surgery^[34].

Other studies have demonstrated that LCS is more expensive and time consuming than open procedures^[74]. The mean operative time reported by Leroy *et al.*^[19] for LTME was 202 min. This figure compared favorably with other data presented by Heald *et al.*^[55] who described a mean operative time of about 4 h for open TME. Traditionally the laparoscopic approach has been associated with longer operating times than open surgeries. It can be assumed that the improved technology over the past decade (i.e. enhanced magnification and improved visualization of the narrow pelvis) coupled with the broad implementation of new laparoscopic techniques and improved technical expertise may explain the strides made in LTME as described by Leroy *et al.*^[19].

The laparoscopic rectal resection with anal sphincter preservation for rectal cancer is laparoscopically feasible and safe and offers short- and long-term outcomes comparable to conventional surgery^[75,76]. Dulucq *et al.*^[75] suggested that elective LTME with anal sphincter preservation for rectal cancer is safely performed in expert hands and gives excellent short-term as well as long-term results. Jayne *et al.*^[76] reported that laparoscopic-assisted surgery for colon cancer is as effective as open surgery in terms of oncological outcomes and preservation of the QoL. Furthermore, they supported the continued use of LCS because also the long-term outcomes of patients undergoing LCCR were comparable to those with open surgery^[76]. Another randomized study by Basse *et al.*^[77] demonstrated in 60 patients that the functional recovery after colonic resection is rapid with a multimodal rehabilitation regimen. There were no differences reported in the open *vs* the laparoscopic operation technique^[77].

The presented studies show that the standards of correct rectal cancer resection including high ligation of the inferior mesenteric artery, a complete lymph node dissection and a complete resection of the mesorectum with an intact visceral pelvic fascia can be met laparoscopically. To further clarify whether the laparoscopic approach is potentially advantageous in certain aspects such as cost effectiveness and potentially in the QoL in comparison to the open surgical procedure, a controlled randomized study is needed. In such a trial, a large number of patients from the same collective should randomly be evaluated for either the LTME or the open TME.

CONCLUSION

The Basingstoke experience of TME has clearly demonstrated that open TME can cure rectal cancer by surgical therapy alone in 2 of 3 patients in all stages and in 4 of 5 patients having curative resections. Within this progress in treating this life threatening disease, a new concept of laparoscopic cancer surgery has evolved and is measured by the impressive achievements and criteria of open TME. LTME is technically feasible and has evolved into a trusted concept in experienced hands. Although certain limitations and shortcomings including insufficient long-term results remain, the technical progress has dramatically improved over the last decade and is no longer considered a major obstacle to safely perform LTME. Surgical and oncological limitations such as port site metastasis and oncological incomplete resections are no longer considered to affect the LTME in terms of oncological correctness and potential harm to patients. Although many studies have shown the benefits of laparoscopy for colorectal cancer including reduced postoperative complications, decreased surgical trauma, faster postoperative recovery, survival rates and long-term survival similar to those of open surgery^[76-80], only a few studies have reported advantages of laparoscopy for rectal cancer^[19,81]. A primary reason for this could be the lack of consensus regarding laparoscopy in the treatment of rectal cancer as well as the high levels of technical skills that are necessary. Future controlled ran-

domized studies, comparing LTME *vs* TME are necessary to answer not only questions such as long-term outcomes, cost effectiveness, oncological correctness and radicality but also patient safety in terms of morbidity, mortality and QoL.

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Clinicopathologic and immunohistochemical profile of ovarian metastases from colorectal carcinoma

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Abstract

Metastasis of colorectal adenocarcinoma of the ovary is not an uncommon occurrence and ovarian metastases from colorectal carcinoma frequently mimic endometrioid and mucinous primary ovarian carcinoma. The clinical and pathologic features of metastatic colorectal adenocarcinoma involving the ovary is reviewed with particular focus on the diagnostic challenge of distinguishing these secondary ovarian tumors from primary ovarian neoplasms. Immunohistochemical stains that may be useful in the differential diagnosis of metastatic colorectal tumors to the ovary and primary ovarian tumors are detailed.

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Key words: Ovary; Colon; Metastatic carcinoma; Mucinous carcinoma; Colorectal carcinoma; Immunohistochemistry; Endometrioid adenocarcinoma

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INTRODUCTION

The ovary is a common site of metastases^[1]. Secondary tumors account for 17.4%-30% of all ovarian malignancies^[2-4] of which nongenital cancer metastases to the ovaries constitute 9%-14.6%^[3-6]. Primary colon cancer has been identified in 10%-33% of metastatic ovarian tumors in various series^[2-10]. In the literature, patients with metastatic colon cancer to the ovary (MCCO) range between 19 and 87 years (median 51 years) with 24%, younger than 40 years^[11,12]. 1.2%-14% of women with intestinal cancer have ovarian metastases at sometime during the course of their disease^[13-16]. Estimates of true incidence of ovarian metastases from a colorectal primary varies depending on whether autopsy data or clinical series are examined. At autopsy of women dying of colorectal cancer, 6%-14 % are found to have ovarian metastases^[17,18]. Up to 45 % of MCCO are thought to be clinically primary ovarian tumors, even though most of the colonic tumors are of Dukes stage B or C^[11,19-21]. These tumors may spread to the ovary *via* blood-borne or lymphatic routes, transperitoneal or by direct extension^[13,22,23].

In this review, clinical and pathological status of MCCO are discussed with special focus on the diagnostic challenge of distinguishing these secondary ovarian tumors from primary ovarian neoplasms. Studies on useful immunohistochemical stains for the differential diagnosis are also discussed in detail.

CLINICAL FEATURES

Common presenting symptoms are usually related to ovarian involvement. Pelvic mass, abdominal and pelvic pain are the most common presenting symptoms^[11,12,24].



Figure 1 Gross appearance of bilateral ovarian metastasis from a colonic adenocarcinoma. The tumor has a nodular growth pattern.

Most patients have changes in bowel habits, rectal bleeding, feeling of abdominal fullness or bloating. Less frequently, patients present with abnormal vaginal bleeding, nausea, vomiting and constitutional symptoms such as fatigue or weight loss. Stromal luteinization is most frequently found in MCCO and increased steroid hormone production in these patients often results in endocrine manifestations^[25]. However significantly younger age of the women, uniform presentation as pelvic masses with few bowel symptoms, elevated CA-125 levels, and occasional presentation as large clinically unilateral tumor can all contribute to misclassification of these metastases as primary ovarian neoplasms^[26,27]. The frequency of metastatic colorectal carcinoma in the ovary relative to primary ovarian neoplasms is sufficient to justify colonoscopy as a preoperative test in women younger than 50 years, even in pregnant women with adnexal masses lacking clinical symptoms referable to the lower intestinal tract^[26,28].

PRIMARY COLORECTAL TUMORS

Colorectal tumors with ovarian metastases are predominantly distal lesions and most of them originate from the rectosigmoid colon^[11,13,29]. Transvers colon, ascending colon, cecum and descending colon are affected with decreasing frequency^[11,13]. Mean size of the primary tumor is less than that of the ovarian metastatic lesion^[16,30]. MCCO are usually associated with advanced metastatic disease^[11,12,15,20]. In a study, out of 19 colorectal tumors with ovarian metastases the stage of the primary tumors was as follows : Dukes stage : B1: 2 ; B2: 7 (Stage B: 47%); C2: 8 (Stage C: 42%); D: 2 (Stage D: 11%)^[13]. In a report by Lash *et al*^[20], none of the intestinal primary tumors were Dukes stage A, 32% were B and 68% were C. In a study by Lewis *et al*^[11], 86 cases of MCCO were reviewed. Primary tumor invaded the full thickness of the bowel wall in 58 cases (pT3), while in 17 cases, perforation of visceral peritoneum or direct invasion of other structures was noted (pT4). Nodal status was reported in 62 cases, of which 87% nodal involvement was documented at the time of resection; 29 (47%) had involvement of four or more nodes (pN2). Eighty one percent of patients had metastatic involvement of nonovarian sites either at or after the time of colectomy, with omental and/or other peritoneal

involvement being the most common. Twenty five patients (40%) had liver metastases at some point during the course of their disease^[11].

GROSS FEATURES OF INVOLVED OVARIES

MCCO may form solid or, more commonly, partially or predominantly cystic masses^[11,15,22,29,31,32]. They are often friable due to extensive necrosis^[15,32] and tend to be associated with surface implants. Careful gross and microscopic inspection of the external ovarian surface for fibrous plaques containing infiltrating carcinoma is helpful in recognition of metastatic colorectal neoplasms^[33]. In the study by Lewis *et al*^[11], among 46 cases for which data were available, 21 featured an ovary with evidence of surface involvement by tumor and 7 showed evidence of surface rupture. Nodular growth pattern (Figure 1) and hilar involvement^[33] are less frequently seen but also highly correlated with metastatic carcinoma. In different series, the size of tumors ranges from 1 to 27 cm with a median of 10-11 cm^[11,15,25,31,33-36]. MCCO are bilateral in more than 80% of the reported cases^[11,12,15,29,31,33-36]. Unilateral metastasis is more frequent in the right ovary^[11,29]. Most commonly, MCCO mimic primary ovarian mucinous or endometrioid adenocarcinoma^[10-12,15,22,29,32-36]. Mucinous carcinomas are reported to comprise 6%-25% of ovarian carcinomas (mean 12%), although recent regimens in the interpretation of histologic features of noninvasive and metastatic mucinous carcinomas suggest that this may be an overestimate. Mucinous carcinomas in the ovaries are commonly metastatic, but the proportion of primary versus metastatic mucinous carcinoma in unselected patients is unknown^[35]. In Seidman's^[35] report, among 52 cases of mucinous carcinoma in the ovaries, 40 (77%) were metastatic and 12 (23%) were primary.

In another report on 74 cases of mucinous carcinomas, 16 were primary ovarian; 52 metastatic, and 6 of indeterminate origin^[34]. An algorithm has been proposed to assist diagnosis in which all bilateral mucinous and those unilateral tumors < 10 cm are classified as metastatic carcinomas whereas unilateral tumors ≥ 10 cm are classified as primary ovarian mucinous carcinomas^[35]. In Khuramornpong's^[34] series, when 6 tumors of indeterminate primary site were excluded, the proposed algorithm correctly classified primary and metastatic tumors in 84% of 68 cases. Of 21 unilateral mucinous adenocarcinomas ≥ 10 cm, 62% were primary ovarian. Of 5 unilateral tumors < 10 cm, 80 % were metastatic. Of 42 bilateral mucinous carcinomas, 95% were metastatic. By adjusting the size criteria to 12 cm, performance of the algorithm is both maintained for primary ovarian tumors and improved for metastases, giving correct classification of 86% of tumors overall including 100% primary tumors and 80% of metastases^[37].

HISTOLOGIC FEATURES

In general, features which assist in distinguishing metastatic

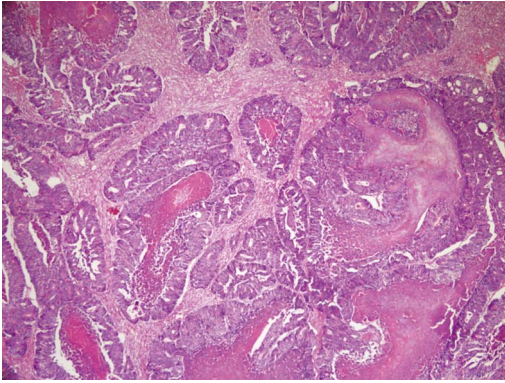


Figure 2 Garland histologic growth pattern with abundant intraluminal “dirty” necrosis and segmental destruction of glands (HE stain, $\times 100$).

colorectal adenocarcinoma from primary ovarian adenocarcinoma are similar to those which apply to other metastatic adenocarcinomas (e.g. bilaterality, nodular pattern of ovarian involvement, surface tumour deposits and extensive lymphovascular permeation especially in hilar and paraovarian vessels, single cell invasion, signet-ring cells) all favour metastatic rather than primary neoplasm. However none of these features is specific^[22,33].

Metastatic colorectal carcinoma involving the ovary may closely mimic primary ovarian endometrioid or mucinous neoplasm^[7,11,12,15,20,22,29,31,32,36,38]. Young *et al.*^[1] introduced a classification of histological aspects of metastatic ovarian carcinomas. They observed the prevalence of glandular endometrioid-like pattern and mucinous-like pattern^[11,15,22,31,32,36].

The following histological features are classic and characteristic of pseudoendometrioid metastases from large intestine; garland and cribriform histologic growth patterns, abundant intraluminal “dirty” necrosis, segmental destruction of glands and absence of mullerian features (squamous differentiation, adenofibromatous components or association with endometriosis)^[11,15,22,30,32,36]. The garland pattern is typified by multiple large cystic glandular structures containing necrotic debris encircled by an array of rounded glands, often with segmental necrosis of their walls (Figure 2). Typically, dirty necrosis consists of densely eosinophilic, coarsely granular necrotic debris containing abundant karyorrhectic material of sloughed carcinoma cells^[20]. Necrosis and intraluminal cellular debris also may occur in primary ovarian carcinoma^[32,33] but often the intraluminal debris consists of thin secretions and degenerating neutrophils^[39]. Thus although dirty necrosis is characteristic of but not specific for colorectal adenocarcinoma, additional histologic features may be helpful in arriving at correct diagnosis. Classic cytological criteria such as marked cytologic atypia (2+ or 3+) and high mitotic index may be considered helpful in the diagnosis of colorectal ovarian metastases^[15,22,29,36].

Other metastatic colorectal adenocarcinomas involving the ovary may mimic ovarian mucinous neoplasm. Some may be cystic, closely mimicking the gross appearance of a primary ovarian neoplasm^[7,11,15,22,29,31]. Histologically there may also be a close resemblance to primary ovarian mucinous cystadenoma as well as obviously malignant

areas with destructive stromal invasion. Analogous to the situation with other metastatic mucinous carcinomas, those morphologically bland foci (maturation phenomenon) have been erroneously interpreted as evidence of primary ovarian neoplasm^[11,15,22]. In a recent study, frequent findings strongly favoring metastatic mucinous adenocarcinoma were; bilaterality, surface implants and an infiltrative pattern of stromal invasion^[33]. Findings that strongly favor primary ovarian mucinous carcinoma were; an “expansile” pattern of invasion and complex papillary pattern^[33]. Stromal luteinization that may occur with any mass lesion in the ovary appears to be more common in metastatic colorectal adenocarcinoma than other metastatic neoplasms^[22]. Rare adenocarcinomas metastatic from the intestine may contain cells with abundant clear cytoplasm, simulating either clear cell carcinoma or the secretory variant of endometrioid carcinoma^[39]. In a recent study the clinical and pathological features of 86 cases of metastatic colorectal adenocarcinoma involving the ovary were reviewed^[11]. Glandular and papillary architecture, “dirty necrosis”, desmoplasia, garland pattern, surface involvement, single infiltrative cells, extracellular mucin, “incomplete glands”, infiltrative nests of cells, cystic glandular dilatation, small glands, low malign potential-like areas, multimodularity and goblet cells were observed in decreasing frequency^[11]. In 19% of cases, foci with benign or low malignant potential appearance were seen. One point worthy of emphasis is the anecdotal experience of Hart^[31] who observed “microscopic nests of carcinoma within corpora lutea or corpora albicantia also points the metastasis”.

IMMUNOHISTOCHEMICAL FEATURES

When the characteristic gross and microscopic distinguishing features are lacking between primary ovarian adenocarcinoma and metastatic colorectal adenocarcinoma, immunohistochemistry may be very useful^[15,40-46]. Tumors with pseudoendometrioid histological pattern are most readily identified by immunophenotyping. However when the tumor is of mucinous type immunostains are less useful. This is due to the high frequency of intestinal differentiation in most primary ovarian mucinous neoplasms which results in considerable overlap in immunophenotype with metastatic mucinous neoplasms^[47]. Use of a panel of antibodies provides the most accurate immunophenotype and can usually assist in correct identification of the site of origin (Table 1). Based on the immunohistochemistry results obtained from recent studies a decision flow chart has been constructed (Figure 3).

Cytokeratin 7 and 20

Use of coordinate expression of cytokeratins 7 and 20 (CK 7/20) for distinguishing primary ovarian tumors from colorectal metastases has been evaluated in large number of studies^[39,42,45,46,48-51]. Combined use of CK 7 and 20 allows discrimination of most metastatic colorectal carcinoma from nonmucinous adenocarcinoma of the ovary^[40].

Nonmucinous ovarian adenocarcinomas are almost always diffusely CK 7 positive and CK 20 negative whereas

Table 1 Primary vs metastatic colorectal carcinoma to the ovary: immunohistochemical profiles

	Primary ovarian carcinoma mucinous type	Primary ovarian carcinoma nonmucinous type	Metastatic colorectal carcinoma
CK 7	+/-	+	-/+
CK 20	-/+	-	+
CEA	-/+	-	+
CA 125	+/-	+	-/+
MUC 2	+/-	? ¹	+
MUC5AC	+	?	-/+
CDX2	+	-/+	+
P504S	?	?	+/-
β-Catenin	-/+	-/+	+
Vimentin	?	-/+	-
ER/PR	-/+	?	-

¹Not known. CK 7, CK 20: Cytokeratin 7 and 20; CEA: Carcinoembryonic antigen; CA 125 : Cancer antigen 125; MUC 2, MUC5AC : Mucin gene products.

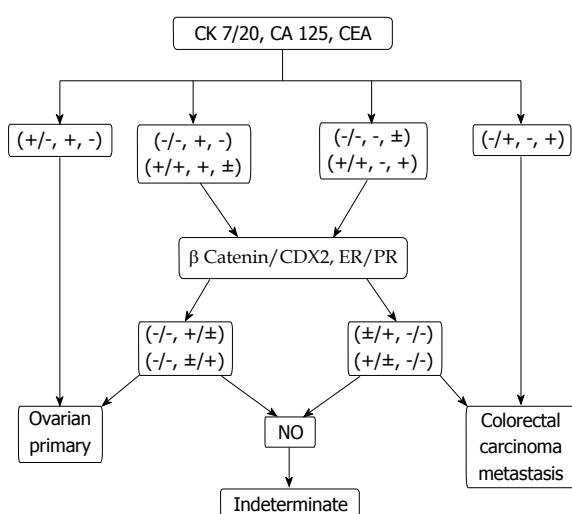


Figure 3 Flow chart showing the decision tree that was constructed based on the immunohistochemistry results. CK 7/CK 20: Cytokeratin 7 and 20; CEA: Carcinoembryonic antigen; CA 125: Cancer antigen 125; ER/PR: Estrogen and progesterone receptors.

the majority of colorectal carcinomas are usually negative for CK 7 and uniformly positive for CK 20^[42,45,46,48-50,52]. A caveat is that a small percentage of colorectal carcinomas, particularly those that are right-sided and high grade, have CK 7 positive and CK 20 negative immunophenotype^[48,53]. Ovarian mucinous tumors are almost always positive for CK 7 but show variable positivity for CK 20 which is often patchy in distribution^[42,45,46,48,49,54]. However, mucinous tumors arising in ovarian mature cystic teratomas which were morphologically and immunohistochemically familiar with gastrointestinal tract-type mucinous tumors were negative for CK 7 and positive for CK 20^[51,52,55]. Intestinal-type mucinous epithelial neoplasm of low malignant potential, intraepithelial carcinomas and invasive adenocarcinomas more frequently had a CK 7-/CK 20+ phenotype (56%, 50% and 100%) respectively. A CK 7+/CK 20- phenotype was rare in these later 3 morphologic groups (6%)^[56].

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA) is a highly glycosylated cell surface protein overexpressed in a variety of tumors

such as colorectal, ovarian, pancreatic, breast and nonsmall cell carcinomas^[57]. When evaluating ovarian tumors its greatest utility is in distinguishing metastatic colorectal carcinoma with pseudoendometrioid pattern from primary endometrioid carcinoma. These pseudoendometrioid metastatic tumors typically demonstrate strong and diffuse staining for CEA especially along the glycocalyceal border, apical cytoplasm or throughout the cytoplasm^[20,58]. However several studies have demonstrated that CEA immunostaining is of no value in the differentiation between secondary ovarian tumors showing a mucinous pattern and primary ovarian mucinous adenocarcinomas because both show equally strong staining^[20,54]. In recent studies 67%-85% of primary ovarian mucinous carcinomas were CEA positive compared to 95%-100% of metastatic colorectal carcinomas^[44,50,54]. It is, however, possible to use CEA in combination with other tumor markers.

Cancer antigen 125

Cancer antigen (CA) 125 shows strong and diffuse staining of serous and endometrioid ovarian carcinomas with positivity ranging from 0-50% in mucinous tumors^[40,50,54,59]. 4%-15 % of colorectal carcinomas are immunoreactive for CA 125 although staining may be weak and focal and the pattern may be cytoplasmic rather than membranous^[15,50,54]. CA 125 may be helpful as a part of a diagnostic panel but its' use as a single test in identifying ovarian adenocarcinoma is not reliable.

Mucin gene products: MUC 2, MUC5AC

In recent studies, 100% of primary mucinous adenocarcinomas were shown to express MUC5AC whereas 0-33% of metastatic colorectal carcinomas expressed the same marker^[45,60]. MUC2 reactivity was found in 90% of metastatic colorectal adenocarcinomas, in 70% of primary mucinous cyadenocarcinomas and all borderline tumors of intestinal type but in none of the cystadenomas or endocervical-like borderline tumors^[58].

CDX2

The CDX2 gene encodes an intestine-specific transcription factor belonging to the homeobox family that plays an important role in the regulation of proliferation and

differentiation of intestinal epithelial cells^[61]. Diffuse and strong CDX2 protein expression is reported in almost all MCO^[41,43,54,59,62-64]. CDX2 expression is observed in up to 70% of primary ovarian tumors^[41,54,62,64,65]. Gaggero *et al*^[66] reported that all 47 endocervical-type mucinous cystadenomas stained negative for CDX2 and two of three intestinal-type cystadenomas stained positive. They concluded that the expression of CDX2 in mucinous tumors is likely to be dependent on the cell type (endocervical or intestinal). In view of the findings of these recent studies, positive CDX2 expression in a tumor involving the ovary should be interpreted with caution as although it may be a primary ovarian adenocarcinoma the possibility of metastatic tumor needs to be carefully excluded. Conversely, none-expression of CDX2 in a tumor would strongly support an ovarian primary.

β-Catenin

A frequently observed genetic change in colorectal carcinoma is an inactivating mutation of the adenomatosis coli gene^[67]. This leads to the accumulation of the protein β-Catenin in the nucleus. In several recent studies, 59%-83% of MCO showed nuclear expression of β-Catenin^[41,44]. In one study, nuclear expression of β-Catenin was noted in only 9% of primary ovarian mucinous carcinomas^[44]. In Logani *et al*^[41] nuclear expression was found in 19% of 23 primary ovarian adenocarcinomas with only one tumor (5%), an endometrioid carcinoma, having a diffuse pattern of expression. Two endometrioid adenocarcinomas had strong nuclear immunoreactivity in foci of squamous metaplasia.

α-methyl-coenzyme a racemase

α-methyl-coenzyme a racemase, also known as P504S, is a mitochondrial and proximal enzyme involved in the metabolism of fatty acids^[68]. Overexpression of P504S has been observed in several tumors, most notably prostate and colorectal carcinoma^[69,70]. Some authors have found that the frequency of P504S expression is decreased in poorly differentiated colonic adenocarcinomas^[60,71]. In Logani's^[41] study, 32% of MCO showed diffuse expression of P504S as versus none in primary ovarian tumors. Although there seems to be value of using P504S in the differential diagnosis of primary ovarian and MCO, its' expression in primary ovarian tumors requires further evaluation.

Vimentin and estrogen/Progesterone receptors

In the current literature some controversy exist about Vimentin expression in mucinous carcinomas. Van Niekerk *et al*^[72] described rather high expression. Viale *et al*^[73] could only show it at a low level in some samples while Moll *et al*^[74] did not find it at all. In a recent publication, Vimentin was found to be substantially present (except for one sample) in colonic carcinomas but was present in only 18% of mucinous ovarian carcinomas^[50]. Therefore it combines a low sensitivity with high specificity.

Estrogen receptor (ER) and progesterone receptor (PR) expression in primary ovarian mucinous tumors and the utility of these markers for distinguishing MCO from primary ovarian mucinous tumors have not been extensively investigated. In one study, all atypical proliferative

mucinous tumors of gastrointestinal type, primary ovarian mucinous carcinomas and metastatic mucinous carcinomas (including 24 metastasis from colorectal primary) were negative for ER and PR with the exception of three metastatic endocervical adenocarcinomas^[8]. The authors concluded that immunohistochemical assesment of hormone receptor expression is of no value in distinguishing the common types of primary ovarian mucinous tumors from the vast majority of mucinous tumors metastatic to the ovary.

FOLLOW-UP

In premenopausal women ovaries have rich blood supply owing to both direct origin of ovarian arteries from the aorta and anastomosis through ovarian branches of the uterine arteries. Approximately ten arterial branches from this arcade penetrate the ovarian hilus, becoming markedly coiled and branched as they course through the medulla^[75]. It is also reported that ovarian metastases from primary colorectal cancer may involve haematogenous spread as the main pathway^[16]. This vascular-rich histology of the ovaries may be the main reason why colorectal tumor metastasis to the ovaries often expand rapidly, resulting in significant size increase compared to the mean size of the primary tumour^[16]. In Judson's study^[26], mean size of the colorectal tumor and ovarian metastasis were 5.1/5.0 cm and 12.8/14.1 cm in undiagnosed and known colorectal adenocarcinoma groups respectively. The large metastatic size is the main reason why patients need resection for this disease in spite of poor prognosis^[24,76,77].

Ovarian metastasis are associated with advanced metastatic disease. In a report of 624 patients with colorectal adenocarcinoma, 19 (7.7%) had ovarian metastasis. They were divided into two groups according to the diagnostic time; Group A: synchronous (9 patients), Group B: metachronous (10 patients)^[13]. 5 year survival in group A was 16% while it was 0 in group B. The authors concluded that resection of primary tumor plus bilateral oophorectomy is suitable for synchronous ovarian metastasis and as palliative treatment for metachronous disease. Miller *et al*^[24] reported on 23 patients with MCO at the time of initial diagnosis. Surgical treatment consisted of colon resection in all but one patients, bilateral or unilateral salpingo-oophorectomy in 22 patients and hysterectomy in nine patients. Only one patient survived 5 years. Sixteen patients died of colon cancer. The median survival time was 17.8 mo, with a range from 1 to 86 mo. Tumor size was of no prognostic importance. Median survival time of patients with peritoneal disease (10.8 mo) was significantly shorter than for patients without peritoneal disease (25.2 mo). In the presence of liver metastasis, the median survival time was, likewise, significantly reduced from 20.1 to 8.1 mo. Some recent reports show that bilateral oophorectomy for MCO has a good impact on disease-free and overall survival (OS) for patients with isolated ovarian metastasis^[78]. McCormick *et al*^[79] observed that patients with metastatic disease confined to the ovaries had a median OS of 61 mo (range 15-120 mo) compared to 17 mo (range 0.5-73 mo) for those with more extensive metastases ($P = 0.0428$).

The observation that optimal cytoreduction was associated with prolonged progression-free survival and OS in both patients with localized ovarian and widespread metastases of colon cancer suggests a role for the management of metastatic colon cancer in women. Chung *et al.*^[80] analysed the clinicopathological and follow-up data on 34 patients who underwent surgical resection of metastatic tumors originating from colorectal cancer. They concluded that surgical resection may be beneficial in selected patients with ovarian metastasis limited to the pelvis. Another report suggested that ovarian metastases are less responsive to chemotherapy compared to other sites and that surgical resection should always be considered for ovarian metastases even in the case of associated extraovarian metastases^[81]. In conclusion, macroscopic metastatic disease to the ovary is a poor prognostic factor in colon cancer. In selected patients who can be rendered disease-free by surgery, prolonged survival is possible and an aggressive approach is recommended.

Controversies exist regarding the role of prophylactic oophorectomy for improving outcome following colorectal cancer surgery. While clinical series report rates of 1.2% to 14% of patients with colorectal carcinoma having ovarian metastasis^[13-16] it is impossible to speculate how many, if any, could have been cured by oophorectomy on the premise that ovarian metastases were initially isolated and therefore treatable. These figures would suggest that a proportion of women with colorectal cancer would benefit from prophylactic oophorectomy. However recent studies have been unable to confirm this hypothesis^[82-84]. Tentes *et al.*^[83] divided the patients into two groups; in 70 of 124 (56.6 %) patients, the ovaries were preserved during surgery and in 54 (43.4%), synchronous prophylactic oophorectomy during primary tumor resection was performed. Seilezneff *et al.*^[84] offered bilateral oophorectomy to all postmenopausal women in a consecutive series of 92 patients. Forty-one agreed to undergo oophorectomy. In both studies comparison of both groups revealed no difference in overall survival.

CONCLUSION

From 1.2% to 14% of women afflicted by colorectal adenocarcinoma are found to have ovarian involvement at some point in the course of their disease^[13-16]. In many of these cases diagnosis of colorectal carcinoma has been established prior to the recognition of the ovarian lesion although in a minority of cases, ovarian mass is the initial manifestation of the disease^[19,24]. In such cases preoperative differential diagnosis centers on the primary ovarian neoplasm. If the possibility of metastatic carcinoma is not raised either at the time of intraoperative consultation or in the final pathology report, clinical management may be adversely affected. Correct classification is important from both therapeutic and prognostic point of view. Unfortunately there is significant overlap between metastatic colorectal adenocarcinoma and those of primary epithelial ovarian neoplasms especially endometrioid and mucinous adenocarcinomas regarding the gross and histologic features^[11,12,15,22,30,32,34-38]. Bilaterality, high-stage disease, multimodularity, surface implants, infil-

trative pattern of invasion, invasion of hilar structures and vascular invasion are strong markers for metastatic ovarian tumors^[11,33,35]. Prominent intraluminal dirty necrosis with a garland and cribriform pattern is characteristic of metastatic colorectal carcinomas^[19]. Features favoring primary ovarian endometrioid or mucinous neoplasm include; unilateral involvement, large size, an expansile pattern of invasion, complex papillary pattern and presence of Mullerian features^[11,22,33]. A recently reported adjusted algorithm for mucinous carcinomas in which bilateral tumors and those unilateral tumors smaller than 12 cm are classified as metastatic has proved to be correct in 86% of cases^[35,37].

Selected immunostains may be helpful in identifying MCCO. Tumors with a pseudoendometrioid histologic pattern are most readily identified by immunophenotyping. However when the tumor is of mucinous type, immunostains are less useful. A panel comprising of CDX2, β -Catenin and P504S is helpful in distinguishing primary mucinous or endometrioid adenocarcinoma from colorectal metastasis to the ovary in the majority of cases and is a useful adjunct to the already established role of differential staining with CK 7/CK 20, CA 125, CEA in this differential diagnosis^[15,41].

Ovarian metastases are associated with advanced stage disease^[13]. Median survival time is 17.8 mo (1-86 mo)^[25] and 5 years survival rates are 16% and 0% in groups with oophorectomy and without oophorectomy respectively^[13].

It is important to reemphasize that both gynecologist and pathologist should have a high level of suspicion of metastasis from another organ when they encounter a mucinous tumor in the ovary in order to prevent misdiagnosing a metastatic neoplasm as primary tumor.

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Molecular regulation of vasculogenic mimicry in tumors and potential tumor-target therapy

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Abstract

"Vasculogenic mimicry (VM)", is a term that describes the unique ability of highly aggressive tumor cells to express a multipotent, stem cell-like phenotype, and form a pattern of vasculogenic-like networks in three-dimensional culture. As an angiogenesis-independent pathway, VM and/or periodic acid-schiff-positive patterns are associated with poor prognosis in tumor patients. Moreover, VM is resistant to angiogenesis inhibitors. Here, we will review the advances in research on biochemical and molecular signaling pathways of VM in tumors and on potential anti-VM therapy strategy.

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Key words: Tumor-target therapy; Signaling pathways; High aggressive tumor; Molecular regulation; Prognosis; Vasculogenic mimicry

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INTRODUCTION

Tumors require a blood supply for growth and hematogenous metastasis. Most attention has focused on the role of angiogenesis^[1]. However, Maniotis *et al*^[2] have described an angiogenesis-independent pathway called "vasculogenic mimicry (VM)", a novel phenomenon in which highly aggressive human melanoma cells mimic endothelial cells and form vascular channel-like structures to convey blood plasma and red blood cells without the participation of endothelial cells. Currently, two distinctive types of VM have been described; tube and patterned matrix types^[3]. VM channels are revealed as periodic acid-schiff (PAS)-positive patterns. VM consists of three elements: the plasticity of malignant tumor cells, remodeling of the extracellular matrix (ECM), and the connection of the VM channels to the host microcirculation system^[4,5]. Different approaches have suggested that these channels provide a mechanism of perfusion and a dissemination route within the tumor that functions either independently of or simultaneously with angiogenesis. Several papers have evidenced the VM channel functional role in tumor circulation by using microinjection method, Doppler ultrasonography, MRI technique and laser scanning confocal angiography^[6-11]. VM and/or PAS-positive patterns are also associated with a poor prognosis, worse survival and the highest risk of cancer recurrence for patients with melanoma^[2,12], cell renal cell carcinoma^[13], breast cancer^[14], ovarian carcinoma^[15], primary gallbladder carcinoma^[16], malignant esophageal stromal carcinoma^[17], mesothelial sarcomas and alveolar rhabdomyosarcomas^[18], hepatocellular carcinoma^[19-22]. In addition, tumor cell plasticity has been demonstrated in prostatic carcinoma^[23], bladder carcinoma^[24], osteosarcoma^[25], astrocytoma^[26] and pheochromocytoma^[27].

The detailed mechanism of tumor VM remains to be further elucidated. At present, novel signaling pathways are discussed, involving factors which promote cell migration, invasion and matrix remodeling. These include vascular endothelial-cadherin (VE-cad)^[28,29], epithelial cell kinase (EphA2)^[30-32], focal adhesion kinase (FAK)^[33,34], phosphoinositide 3-kinase (PI3-K), matrix metalloproteinase (MMPs), laminin 5 (Ln-5) γ^2 chain^[35-38], tissue factor (TF), TF pathway inhibitor (TFPI)^[11], Vascular endothelial growth factor-a (VEGF-a)^[39]. Therefore, understanding the key molecular mechanisms that regulate VM would serve as an important target for new cancer therapies.

MOLECULE MECHANISMS OF TOMOR VM

VM describes the unique ability of highly aggressive tumor cells to express endothelial cell-associated genes (such as EphA2 and VE-cad) and form ECM-rich, patterned tubular networks when cultured on a three-dimensional matrix. However, the exact mechanism underlying VM still needs to be unraveled. Up to now, several molecules have been identified which have a functional role (Figure 1).

PI3-K, MMPs and Ln-5 γ^2 chain

PI3-K is a lipid kinase that phosphorylates phosphatidylinositol or its derivatives on the 3-hydroxyl of the inositol head group. PI3-Ks are made up of four different 110-kDa catalytic subunits (p110a, p110b, p110g, and p110d) and a smaller regulatory subunit. The main product of PI3-K activity, PI(3,4,5)-P3 acts as a binding site for many intracellular proteins that include pleckstrin homology (PH) domains with selectivity for this lipid. The PI3-K signaling pathway plays an integral role in many normal cellular processes, including survival, proliferation, differentiation, metabolism and motility, in a variety of cell types^[40].

In highly aggressive melanoma tumor cells, a recently published paper has indicated that PI3-K is an important adjustor of VM directly affecting the cooperative interactions of membrane type 1 (MT1)-MMP and matrix metalloproteinase-2 (MMP-2) activity. PI3-K regulates MT1-MMP activity, which promotes the conversion of pro-MMP into its active conformation through an interaction with TIMP-2. Both enzymatically active MT1-MMP and MMP-2 may then promote the cleavage of the Ln-5 γ^2 chain into pro-migratory γ^2 and γ^{2x} fragments. The deposition of these fragments into the tumor extracellular milieu may result in increased migration, invasion and VM formation. Poorly aggressive melanoma cells seeded on collagen matrices, preconditioned by aggressive tumor cells, formed tubular networks along the Ln-5 γ^2 chain-enriched tracks deposited by the aggressive cells. These observations indicate that the Ln-5 γ^2 chain in the ECM is able to promote VM formation^[35,36]. Another observation showed that highly aggressive melanoma tumor cells can secrete the Ln-5 γ^2 chain and that the γ^2 and γ^{2x} chains, antisense oligonucleotides to the Ln-5 γ^2 chain and antibodies to

MMP-2 or MT1-MMP may inhibit VM formation. Special inhibitors of PI3-K may impair VM formation and decrease MT1-MMP and MMP-2 activity. Furthermore, inhibition of PI3-K blocked the cleavage of Ln-5 γ^2 chain, resulting in decreased levels of the γ^2 and γ^{2x} pro-migratory fragments^[37]. So, PI3-K may represent a predominant target for cancer therapy.

Similarly, in aggressive ovarian tumor cells, MMP-2 or MT1-MMP seems to play an important role in the VM channel. Human ovarian cancers with MMP over-expression are more likely to have tumor cell-lined vasculature^[38].

Protein tyrosine kinases, EphA2, FAK and VE-cad

Protein tyrosine kinases (PTKs) have been shown to play important and diverse roles in regulating cell adhesion, migration and invasion^[30]. Highly invasive malignant melanomas appear to express higher levels of PTKs with their phosphorylation centered specifically in the area where VM channels formed^[30,41]. Thus, it could be concluded PTKs were pivotal factors of VM. Additionally, one of the receptor PTKs that was up-regulated in the aggressive melanoma cells was EphA2^[30]. EphA2, a receptor tyrosine kinase and a member of the Eph (ephrin-receptor) family of PTKs, has been found to play an important role in angiogenesis^[42,43]. Eph is a large family containing 14 members. The binding of EphA2 to its ligand ephrin-A1 results in the phosphorylation of EphA2. Other potential binding partners of EphA2 may be PI3-K and FAK^[44]. FAK, a non-receptor protein tyrosine kinase, is a 125-kDa cytoplasmic tyrosine kinase associated with focal adhesions and is the major protein to become tyrosine phosphorylated after integrin activation. It localizes to regions of the cell that attach to the ECM, the focal adhesions. FAK localization is predominantly cytoplasmic in proliferating cells with punctate areas located at the periphery, presumably at the cell membrane, indicating integration in focal contacts. VE-cad is an adhesive protein, known to be expressed exclusively by endothelial cells, which belongs to the cadherin family of transmembrane proteins which promote homotypic cell-to cell interaction.

Microarray analyses revealed that EphA2 and VE-cad were dramatically over-expressed in aggressive human cutaneous and uveal melanoma cells, although not in poorly aggressive melanoma cells. Transient knockout of EphA2 and VE-cad *in vitro* abrogated the ability of highly aggressive melanoma cells to form the vasculogenic-like networks^[28,30]. VE-cad and EphA2 are co-localized at sites of cell-cell adhesion. Additionally, knockdown of EphA2 expression does not affect the localization of VE-cad at sites of cell-cell adhesion, but does result in a redistribution of EphA2 on the cell-membrane, and an inability of cells to form vasculogenic structures. Collectively, association between VE-cad molecules on adjacent cells facilitates the organization of EphA2, either by interacting directly or indirectly with EphA2 on the cell membrane. When organized on the cell membrane, EphA2 is capable of binding to its ligand EphA1, resulting in the phosphorylation of the receptor, i.e. phosphorylated

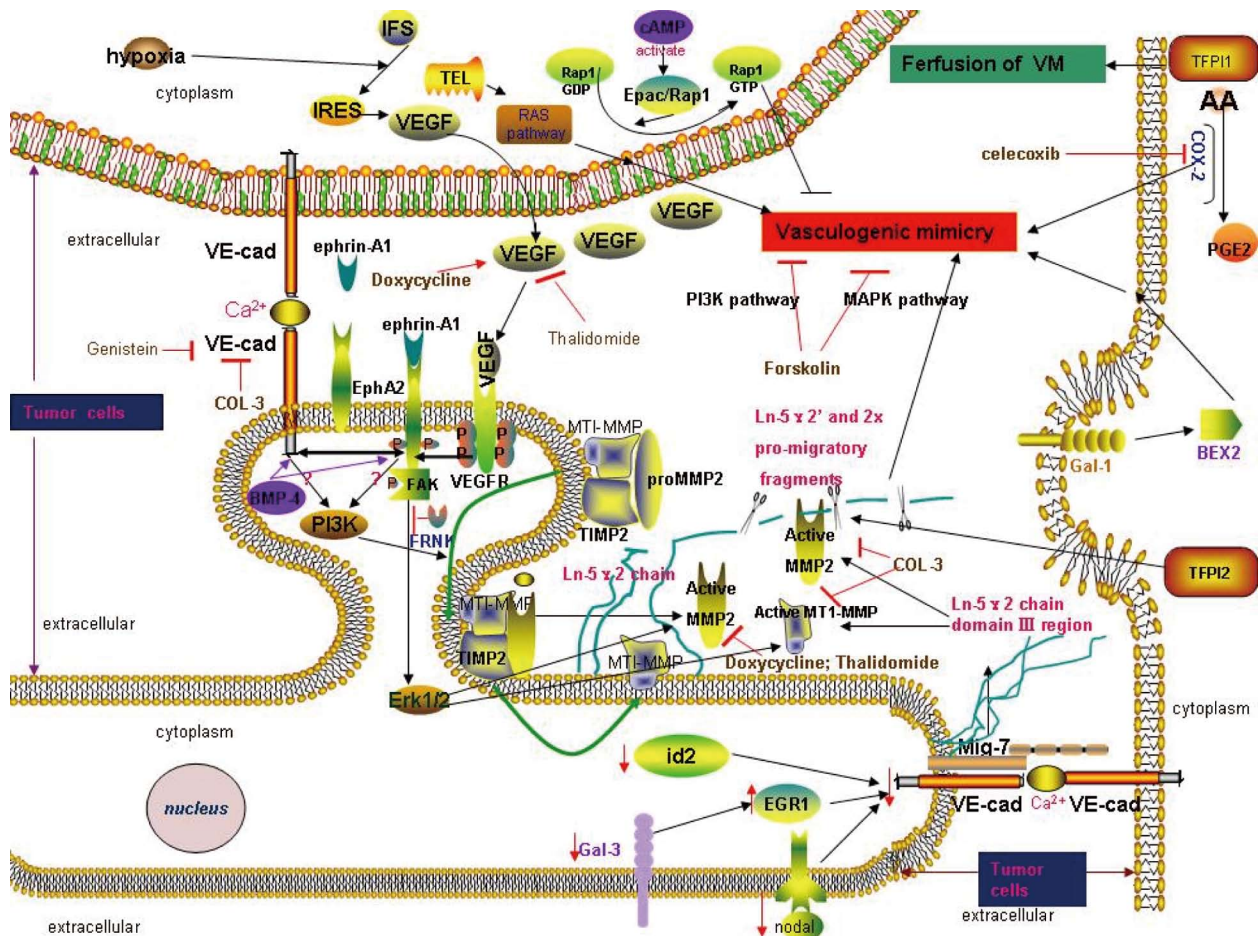


Figure 1 Hypothetical model for the molecular signaling pathways of vasculogenic mimicry in tumors and anti-vasculogenic mimicry (VM) therapy strategies. (1) The down-regulation of BMP-4 activity can lead to reduce expression of EphA2 and VE-cad; (2) TEL regulate VM by synergizing with signaling pathways downstream of RAS; (3) Celecoxib, COX-2 inhibition, may inhibit vascular channel formation, which is abrogated by addition of PGE2; (4) cAMP inhibits VM by activating Epac/Rap1 which produces Rap1-GTP; (5) Activation of Nodal signaling supports VM and expression of the VE-cad. Inhibition of the Nodal signaling pathway results in a reduction in keratin and VE-cad; (6) Knockdown of Id2 expression can inhibit VE-cad expression and abrogate the formation of tubular networks; (7) Gal-3 silencing can result decrease of VE-cadherin activities due to enhanced recruitment of EGR-1; (8) The decreasing in Gal-1 expression can provoke a marked decrease in BEX2, which impairs vasculogenic mimicry channel formation; (9) Over-expression of Mig-7 increased $\gamma 2$ chain domain III fragments. Laminin 5 is the only laminin that contains the $\gamma 2$ chain, which following cleavage into promigratory fragments, the domain III region, causes increased levels of MMP-2, and MT1-MMP cooperate to cleave $\gamma 2$ chain into fragments that promote tumor cell VM; (10) Hypoxia→VEGF→EphA2→MMPs→VM; (11) VE-cadherin can promote the interaction between FAK and EphA2, phosphorylated EphA2 can form an interaction with FAK, which would lead to phosphorylation and activation of FAK. The signal transduction pathways activated through VE-cad and EphA2 can converge, resulting in activation of PI3K; (12) PI3K regulates MT1-MMP activity, which promotes the conversion of pro-MMP into its active conformation through an interaction with TIMP-2. Both enzymatically active MT1-MMP and MMP-2 may then promote the cleavage of the laminin 5(Ln-5) $\gamma 2$ chain in pro-migratory $\gamma 2$ and $\gamma 2^*$ fragments, the deposition of these fragments into tumor extracellular milieu may result in VM formation; (13) Blockade of TFPI-2 is able to suppress MMP-2 activation and prevent VM formation. Moreover, TFPI-1 has anticoagulant function of relevance for perfusion of VM; (14) Several drugs express specific anti-VM effects. Genistein inhibits VE-cad expression; COL-3 inhibits VE-cad and MT1-MMP expression respectively. Doxycycline inhibits MMP-2 expression. Thalidomide inhibits MMP-2 and VEGF expression. In addition, forskolin inhibits VM formation through MAPK and PI3K pathway. VM: Vasculogenic mimicry; COX: Cyclooxygenase; VE-cad: Vascular endothelial-cadherin; MMPs: Matrix metalloproteinase; EphA2: Epithelial cell kinase; FAK: Focal adhesion kinase; VEGF: Endothelial growth factor.

EphA2. VE-cad and EphA2 may converge to activate the PI3-K pathway leading to the activation MMP-2, and consequent cleavage of Ln-5 $\gamma 2$ ^[228-32]. Also, similar to VE-cad localization, the localization of EphA2 in aggressive human melanoma tissues is associated with areas containing and patterned, vasculogenic-like networks.

Recently, researches have demonstrated FAK to be an important key mediator of the aggressive melanoma phenotype, including VM^[33,34]. FAK is phosphorylated on Tyr³⁹⁷ and Tyr⁵⁷⁶ in aggressive human cutaneous and uveal melanoma cells cultured on a three-dimensional type 1 collagen matrix *in vitro*, as well as in radial and vertical

growth phase melanomas *in situ*. Furthermore, expression FAK-related non-kinase in melanoma cells, which acts to disrupt FAK signaling, directly results in the inhibition of the aggressive phenotype, as demonstrated by decreased invasion, migration and VM potential. FAK signaling regulates invasion, migration and VM through two different signaling pathways. Firstly, FAK signals through Erk1/2 to increase the levels of urokinase activity, thus regulating invasion of the aggressive melanoma cells. Additionally, FAK seems to signal through unknown downstream effectors to promote migration in aggressive melanoma cells that may contribute to an increase of VM

potential. Secondly Erk1/2 regulates MMP-2 and MT1-MMP activity, thus promoting melanoma invasion and VM^[33,34]. Collectively, these observations implicate FAK as a promoter of the aggressive melanoma phenotype, thereby identifying it as a rational target for therapeutic intervention of malignant melanoma.

In conclusion, VE-cad appears to promote the interaction between FAK and EphA2 through regulation of EphA2's ability to translocate to the membrane. Interaction between EphA2 and its membrane-bound ligand results in phosphorylation of EphA2. Phosphorylated EphA2 then forms an interaction with FAK, which leads to phosphorylation and activation of FAK. The signal transduction pathways activated through VE-cad and EphA2 converge, resulting in activation of PI3-K which then leads to VM *via* activation of MMP-2, finally resulting in cleavage of the Ln-5 γ 2 chain^[30,32]. These results suggest that VE-cad, EphA2 and FAK act in a coordinated manner as a key regulatory element in the process of melanoma VM and illustrate a novel signaling pathway that could be potentially exploited for therapeutic intervention.

TF and TFPI-1, TFPI-2

TF, which is expressed in endothelial cells, macrophages, smooth muscle cells, and a variety of solid tumors and tumor cell lines^[45-47], is a 47-kDa transmembrane protein that binds plasma factor VII/VIIa^[48]. This bimolecular complex initiates blood coagulation by activating both factor X and factor IX, which leads to the generation of thrombin, fibrin deposition and platelet activation. In addition, TF is also involved in vascular development and is induced in angiogenic endothelial cells^[49,50]. The TF/factor VIIa (TF-VIIa) complex is inhibited by a Kunitz-type protease inhibitor called TFPI, which is typically associated with glycosyl-phosphatidyl inositol-anchored receptors on the cell surface. TFPI type 1 (TFPI-1) consists of three TFPI Kunitz-type inhibitory domains and a proteoglycan-binding COOH terminus. TFPI-1 locks TF into an inactive TF-VII-X a-TFPI-1 complex by binding simultaneously to factors VII a and X a. TFPI type 2 (TFPI-2) is a 32-kDa member of the Kunitz-type family of serine protease inhibitors with strong homology to TFPI type 1 (TFPI-1). As an important factor associated with coagulation, TFPI-2 exhibits inhibitory activity toward a broad spectrum of proteases including the TF/factor VIIa catalytic complex, plasmin and plasma kallikrein^[51,52]. TFPI-2 also participates in the regulation of ECM remodeling and pericellular proteolysis through plasmin-dependent manner and the action of MMPs^[53,54]. However, TFPI-2 expression has also been shown to enhance the migration of certain tumor cells^[55]. In addition, TFPI-2 is synthesized by endothelial cells and supports their firm adhesion by mechanisms that are independent of inhibition of plasmin. Recent data from several sources suggest that matrix-associated TFPI-2 can regulate adhesion and migration of endothelial cells and tumor cells in a context-dependent manner^[55].

A recent study reported that aggressive melanoma cells *in vivo* over-expressed TF, TFPI-1 and TFPI-2. TFPI-1

has an anticoagulant function which is of relevance for perfusion of VM. In conclusion, the over-expression of TFPI-1 by aggressive melanoma cells might help to explain the possible dynamic conduction of blood through a VM tumor cell-lined meshwork. TFPI-2 associated with a three-dimensional collagen matrix can induce the VM phenotype in poorly aggressive melanoma cells. Blockage of TFPI-2 is able to suppress MMP-2 activation and prevent VM formation. Therefore, TFPI-2 appears to regulate an essential pathway of VM^[11].

Vascular endothelial growth factor, hypoxia and hypoxia-inducible factor-1 α

Vascular endothelial growth factor (VEGF-a/VEGF) secreted by tumor cells and fibroblasts plays a crucial role in tumor angiogenesis, lymphangiogenesis and VM formation^[56-60]. Moreover, VEGF is the most potent endothelial-specific mitogen; it directly participates in angiogenesis by recruiting endothelial cells into hypoxic and avascular areas and stimulating their proliferation^[61,62]. Recently, it has been reported that the expression of VEGF in bi-phase differential malignant tumor with VM is less than that in those without VM proving that VM can sustain tumor blood supply^[58]. Inhibition of VEGF expression by sequence-specific siRNA can suppress VM formation in osteosarcoma cells and hence, VEGF appears to be crucial for formation of VM.

It is believed that hypoxia is able to induce VM channel formation directly to enhance the ability of tumor to metastasize^[63]. VEGF has been shown to increase with hypoxia challenge, a response which seems to depend on hypoxia regulated in the 5 and 3 regions of the VEGF gene. The hypoxia-inducible protein complex hypoxia-inducible factor1- α (HIF-1 α) binds to the enhancer sequences of the VEGF gene, and both transcription and RNA stability are enhanced^[64,65]. Su *et al.*^[65] have shown that the HIF-1 α inhibitor, rapamycin, could prevent VM and phenotype transformation of human ovarian cancer cells, HIF-1 α protein expression correlated with CD31 and Factor VIII protein expression. These findings indicate that VM might be associated with HIF-1 α . EphA2 or/and VE-cad regulate the activity of MMPs, which promote the cleavage of Ln-5 γ 2 chain into promigratory γ 2, and γ 2^x fragments. The release of these fragments into the tumor microenvironment can increase the VM formation of aggressive melanoma^[35]. It has been indicated that VEGF may significantly stimulate EphA2 and VE-cad expression at the protein and mRNA levels in ovarian tumor cells, MMP-2 and MMP-9 which act as effector molecules, induced by EphA2, are controlled by VEGF. Through this process, aggressive human ovarian tumor cells enhance their capacity for migration, invasion and VM formation. Moreover, the down-regulation of EphA2 following VEGF stimulation can also decrease VM formation in human ovarian tumor cell 3D cultures after EphA2 knockdown, whereas there is no significant change in VE-cad^[39]. Additionally, hypoxic activation of HIF-1 α might be involved in driving VM in Ewing sarcoma

tumors. However, the relationship between tube formation by Ewing sarcoma tumor cells and VEGF regulated by hypoxia could not be identified^[66].

The amount of VM channels and gene expression of HIF-1 α , MMP-2, MMP-9, and VEGF was increased significantly in the ischemic group than that in non-ischemic group of melanoma tumors^[67]. It has been proposed that thalidomide inhibits VM channel and mosaic vessel formation in melanoma through inhibiting VEGF, MMP-2 and MMP-9 expression^[68]. The VEGF expression and reactive oxygen species (ROS) level are key requirements for formation of capillary-like structures (CLS) formation. Antioxidants (AOs) may induce a significant decrease of VEGF expression in melanoma cells. The reduction of ROS generation in melanoma cells by AOs may completely abolish CLS^[69]. Recent studies have reported that CLS formation requires apoptotic cell death through activation of caspase-dependent mechanisms. Apoptosis occurs before CLS but not after CLS assembly and the formation of CLS is related to the ROS levels^[70,71].

Migration-inducing protein 7

Migration-inducing protein 7 (Mig-7) is the cysteine-rich protein found in cell membranes and the cytoplasm of carcinoma cells. Mig-7 is also an early marker of migration and circulation in carcinoma cells. Several tumor cells that form vessel-like structures and embryonic cytotrophoblast cells can masquerade as endothelial cells by expressing VE-cadherin and Factor VIII-associated antigen^[4,30,34,66]. RTK c-Met activation of the hepatocyte growth factor/scatter factor (HGF/SF) receptor can induce Mig-7 expression^[72,73]. Integrin $\alpha\text{v}\beta^5$ ligation is required in cross-talk signaling with RTK c-Met to initiate Mig-7 expression^[72]. Furthermore, receptor tyrosine kinase ligands, such as HGF or epidermal growth factor (EGF) and $\alpha\text{v}\beta^5$ Integrin have been reported to induce expression of Mig-7 in carcinoma cells. Petty *et al.*^[74] observed that Mig-7 protein over-expression was found in aggressive invasive melanoma cells capable of VM but not in poorly invasive cells that do not form the tumor-lined structure. Mig-7 protein was primarily co-localized with VM markers VE-cad, Factor VIII-associated antigen and Ln-5 γ^2 chain domain III fragment in lymphnode metastases. Over-expression of Mig-7 increased γ^2 chain domain III fragments that are known to contain EGF-like repeats that can activate EGF receptor. EGF can also induce Mig-7 expression. Ln-5 is the only laminin that contains the γ^2 chain the domain III region of which following cleavage into promigratory fragments, causes increased levels of MMP-2. MMP-2 and MT1-MMP cooperate to cleave γ^2 chain into fragments that promote melanoma cell invasion and VM.

Galectin-3, galectin-1 and brain-expressed X-linked gene 2

Galectin-3 (Gal-3) is a 31 kDa member of the galectin family which consists of three distinct structural domains: (1) a short NH₂-terminal domain that controls its cellular targeting; (2) a repetitive collagen-like sequence rich in glycine and proline, which serves as a substrate for MMPs; and

(3) a COOH-terminal domain which a globular structure that encompasses the carbohydrate-binding site^[75-77]. Gal-3 has pleiotropic biological functions which depending on its subcellular location. Extracellular Gal-3 mediates cell migration, cell adhesion and cell-to-cell interaction^[78]. Intracellular Gal-3 inhibits Fas-induced T-cell apoptosis^[79]. Mourad-Zeidan AA and colleagues^[80] proposed that Gal-3 is a important upstream regulator of interleukin-8 (IL-8) and MMP-2 expression in melanoma and a key gene in VM formation. Gal-3 silencing could result in a decrease of VE-cad and IL-8 promoter activities due to enhanced recruitment of early growth response-1 (EGR-1). Gal-3 silencing could also inhibit melanoma cell invasion capability through Matrigel-coated filters and VM formation. EGR-1, described as a tumor suppressor, acts as a negative regulator of the VE-cad and IL-8 promoters. Thus the over-expression of EGR-1 results in the inhibition of VE-cad and IL-8 expression and of their promoter activities, and Gal-3 acts upstream to prevent EGR-1 binding. In addition, Gal-3 causes tumor angiogenesis and melanoma VM by inducing the expression of fibronectin-1 and endothelial differentiation sphingolipid G-1 (EDG-1) genes.

Gal-1 is a 14 kDa β -galactoside binding protein, capable of forming lattice-like structures with glycans of cellular glycoconjugates and inducing intracellular signaling. Gal-1 is present both inside and outside cells. As an extracellular effector, it can bind to cell-surface glycoconjugates that contain suitable galactose-containing oligosaccharides, acting as a homobifunctional cross-linker. It also binds to some of the glycoproteins in the ECM, such as laminin, fibronectin and elastin. As an intracellular effector, Gal-1 shuttles between the nucleus and the cytoplasm. It is active in processes that are essential for basic cellular functions, like pre-mRNA splicing, cell growth, apoptosis and cell cycle regulation^[81].

Recent observations have indicated that the decrease in Gal-1 expression in Hs683 cells through targeted small interfering RNA could provoke a marked decrease in brain-expressed X-linked gene 2 (BEX2) expression. BEX2, described as a tumor suppressor gene in astro gliomas, has been implicated in apoptotic features of breast cancer. Decreasing BEX2 expression impairs VM channel formation *in vitro* and angiogenesis *in vivo* by inducing the up or down-regulation of a number of genes involved in migration including MMP-2, plexin C1, integrin $\beta 6$ and SWAP70^[82].

Inhibitor of DNA binding 2

The inhibitors of DNA binding (Ids) proteins are a family of helix-loop-helix (HLH) proteins that lack the basic domain necessary for DNA binding. Id proteins, including Id1-Id4, are inhibitors of basic helix-loop-helix (bHLH) transcription factors. Id2 is involved in the regulation of cell differentiation, proliferation, development, cell cycle regulation, myogenesis, tumorigenesis and neurogenesis^[83-85]. Recently, it has been believed that knockdown of Id2 expression can significantly inhibit VE-cad expres-

sion and abrogate the formation of tubular networks in highly aggressive uveal melanoma cells in 3D culture. VE-cad may be the target molecule of Id2 during VM formation^[86].

Cyclic AMP and nodal

Cyclic AMP, a second messenger controlling many cellular processes with idiosyncratic responses depending on cell type, is produced by adenylyl cyclase after binding of physiologic ligands (α MSH, VIP and ADR) to G protein-coupled receptor (GPCR). Cyclic AMP phosphorylates several substrates involved in signal transduction pathways after binding to PI3K-dependent protein kinase Akt (PKA). In particular, the mitogen-activated protein kinase (MAPK) cascade consists of small GTP-binding protein Ras/B- and/or C-Raf kinase 1/2 (MEK1/2) and ERK1/2^[87]. Recent observation indicates that cyclic AMP (Epac) Epac1 and Epac2 can mediate PKA-independent cell responses. Epac1 and Epac2 are unique exchange factors of small the GTPases, Ras-associated proteins (Rap) 1 and 2, which become activated upon releasing GDP and binding GTP^[88,89]. However, Epac responses can cooperate with PKA responses^[88,90]. Numerous studies have suggested the link between PKA activation and Epac. Akt is a major effector of the PI3K signal and the PI3K/Akt pathway is frequently altered in cancers^[91]. It has been reported that cyclic AMP could mediate a physical association between Epac, Rap1 and phosphorylated Akt^[92,93].

Cyclic AMP can inhibit VM formation through multiple signaling pathways in aggressive melanoma cells *in vitro*. Firstly, cyclic AMP results in the inhibition of VM mediated by activation of Epac/Rap1 producing Rap1-GTP; PKA is not mediator of VM. Secondly, forskolin inhibits VM formation through inhibiting PI3K/Akt signals (dephosphorylation of Akt-activating kinase domain, pAkt) but not through GPCR ligands α MSH or VIP; whereas, GPCR ligands only act as stimulators. Finally, forskolin also inhibits ERK1/2 activity-related phosphorylation (pERK1/2) independently of Epac and PKA, consequently inhibiting VM formation through the MAPK pathway^[94].

The human Nodal gene, containing three exons, is located on Chromosome 10q22.1. Nodal is a member of the transformation growth factor β (TGF- β) superfamily and is pivotal in inhibition of human embryonic stem cells (hESCs) differentiation. Indeed, Nodal has been shown to maintain the pluripotency of ESCs and is one of the first genes to be down-regulated as totipotent hESCs differentiate during embryoid body formation. Moreover, as a melanoma plasticity biomarker, Nodal plays an instrumental role in the maintenance of melanoma cell plasticity and tumorigenicity. Nodal expression is positively associated with melanoma tumor progression; tumorigenic melanoma cells lines express high levels of Nodal. There are four known mammalian Notch receptors (Notch1-4) and five ligands. Recent studies have proven that Nodal is up-regulated by Notch-4 in aggressive melanoma cells^[95]. Activation of Nodal signaling supports

VM and expression of the VM plasticity marker VE-cad in aggressive melanoma cells. Inhibition of the Nodal signaling pathway results in a reduction in keratin and VE-cad. Inhibition of the Nodal signaling pathway can also decrease melanoma cell invasiveness and impair the ability of aggressive melanoma cells to form vascular networks on a three-dimensional collagen matrix by down-regulation the expression of keratin and VE-cad^[96]. Furthermore, through an Epac/Rap1 signaling, the cyclic AMP can reinforce endothelial barrier properties *via* the redistribution of VE-cad and strengthened cell adhesion. The cyclic AMP-mediated activation of Nodal signal may result in the inhibition of VM formation^[94].

Cyclo-oxygenase-2

Cyclooxygenase (COX) is the enzyme catalyzing the rate-limiting step in prostaglandin synthesis. It has two isoforms, COX-1 and COX-2. COX-1 is constitutively expressed in normal cells and is involved in homeostasis. However, COX-2 is not found in normal conditions but is induced by a variety of pathophysiological factors, such as growth factors, inflammatory stimuli, oncogenes and tumor promoters. COX-2 has been shown to promote cell survival, proliferation, and angiogenesis and prohibit apoptosis, all process influencing cancer development^[97].

Recent reports have revealed that highly invasive human breast cancer cells that exhibit higher COX-2 expression can develop vascular channels when cultured on three-dimensional Matrigel, whereas non-invasive cell lines that express low levels of COX-2 cannot develop such channels. Moreover, human high-grade invasive tumor specimens that expressed high levels of COX-2 proteins had detectable vascular channels. Low-grade tumors with no or low COX-2 expression showed little evidence of VM^[98]. COX-2 inhibition by celecoxib or specific siRNA may inhibit vascular channel formation in human breast cancer cells. Vascular channel formation was abrogated by addition of exogenous prostaglandin E₂ (PGE₂). Therefore, the effect of celecoxib in inhibiting vascular channels is probably related to the dependence on PGE₂^[99].

Translocation-Ets-Leukemia/ETV6

Translocation-Ets-Leukemia (TEL) or ETV6 is a member of the ETS family of transcription factors, and is frequently a target of chromosomal translocations in several forms of acute leukemia. A translocation between region 12p13, which contains the *ETV6* gene, and 21q22, which contains the *RUNX1* gene, creates an *ETV6/RUNX1* chimeric gene. The fusion protein, ETV6/*RUNX1*, contains amino acids 1-336 of ETV6 linked to residues 21-480 of *RUNX1*^[100]. *ETV6* functions as a transcriptional repressor by recruiting the co-repressors mSin3A (N-CoR) and HDAC3 to the promoters of target genes. Several studies have suggested that cytogenetic abnormalities of chromosome 12p13 involving the *TEL/ETV6* gene exist in a variety of hematopoietic neoplasms including acute leukemias, myelodysplastic syndromes, and myeloproliferative disorders^[101]. Furthermore, TEL is also

expressed in endothelial cells in large mature blood vessels during normal and tumor angiogenesis.

A study demonstrated that TEL-transduced NIH3T3-UCLA cells exhibit hollow cellular cords with a diameter of several cell bodies (15-25 μm), which would be wide enough to allow the transport of fluids and red blood cells. In addition, TEL can act in synergy with RAS expression to induce aggregation in MS1 (endothelial cell line) and NIH3T3 cells. Dominant-negative (DN)-RAS expression can also induce slower growth in parallel with effects of TEL in these cell lines. Thus TEL might play a key role in aggregation and VM by synergizing with signaling pathways downstream of RAS^[102].

Bone morphogenetic protein-4

Bone morphogenetic proteins (BMPs) are members of the TGF- β superfamily. The more than 30 members in the BMP family are described either as BMPs, osteogenic proteins, growth/differentiation factors, or cartilage-derived morphogenetic proteins^[103]. They exert their biological activities by binding to a complex of serine/threonine kinase receptors type I (i.e. BMPR-IA, BMPR-IB, or ALK2) and type II (i.e. BMPR-II)^[104]. BMP-4, a representative member of the BMP family, is required for several different processes in early development beginning with gastrulation and mesoderm formation.

In a study by Rothhammer *et al.*^[105], BMP-4 was identified as an important molecule in melanoma migration and invasion. Further study revealed that melanoma cells with reduced BMP-4 activity were not able to form tube-like structures at all. In addition, melanoma and endothelial cells were able to form chord-like networks in a cooperative manner on Matrigel. Co-cultures of endothelial cells and different melanoma cell clones revealed the formation of tubular structures only in those cell clones with unchanged BMP levels. The antisense BMP-4 and chordin-overexpressing cell clones were not able to form networks and even prevented tube formation by endothelial cells. Furthermore, the down-regulation of BMP-4 activity could lead to reduced expression of genes involved in VM, including EphA2 and VE-cad. On the basis of these studies, it is considered that BMP-4 is a pivotal factor of VM^[106].

VM AND CANCER THERAPEUTICS

Tumor growth and metastasis require a blood supply for survival and aggressive cancers use several mechanisms to increase tumor perfusion. Most of the anti-vascular therapy in tumors is antiangiogenic, aimed at blocking the function of specific growth factors or receptors. The endothelial cells isolated from tumors can grow independently of the presence of endothelial growth factors, suggesting that tumor endothelial cells can acquire some characteristics that make them less sensitive to anti-angiogenic therapy. Not all tumors are dependent on some specific factor or receptor in order to be vascularized. VM, an angiogenesis-independent novel pathway, is thought to

provide a mechanism of perfusion and a dissemination route within the tumor that functions either independently of or simultaneously with angiogenesis. VM was also reported to be resistant to angiogenesis inhibitors such as endostatin and TPN-470 in melanoma tumor cells and the B16F10 murine melanoma model^[73]. So, therapies that target angiogenesis must not be the only strategies that target the tumor microcirculation. Additional tumor-target therapy for non-angiogenic pathways of tumor perfusion and metastasis should be considered. VM, an independent risk factor of prognosis, and/or PAS-positive patterns was associated with poor prognosis in tumor patients^[12,12-22]. Hence, it would be prudent, and possibly essential, to target VM in developing strategies for tumors therapy.

Until now, a variety of genes have been investigated for their role in tubular network formation in tumor cells. An option for therapy is the use of monoclonal antibodies and antisenseoligonucleotides to these molecular for drug targeting. It has been reported that MMP inhibitor, PI3K inhibitor, PSMA (prostate-specific membrane antigen) inhibitor, a knockout EphA2 gene, down-regulation VE-cad, and an antibody against Ln-5 γ^2 chain antisense oligonucleotides have an effect in the inhibition of VM. A number of recent papers demonstrated that several drugs demonstrate specific anti-VM effects. Genistein, a predominant isoflavone in soybeans, was able to inhibit VM formation of uveal melanoma through down-regulation of VE-cad *in vitro*. The ectopic model study showed that VM in uveal melanoma specimens were significantly reduced by Genistein *in vivo*^[107]. Zhang *et al.*^[68] have discovered thalidomide, which was used to treat morning sickness during pregnancy in the 1960s but was banned for its side effects (caused phocomelus), could inhibit VM through the regulation of vasculogenic factors. Doxycycline may inhibit the growth of engrafted melanoma and result in reduced expression of MMP-2, MMP-9 and VM formation. However, VEGF expression in the tumors increased in the doxycycline-treated animals. VM channel and endothelium-dependent vessels were reduced, suggesting that microcirculation patterns were inhibited by doxycycline administration, aggravating hypoxia, and increasing VEGF expression^[108]. It was recently reported that Rapamycin, a HIF-1 α inhibitor, could inhibit VM and phenotype transformation of SKOV3ip^[65].

6-demethyl-6-deoxy-4-dedimethylamino-tetracycline (COL-3) was used to evaluate for treatment of patients with refractory solid tumors. The administration of COL-3 to aggressive melanoma cells in three-dimensional culture inhibited MMP-2, MMP-9, MT1-MMP, and VE-cad expression. In addition, Ln-5 γ^2 chain was inhibited and decreased vascular network formation was observed^[36]. Celecoxib is a highly selective COX-2 inhibitor, which may inhibit vascular channel formation in human breast cancer cells through PGE₂ pathway^[99]. Imatinib, an inhibitor of PTKs, has been extensively used in the clinical treatment of gastrointestinal stromal tumors (GIST). It is primarily being targeted toward inhibiting continuous activation of Kit PTK caused by the mutation of oncogene c-kit

in GIST. The capacity of inhibition of PTK to decrease VM could be one of the reasons why such drugs could be successfully used in the treatment of GIST^[17]. In aggressive human melanoma cells *in vitro*, forskolin was shown to inhibit VM channel formation through MAPK and PI3K pathway^[94]. However, the study of VM in tumors is still at early stage, VM makes tumor growth inhibition even more complex and it is difficult to propose a precise anti-VM therapy strategy. An efficient anti-VM therapy should focus on three aspects: remodeling of the ECM and tumor microenvironment, blocking biochemical and molecular signaling pathways of VM, inhibiting plasticity of tumor cells. However, there is still a long way to go to completely elucidate mechanisms of VM and to translate tumor angiogenesis into efficient tumor therapies which can be applied to human cancer treatments.

CONCLUSION

Tumor vascularization can be explained by angiogenesis, mosaic blood vessel formation and VM. As a novel and functional tumor microcirculation, VM has been described in more and more tumors. VM and the level of VM density are associated with shorter survival and poor prognosis. To date, relatively little is known about the ability of tumor cells to form highly patterned vascular channels at the molecular level.

Tumor cell plasticity underlies VM and aggressive tumor cells may revert to an undifferentiated stem cell-like phenotype. A study by Monzani *et al*^[109] showed that a stem cell population which could increase the melanoma progression was found in melanoma biopsy. Therefore, the cancer stem cells (CSCs) subpopulation inside the tumor can organize VM and a mosaic network, depending on the environmental conditions. At least for melanoma, VM or mosaic vessel formation is due to the trans-differentiative capacity of the CSCs subpopulation. The evidence of such a subpopulation, of course, opens a new perspective for the treatment of melanoma. CSCs afford an opportunity to investigate tumor cell plasticity characteristics and a new therapeutic perspective. In addition, recent reports have indicated that bone marrow macrophages and dendritic cells have trans-differentiative capacity and that macrophages contributed to building neovessels in active multiple myeloma through VM^[110]. Further research about VM has demonstrated that Mast cells (MCs) contributed to neovascularization; MCs were located in the vessel wall that connect with endothelial cells (ECs) to line the vessel lumina. This behavior of MCs could be regarded as an example of VM like that of melanoma or other tumor cells, which themselves form vascular channels^[111]. Hence, there further research required to explore the mechanisms how the tumor microenvironment and ECM influence both tumor cells and normal cells.

The relationships between VM channels, mosaic blood vessels, endothelium-dependent blood vessels, and lymphatic tubes need to be elucidated. Mosaic blood vessels constitute 4% of the total surface area of tumor microcirculation. Some researchers believe that Mosaic blood vessels are not

related to VM channels and are a mosaicism of endothelial and tumor cells. Mosaic blood vessels are a transient phenomenon and a three-stage phenomenon including VM channels, mosaic blood vessels, endothelium-dependent blood vessels was proposed by Zhang *et al*^[4]. During the early stages of transplanted melanoma, all three patterns are observed in tumor tissues, especially VM. With the tumor growing, more mosaic blood vessels, endothelium-dependent blood vessels are observed, and in the later stages endothelium-dependent blood vessels become the main blood supply pattern. Hence, it is very important to choose the right time node for anti-VM therapy.

Results from a recent study showed that aggressive melanoma tumor cells could express VEGF-C and lymphatic-vessel endothelial hyaluronan receptor 1^[112]. These results raise the intriguing possibility that the fluid-conducting meshwork could mimic a lymphatic-like network. VM might be associated with lymphatic circulation, and a lymphatic-like network probably exists in tumor tissues.

The full range of molecular players and their specific roles in VM are still to be elucidated. The exploration of drugs targeted at molecular signaling pathways in VM is a field filled with challenges and hope. Therapies targeting VM have only been attempted in experimental research till date. VM provides an avenue to investigate the interrelationships between the genetically dysregulated invasive tumor cell, tumor microenvironment, and the malignant switch. Perhaps, the combination of anti-VM with other therapy strategies, such as chemotherapy, anti-angiogenesis, and anti-lymphangiogenesis will prove to be promising option.

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Current status of radiofrequency ablation of hepatocellular carcinoma

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Abstract

Loco-regional treatments for hepatocellular carcinoma (HCC) are important alternatives to curative transplantation or resection. Among them, radiofrequency ablation (RFA) is accepted as the most popular technique showing excellent local tumor control and acceptable morbidity. The current role of RFA is well documented in the evidence-based practice guidelines of European Association of Study of Liver, American Association of Study of the Liver Disease and Japanese academic societies. Several randomized controlled trials have confirmed that RFA is superior to percutaneous ethanol injections in terms of local tumor control and survival. The overall survival after RFA is comparable to after surgical resection in a selected group of patients with smaller (< 3 cm) tumors. Currently, the clinical benefits of combined RFA with transarterial chemoembolization for intermediate stage HCC are increasingly being explored. Here we review the ongoing technical advancements of RFA and future potential.

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Key words: Image-guided tumor ablation; Radiofrequency

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer worldwide and the third most frequent cause of death from cancer. Chronic hepatitis B and C viral infections are the predominant factors predisposing patients to HCC in Southeast Asia, Africa, Western countries and Japan. The incidence of HCC is increasing in Western countries and is expected to equal that currently reported in Asian countries^[1-3].

Liver transplantation is the best curative option with good survival rates, although its use is restricted by the shortage of donor organs. Surgical resection was accepted as a treatment of choice before the era of transplantation. However, the tumors in most patients are unresectable because of a variety of factors including: poor hepatic reserve, multifocal disease or inability to obtain an optimal tumor free margin^[4,5]. Therefore, for the majority of patients with HCC, loco-regional treatment is the only alternative treatment option^[6-12].

The image-guided loco-regional treatment for patients with unresectable HCC includes chemical or thermal ablative techniques and catheter-based approaches. Among the ablative techniques, radiofrequency ablation (RFA) has been used as the most popular method for treating early

stage HCC (single or 3 nodules less than 3 cm in diameter). During the past two decades, many clinical studies have confirmed the safety and therapeutic efficacy of RF^[13-19]. The purpose of this article is to review and summarize the current status of RFA for HCC. The current and potential roles of RFA in treating HCC will be presented with a review of the evidence of its safety and therapeutic efficacy.

CURRENT ROLE OF RFA IN THE TREATMENT OF HCC

It is difficult to define the current role of RFA in the treatment of HCC because it is still an evolving technique. However, consensus meetings of major scientific societies have presented guidelines for its use. The evidence-based practice guidelines for management of HCC have been proposed by the European Association of Study of Liver (EASL) and the American Association of Study of the Liver Disease (AASLD)^[4,20]. In both guidelines, RFA is recommended as a non-surgical technique for the treatment of early stage (Child A or B, solitary HCC or up to 3 nodules < 3 cm in size) HCC.

According to the EASL and AASLD guidelines, local ablation using RFA and percutaneous ethanol injections (PEI), is accepted as a safe and effective therapy for patients that cannot undergo resection or as a bridge to transplantation based on level II (nonrandomized controlled trials, cohort or case-control analytic studies, multiple time series, dramatic uncontrolled experiments) evidence. In addition, RFA is as effective as PEI for smaller (< 2 cm) tumors but clearly superior to PEI for larger tumors based on level I (randomized controlled trial) evidence^[4,20].

The barcelona clinic liver cancer staging and treatment assessment system is widely used worldwide. Using this system, RFA is classified as a treatment option for early stage HCC. Patients with early stage disease can be effectively treated by resection, transplantation or percutaneous ablation with the possibility of long-term cure and a 5-year survival rate ranging from 50% to 75%. However, many issues regarding the treatment of choice remain to be resolved by further investigations; currently there are no studies available that have compared treatments considered to be effective for early stage disease (surgical resection, transplantation and percutaneous ablation) or comparing these methods of treatment to no treatment (Figure 1)^[4,20,21].

According to the Japanese evidence-based guidelines, if there is only one tumor in a patient with Child A or B disease, hepatectomy is recommended regardless of the diameter of the tumor. However, percutaneous local ablation may also be selected if the severity of liver damage is class B and the diameter of the tumor is not more than 2 cm. If there are 2 or more tumors and their diameters are no more than 3 cm, hepatectomy or ablation is recommended. If there are 2 or 3 tumors and their diameters are 3 cm more, hepatectomy or hepatic artery embolization is recommended. If there are more than 4 tumors, transarterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy is recommended (Figure 2)^[22]. Recently, the expert panel of the Japanese

Society of Hepatology established a consensus-based treatment algorithm based on therapeutic protocols used in Japan. This algorithm essentially follows the evidence-based algorithm; however, the treatments widely performed in Japan were included by consensus, even though the evidence was not always present^[23].

SAFETY OF RFA

One of the most attractive features of local ablation therapy, including RFA, is that the procedure is minimally invasive compared to curative surgical resection or transplantation. Although RFA is considered to be much safer than surgical treatment, it is not a complication-free procedure. Thus, an operator should be aware of all major complications with the potential morbidity and mortality and should be ready to detect complications as early as possible and manage them appropriately^[24-26].

There have been several multicenter studies on the complications in patients after RFA procedures for hepatic tumors. In 2002, the collaborative Italian Group, using the Cool-tip electrode, reported the results of a multicenter study of the complications that occurred in patients after RFA procedures. The mortality, major and minor complication rates were 0.3%, 2.2% and 5% respectively^[27]. Another Italian group, using the multi-tined expandable electrodes, reported the complications in 872 patients. The mortality, major and minor complication rates were 0.1%, 3.1% and 6.3% respectively^[28]. A Korean multicenter study on complications was performed on 1139 patients treated by RFA. The mortality and major complication rates were 0.1% and 2.4%^[29]. A French study with 312 patients reported that the mortality, major and minor complication rates were 1.4%, 10.6% and 6.3% respectively^[30].

An extensive meta-analysis of 82 independent reports including 3670 patients, reported by Mulier *et al.*^[24], revealed that the overall mortality rate was 0.5%, and the major/minor complication rate was 8.9%. The most common complications were abdominal hemorrhage, abdominal infection (abscess), biliary tract damage, liver failure, pulmonary complications and ground pad burns. The broad spectrum and incidence of major complications are similar to the findings of many single center studies.

There have been many investigations that have focused on methods to minimize the complications associated with RFA procedures^[31-38]. The most useful method to prevent collateral thermal injury of abutting organs is the use of artificial fluid or air injected into the peritoneal or pleural spaces. Song *et al.*^[38] recently reported the feasibility and efficacy of artificial ascites in 143 patients with HCC abutting the diaphragm or bowel. Artificial ascites separates the organs at risk for damage from the RF ablation zone and improves the sonic window by downward displacement of the liver^[31,34,36,38].

THERAPEUTIC EFFICACY OF RFA

It is difficult to objectively review and compare the therapeutic efficacy data of treatment modalities. This is because

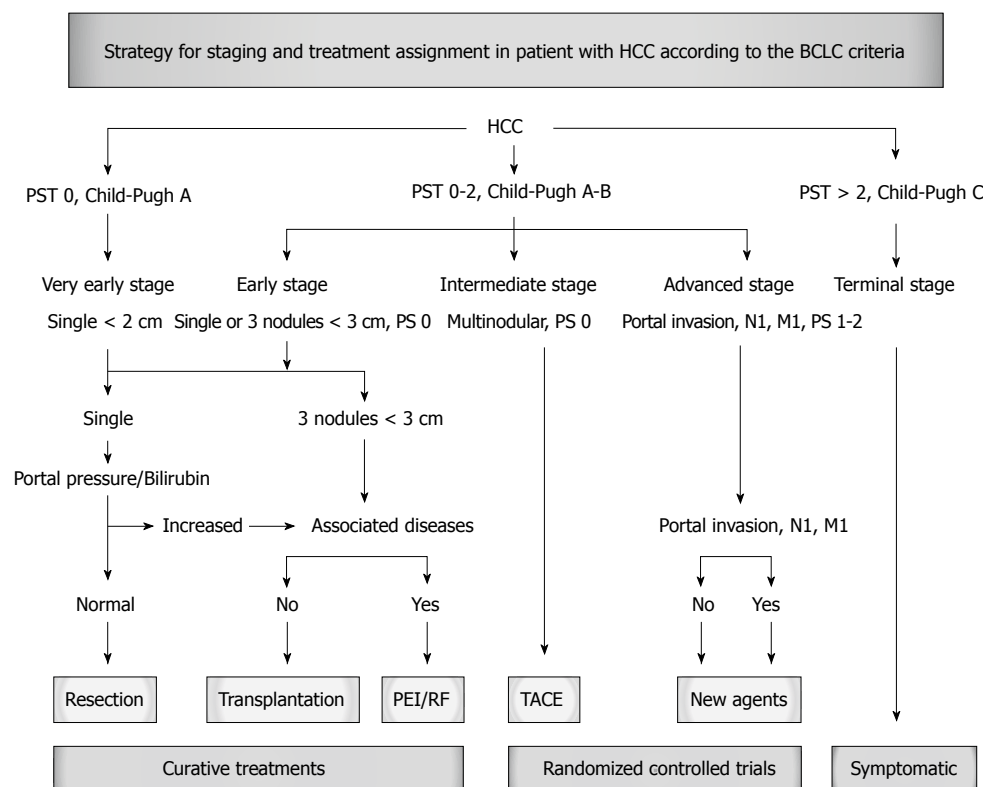


Figure 1 Strategy for staging and treatment assignment in patient with hepatocellular carcinoma (HCC) according to the barcelona clinic liver cancer (BCLC) criteria. BCLC staging system was developed based on the collection of data from several independent studies representing different disease stages and/or treatment modalities. It includes variables related to tumor stage, liver functional status, physical status and cancer related symptoms. The main advantage of the BCLC criteria staging system is that it links staging with treatment modalities and with an estimation of life expectancy that is based on published response rates to the various treatments. Early stage disease includes patients with preserved liver function (Child-Pugh Class A and B) with solitary HCC or up to 3 nodules < 3 cm in diameter. These patients can be effectively treated by resection, transplantation or percutaneous ablation with the possibility for long-term survival ranging from 50% to 75%.

there are significant variations among studies in terms of study design and the technical details of treatment. In addition, patient demographics, including etiology and extent of liver disease, as well as tumor features (number, size, location), vary considerably from one study to another^[39-41]. Currently, the international working group of image-guided tumor ablation has proposed a “Proposal for Standardization for Terms and Reporting Criteria”, which was acknowledged by the society of interventional radiology. The aim of the proposal is to facilitate the effective communication of ideas and appropriate comparisons among treatments^[42]. Currently, there are so many non-surgical ablation techniques including radiofrequency, ethanol, microwave, laser, high intensity focused ultrasound, radioembolization and TACE with novel drug eluting beads. However, only RFA and PEI are being widely performed worldwide and accepted as a standard treatment in all the guidelines supported by considerable evidence with many investigations including a randomized controlled study.

Below, we summarize the current therapeutic efficacy of RFA for treating HCC according to the following categories of treatment: (1) RFA alone; (2) Comparison between RFA and PEI; (3) Comparison between RFA and surgery; and (4) RFA combined with surgery or TACE.

RFA alone

Since 2005, six clinical cohort studies with large series of

patients (more than 200 patients) have been reported in the medical literature. The survival results are summarized in Table 1.

Lencioni *et al*^[13] performed a prospective, intention-to-treat clinical trial with 206 patients with early stage unresectable HCC (mean size 2.8 cm). No procedure-related death was observed. Major complications were observed in three (2%) of 187 patients, including two cases of intraperitoneal bleeding and one tumor seeding along the needle track. Overall survival rates were 97%, 67% and 41% at 1, 3 and 5 years respectively. The prognostic factors related to overall survival were Child Class and tumor multiplicity. The 1-, 3- and 5-year local tumor progression rates were 4%, 10% and 10%.

Tateishi *et al*^[14] reported therapeutic results of 1000 RFA procedures used to treat 2140 HCC nodules (mean size, 2.6 cm) in 664 patients. Major complications occurred in 4% per treatment and 1.9% per session. The most common complications were tumor seeding along the needle track, hepatic abscess formation requiring drainage and intraperitoneal hemorrhage, in order of decreasing frequency. There were no deaths related to the RFA procedure. The 1-, 3- and 5-year overall survival rates for 319 patients treated, as the first line treatment were 95%, 78% and 54%. Child-Pugh Class, tumor size, and AFP levels were prognostic factors for overall survival.

Chen *et al*^[15] reported on the long term outcome of RFA for HCC (mean size 3.8 cm) in 256 patients. Major

Table 1 Summary of therapeutic results of 6 large series cohort studies with percutaneous RFA alone

Year	Author	Patient No.	Size (cm) ¹	FU (mo) ²	LTP (%) ³	New recur (%) ⁴	Major Cx (%) ⁵	Overall survival (%)			Median survival (mo)	Evidence ⁶
								1 yr	3 yr	5 yr		
2005	Lencioni <i>et al</i> ^[13]	206	< 5	24	10	49	2.0	97	67	41	57	2
2005	Tateishi <i>et al</i> ^[14]	319	< 5	28	8.7	60	4.0	95	78	54	NA	2
2005	Chen <i>et al</i> ^[15]	256	< 8	2-69	NA	NA	2.4	83	67	41	NA	2
2007	Choi <i>et al</i> ^[16]	570	< 5	30	11.8	52	1.9	95	70	58	77	2
2008	Livraghi <i>et al</i> ^[17]	216	< 2	31	0.9	NA	1.8	NA	76	55	NA	2
2009	N'Kontchou <i>et al</i> ^[18]	235	< 5	27	11.5	42	0.9	NA	60	40	48	

RFA: Radiofrequency ablation; ¹Maximum diameter of tumor; ²Mean follow-up period; ³Rate of local tumor progression; ⁴Rate of new recurrence including intrahepatic remote and extrahepatic metastasis; ⁵Rate of major complications requiring additional hospitalization or therapeutic procedure; ⁶Level of evidence.

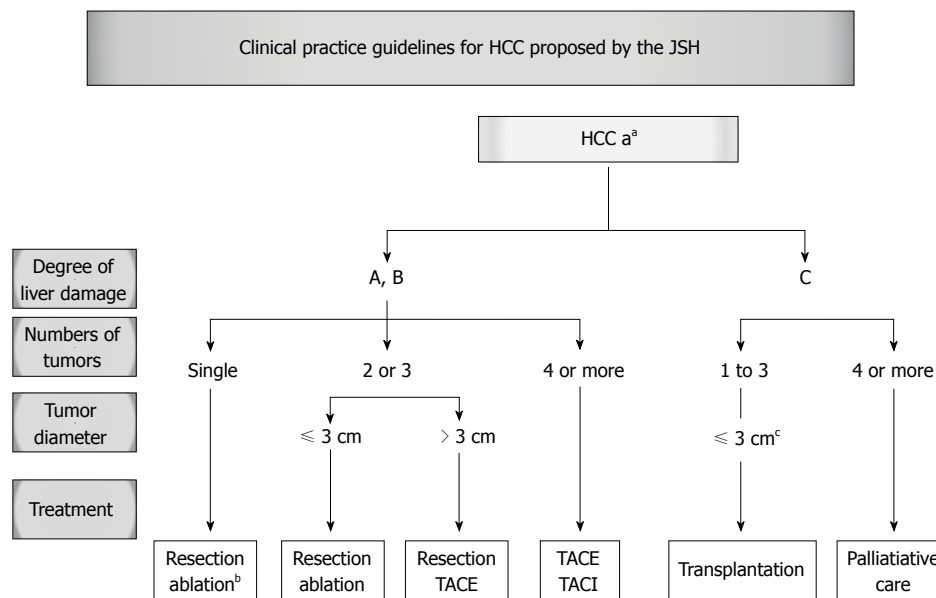


Figure 2 Clinical Practice Guidelines for HCC proposed by the Japan Society of Hepatology. ^aPresence of vascular invasion or extrahepatic metastasis to be indicated separately; ^bSelected when the severity of damage is class B and the tumor diameter is no greater than 3 cm; ^cTumor diameter should be no greater than 5 cm when there is only one tumor; JSH: Japan society of hepatology.

complications had an incidence of 2.4% and included track tumor seeding, intraperitoneal hemorrhage and bowel perforation. The overall survival rates were 83% at 1 year, 67% at 3 years and 41% at 5 years.

Choi *et al*^[16] evaluated the long-term results and prognostic factors in 570 patients with 674 early stage HCCs. There were no procedure-related deaths. The incidence of major complications was 1.9% per treatment. The cumulative survival rates at 1, 3 and 5 years were 95%, 70% and 58% respectively. The local tumor progression rates at 1, 2 and 3 years were 8%, 11% and 12% respectively. The prognostic factors for survival were Child-Pugh Class, age and pre-treatment AFP levels.

Livraghi *et al*^[17] reported on the therapeutic results after RFA procedures for very early HCC in 218 patients. They assessed two primary end points that could be easily compared to surgical resections: (1) the rate of sustained, local and complete response; and (2) the rate of treatment-related complications. The secondary end point was the 5-year survival in 100 patients that had tumors that were considered potentially operable. The sustained complete response rate was 97.2%. The perioperative mortality,

major complication rate and 5-year survival were 0%, 1.8% and 69% respectively. They concluded that RFA could be considered the treatment of choice for patients with a single HCC less than 2 cm in diameter, even when surgical resection was possible.

Recently, N'Kontchou *et al*^[18] evaluated the long-term results and prognostic factors in 235 consecutive patients with HCC (mean size 2.9 cm). Major complications occurred in three patients (0.9%), including one treatment-related death. The overall 5-year and recurrence-free survival rates were 40% and 17% respectively. However, the overall 5-year survival rate was 76% for operable patients. The prognostic factors associated with overall survival were prothrombin time and serum AFP levels. The tumor size was associated with local tumor progression but not with overall and tumor-free survival.

RFA vs PEI

In addition to the many studies on RFA alone, there have been many comparative studies performed to confirm the therapeutic efficacy of RFA by comparing other ablative techniques (especially PEI). During the past few years, five

Table 2 Summary of 5 randomized controlled studies on comparison between RFA and PEI

Year	Author	Treatment	Patient No.	FU (mo) ¹	Initial CR ² /Tumor (%)	Initial CR ² /Patient (%)	Overall survival (%)			Evidence ⁴
							1 yr	2 yr	3 yr	
2003	Lencioni <i>et al</i> ^[43]	RFA	42	23	91	NA ³	100	98	NA	2
		PEI	44	22	82	NA	96	88	NA	
2004	Lin <i>et al</i> ^[44]	RFA	52	24	96	96	90	82	74	1
		PEI	105	24	91	91	87	62	48	
2005	Lin <i>et al</i> ^[45]	RFA	62	28	97	97	93	81	74	1
		PEI	62	26	88	89	81	66	51	
2005	Shiina <i>et al</i> ^[46]	RFA	118	~4.3 yr	100	97	97	91	81	1
		PEI	187	~4.2 yr	100	91	91	81	67	
2008	Brunello <i>et al</i> ^[47]	RFA	70	26	NA	96	NA	NA	63	1
		PEI	69	25	NA	66	NA	NA	59	

PEI: Percutaneous ethanol injections; ¹Mean follow-up period; ²Complete response rate; ³Not available; ⁴Level of evidence.

Table 3 Summary of 6 clinical studies on comparison between RFA and surgical resection

Year	Author	Study	Treatment	Patient No.	FU (mo) ¹	Tumor size (cm)	Overall survival (%)					P-value	Evidence ³
							1 yr	2 yr	3 yr	4 yr	5 yr		
2004	Vivarelli <i>et al</i> ^[51]	NR ⁴	RFA	79	29	< 5	78	NA	33	NA	NA	0.020	2
			Resection	79			88	NA	65	NA	NA		
2005	Montorsi <i>et al</i> ^[52]	NR	RFA	58	NA ²	< 5	85	75	61	45	NA	0.139	2
			Resection	48			84	79	73	61	NA		
2005	Hong <i>et al</i> ^[53]	NR	RFA	55	35	< 5	100	NA	74	NA	NA	0.240	2
			Resection	93			98	NA	84	NA	NA		
2005	Chen <i>et al</i> ^[54]	R ⁵	RFA	47	36	< 5	93	82	64	NA	NA	0.753	1
			Resection	65			93	86	67	NA	NA		
2006	Lü <i>et al</i> ^[55]	R	RFA	51	NA	< 5	94	87	87	NA	NA	0.808	1
			Resection	54			91	86	86	NA	NA		
2009	Ueno <i>et al</i> ^[56]	NR	RFA	110	36	< 5	98	NA	92	NA	63	0.060	2
			Resection	123			99	NA	92	NA	80		

¹Mean follow-up period; ²Not available; ³Level of evidence; ⁴Non-randomized study; ⁵Randomized controlled study.

randomized clinical trials and three meta-analysis studies on the therapeutic efficacy of RFA *vs* PEI have been published^[43-50]. The data of seven studies are summarized in Table 2.

The key points from the five randomized controlled trials and three meta-analysis studies are that PEI and RFA are equally effective for tumors less than 2 cm. However, the necrotic effect of RFA is more predictable for all tumor sizes and its efficacy is clearly superior to that of PEI in larger tumors (level I)^[4,20,43-50]. Overall, RFA demonstrated superior efficacy in regard to lower local tumor progression and a longer disease-free survival. The local tumor control rate was reported to range between 91% and 96% for RFA and between 65% and 88% for PEI. Both treatment groups presented similar adverse events; only one study found RFA associated with more major complications^[43].

RFA vs surgical resection

After the introduction of percutaneous ablation therapy, the efficacy compared with curative treatment, namely surgical resection, for the treatment of small HCC has been debated^[51-57]. The therapeutic efficacy reported by these comparative studies of RFA and surgical resection are summarized in Table 3.

Several non-randomized studies have demonstrated equivalent outcomes for RFA and surgery. Montorsi *et al*^[52] performed a prospective nonrandomized trial comparing RFA (58 patients) with surgery (40 patients) in 98 patients with a single HCC less than 5 cm in diameter. While long-term (up to 4 years) survival was equivalent in both treatment groups, RFA resulted in significantly higher rates of intrahepatic recurrence compared to the surgical resection group. Another nonrandomized comparative study reported by Hong *et al*^[53] demonstrated that RFA was as effective as surgical resection for single small (< 5 cm) HCC in patients with Child A disease, similar to the results reported by Montorsi *et al*^[52]. A large Japanese prospective study with 7185 patients with small HCC demonstrated no significant difference in overall survival for hepatic resection *vs* RFA *vs* PEI group, although the time-to-recurrence rates were better for the hepatic resection group^[57]. Ueno *et al*^[56] performed a retrospective study on 278 consecutive patients with HCC classified by the Milan criteria that were treated by surgical resection (123 patients) and RFA (155 patients). The overall survival and disease-free survival was significantly better in the surgical resection group than in the RFA group, although differences in liver function reserve existed. A recent study by Livraghi *et al*^[17] focused on early stage disease and

demonstrated a sustained local complete response after RFA comparable with that of hepatic resection.

Two randomized controlled trials compared RFA to hepatic resection in patients with early HCC. Chen *et al.*^[54] reported a randomized controlled trial in 112 patients with a single HCC less than 5 cm that received either resection (65 patients) or percutaneous RFA (47 patients). No significant differences in local recurrence, overall survival or disease-free survival were detected between the two groups. Most clinical trials, including randomized controlled trials, have shown that RFA is comparable to surgical resection in terms of overall survival; in addition, it is less invasive and associated with lower complication rates and lower costs^[51-57].

Direct comparison by a well designed randomized controlled trial is the only way to assess whether RFA might replace surgical resection for treating early stage, resectable HCC. The difference in survival between the two treatments appears to be fairly small, based on the currently available data. The sample size required to ensure meaningful conclusions should be quite large. Thus, this kind of randomized controlled study may be not feasible^[17].

RFA combined with other treatments (surgery or TACE)

RFA combined with surgery: RFA can be used as one complimentary method for multifocal or larger tumors. In patients with multifocal HCCs that are not feasible for hepatic resection, resection of the dominant tumors can be performed first and then the remaining small tumors can be simultaneously ablated by RFA. Using this approach, more patients previously considered inoperable become eligible for a curative resection^[58-61]. Choi *et al.*^[62] reported acceptable perioperative morbidity and long-term survival in a series of 53 patients that had combined hepatectomy and RFA for multifocal HCCs. They confirmed an important role for RFA in increasing the chance of curative treatment for patients with multifocal tumors that might be traditionally considered unresectable. However, further investigation is needed to compare the outcome of hepatectomy plus RFA with that of hepatectomy alone to assess whether the survival results are truly comparable^[58,59].

RFA combined with TACE: Another promising role of RFA is combined treatment with TACE for intermediate to large tumors. Although RFA shows excellent local tumor control for small tumors less than 3 cm, the limited size of the ablation zone usually fails to achieve complete ablation of large HCC greater than 5 cm^[12-18,63]. To obtain a large coagulation area, various techniques including multiple overlapping ablations^[64-67], saline-enhanced ablation to reduce the tissue impedance^[68,69] and temporary occlusion of tumor blood supply have been attempted^[64,70-73]. The combination of TACE with RFA has two theoretical merits: (1) Occlusion of hepatic arterial flow by means of embolization may contribute to the decrease in the heat-sink effects during RFA and increase the ablation volume by RFA; and (2) Combined treatment may have the effect of anticancer agents on cancer cells, which is enhanced by

the hyperthermia.

Yamakado *et al.*^[74] compared the therapeutic efficacy of combined TACE plus RFA and Surgical resection in 142 patients with HCC (< 5 cm, up to 3 in number). The 1-, 3- and 5-year overall survival rate after TACE followed by RFA (98%, 94% and 75%) were similar to surgical resection (97%, 93% and 81%)^[75]. In addition, they reported another study with 20 patients with HCC larger than 5 cm. The overall and recurrence-free survival rates were 100% and 71% at 1 year, 62% and 28% at 3 years and 41% and 14% at 5 years. Recently, Shibata *et al.*^[76] reported a prospective study comparing the therapeutic efficacy of a combined TACE and RFA group (46 patients) with a RFA alone group (43 patients). They concluded that combined TACE with RFA had equivalent effectiveness for the treatment of small (< 3 cm) HCCs; therefore, combined treatment may not be necessary for small tumors.

PERSPECTIVE ON RFA

Based on current evidence, RFA will remain the mainstay of local treatment for early stage HCC because of its excellent local tumor control and minimal morbidity. The therapeutic efficacy of RFA will continue to be refined with advancements in technology in terms of planning, targeting, monitoring, controlling and assessment of therapeutic efficacy. The technical advancements will include novel guiding modalities (CE-US, fusion imaging or robotic guidance)^[77-81], more powerful ablation strategies (multiple applicators) and combined treatment with adjuvant therapy such as thermo-sensitive drugs or targeted agents such as sorafenib^[22,82-84]. However, RFA technology will be challenged by other ablative techniques including novel microwave or cryosurgery technologies as well as non-invasive emerging techniques such as high intensity focused ultrasound treatment and irreversible electroporation in the near future^[85-90].

CONCLUSION

RFA is the most popular non-surgical technique for treating early stage unresectable HCC because of its excellent local tumor control and acceptable morbidity. RFA is superior to PEI in terms of local tumor control and survival. Overall survival of RFA is comparable to surgical resection in a selected group of patients with smaller tumors. Currently, combined RFA with TACE is increasingly being investigated for the treatment of intermediate stage HCC. Considering the ongoing technical advances, RFA remains an attractive technique with additional potential to be explored by further investigations.

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Concurrent and subsequent radiofrequency ablation combined with hepatectomy for hepatocellular carcinomas

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Abstract

Partial hepatectomy has long been the standard treatment modality for patients with hepatocellular carcinoma (HCC), although the majority of patients with HCCs are not candidates for curative resection. Radiofrequency ablation (RFA) has been widely used as the preferred locoregional therapy. RFA and hepatectomy can be complementary to each other for the treatment of multifocal HCCs. Combining hepatectomy with RFA permits the removal of larger tumors while simultaneously ablating any smaller residual tumors. By using this combination treatment, more patients might become candidates for curative resection. For treating recurrent tumors involving the liver after hepatectomy, RFA has been performed recently instead of transcatheter arterial chemoembolization or ethanol ablation. Many retrospective studies on the combination of RFA and hepatectomy demonstrate favorable results of effectiveness and safety. However, further investigation of prospective design will be needed to confirm these encouraging results.

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Key words: Radiofrequency ablation; Hepatocellular carcinoma; Hepatectomy; Combination treatment

INTRODUCTION

Liver transplantation is the most effective treatment modality for patients with hepatocellular carcinoma (HCC), as it not only completely removes HCCs in the liver but also treats the underlying cirrhosis^[1]. However, transplantation has been performed restrictively owing to a shortage of donors and the long waiting time^[1]. Thus, partial hepatectomy has long been the standard treatment modality for patients with HCCs. However, the majority of patients with HCCs cannot undergo curative resection owing to inadequate functional hepatic reserve, multifocality, or both^[1-4].

Among many locoregional treatment modalities, transcatheter arterial chemoembolization (TACE), ethanol ablation and radiofrequency ablation (RFA) have been widely used. TACE is usually applied to patients with multiple tumors and relatively preserved function of the liver whilst ethanol ablation and RFA is usually performed on patients with a small number of tumors^[1-4]. RFA is increasingly used as the preferred therapy because it produces more consistent local tumor control and good survival results^[5-9]. Moreover, several recent studies reported that RFA might achieve long-term survival results similar to those for resection for small HCCs^[10-14]. A most recent report asserted that RFA can be considered the treatment of choice for patients with single 2 cm or smaller HCC, even when surgical resection is possible^[15].

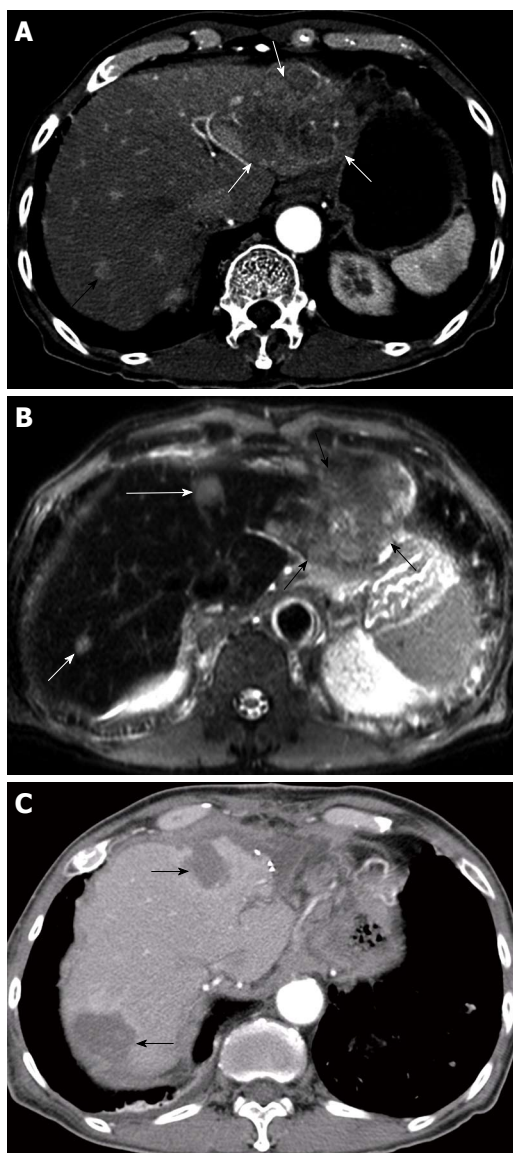


Figure 1 Successful radiofrequency ablation (RFA) combined with hepatic resection for multifocal hepatocellular carcinomas (HCCs) in a 74-year-old man. A: Contrast-enhanced transverse helical CT scan obtained during the arterial phase before treatment shows two HCCs in the both hepatic lobes. There are 11.0-cm-diameter HCC (white arrows) in left lateral segment and 1.1-cm-diameter HCC (black arrow) in liver segment 7; B: Ferucarbotran-enhanced T2-weighted fast spin echo MR image shows another 1.5-cm-diameter HCC (long white arrow) in liver segment 4. He underwent resection for a large tumor and concurrent RFA for two small tumors; C: Contrast-enhanced transverse helical CT scan obtained 1 mo after combined hepatectomy and RFA shows two round ablation zones (arrows) of low attenuation that suggests technical success of ablation. At 4 mo after treatment, multiple metastatic tumors were found in the both lungs (not shown).

PRINCIPLE OF CONCURRENT RFA AND HEPATECTOMY

RFA is competitive with hepatectomy in the treatment of small HCCs, although RFA and hepatectomy can be complementary to each other for the treatment of multifocal HCCs^[16]. In order to permit complete treatment of unresectable multifocal hepatic tumors including metastases from colorectal cancer, RFA or other locoregional

therapies combined with hepatic resection have been introduced^[17-20]. A prior report proposed that reduction surgery allowed a survival benefit for patients with multiple HCCs when combined with intraoperative adjuvant therapy for remaining satellite tumors^[20]. This study found that the cumulative survival results of these patients with reductive hepatic resection were better than those of patients treated non surgically with TACE or ethanol ablation. Figure 1 shown a RFA combined with hepatic resection for multifocal HCCs in a 74-year-old man.

When compared to colorectal liver metastasis, combining hepatectomy with RFA may play a more important role in treating HCC because of the high frequency of multifocal tumors and associated liver cirrhosis^[16]. In a previous study of patients with bilobar HCCs, combined resection of HCC in one lobe and wedge resection or ethanol ablation of lesions in the contralateral lobe showed better long-term survival than nonsurgical treatments^[21]. However, wedge resection for contralateral lobe lesions can be performed only for superficial tumors, and ethanol ablation is reported to be inferior to RFA in terms of local tumor control. RFA is a better modality for treatment of contralateral lesions and can be performed for deep tumors^[16].

In patients with multifocal HCCs that are untreatable with hepatectomy alone, the dominant tumors are resected first, and the remaining small tumors can be treated simultaneously with RFA. This makes more patients potential candidates for curative resection. All sonographically-detectable small tumors can be completely eradicated with preserving hepatic reserve^[22,23]. Intraoperative RFA can be performed for some tumors ineligible for percutaneous RFA. Tumors near the hepatic hilum, stomach, colon, or diaphragm can easily be treated with intraoperative RFA.

CLINICAL RESULTS OF CONCURRENT RFA AND HEPATECTOMY

Recently, Choi *et al.*^[22] reported good perioperative results and long-term survival in a series of 53 patients who had undergone combined hepatectomy and RFA for multifocal HCCs. During a single operation, as well as hepatectomy the intraoperative RFA procedures were performed for one or more (up to three) of 59 small (4 cm or smaller in maximum diameter) unresectable HCCs^[22]. This study also found that resected tumor size was a significant prognostic predictor of long-term survival. They confirmed an important role for RFA in enhancing the chance of curative treatments for patients with multifocal tumors that might traditionally be considered unresectable.

In patients with HCC in a cirrhotic liver, preoperative evaluation including Child-Pugh classification, indocyanine green retention test, and volumetric analysis is essential^[2,3,24-29]. Although survival after resection for properly selected candidates can reach 70% at 5 years^[2], large series of resections for HCCs reported moderate or good, 3-year and 5-year survival rates between 51%-73% and 34%-59%, respectively^[29-32]. Choi *et al.*^[22] demonstrated that resection plus RFA provided long-term survival comparable to that with hepatectomy alone. This study

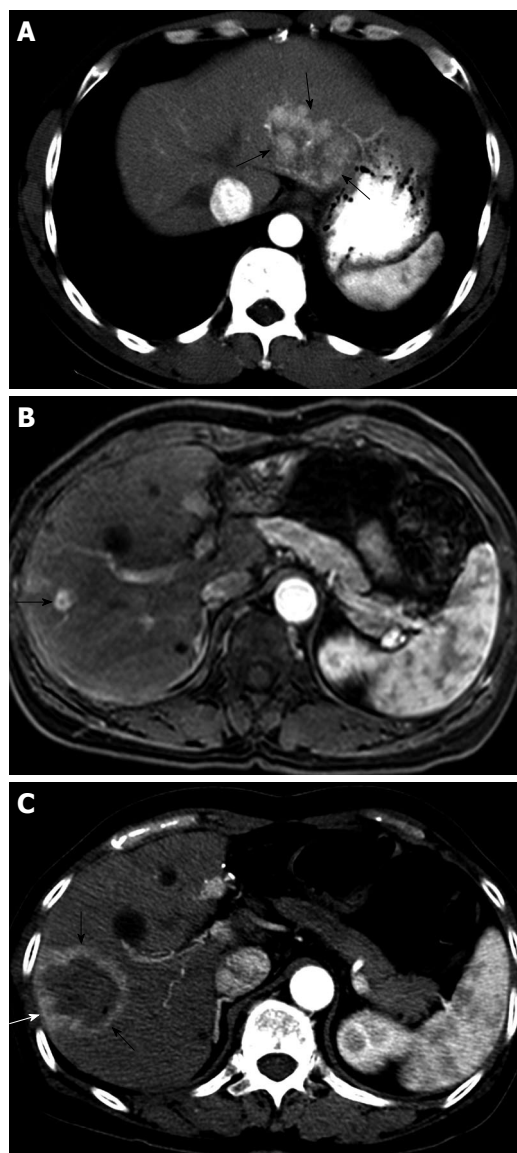


Figure 2 Successful RFA of intrahepatic recurrent HCC in a 49-year-old man. A: Contrast-enhanced transverse helical CT scan obtained during the arterial phase before hepatectomy shows a 5.7-cm-diameter HCC (arrows) in left lateral segment; B: At 5 years after left lateral segmentectomy, Gd-EOB-DTPA-enhanced T1-weighted MR image obtained during the arterial phase before RFA shows a 1.0-cm-diameter recurrent HCC (arrow) in liver segment 8; C: Contrast-enhanced transverse helical CT scan obtained 1 h after RFA shows a round ablation zone (arrows) of low attenuation with peripheral rim hyperemia. The patient has been alive without recurrence for 14 mo.

reported that the cumulative survival rates at 1, 3 and 5 years were 87% 80% and 55%, respectively. However, in spite there being only one case with incomplete ablation and two others with local tumor progression after ablating 66 tumors, the 5-year cancer-free survival was 0%. Either tumor recurrence at the other parts of the liver or extrahepatic metastasis is very common where multifocal HCCs are treated. Although small recurrent tumors in the liver could possibly be ablated, novel adjuvant therapies such as sorafenib may be needed^[33-35].

Despite the theoretical appeal of combining hepatectomy with RFA, safety can be a concern because both resection and intraoperative RFA are procedures that may

potentially cause morbidity^[22,23]. Choi *et al.*^[22] reported no operative mortality and an 8% of major complication rate in a study of combined hepatectomy and RFA for multifocal HCCs. Their selection criterion for lobectomy of 10% or less indocyanine green retention at 15 min is conservative. The strategy of hepatectomy and RFA may reduce the surgical risk when compared with an extended resection, although this is still a high-risk procedure in patients with limited hepatic reserve.

RFA FOR RECURRENT HCCS AFTER HEPATECTOMY

Another combination treatment is subsequent RFA for recurrent HCCs after hepatectomy. In spite of curative hepatectomy, recurrent tumors are found in more than 70% of patients within 5 years after hepatectomy, and repeat hepatectomy is recommended for intrahepatic recurrence^[36-42].

However, this is not feasible in the majority of patients because of significant hepatic dysfunction or multiplicity of recurrent HCCs^[41,43-45].

In the past, such patients underwent TACE or ethanol ablation^[45-48]. Recently, RFA has increasingly been performed for treating recurrent tumors in the remnant liver after hepatectomy^[49-54]. In addition to some initial reports introducing the possibility of RFA to treat recurrent HCCs after hepatectomy^[49-51], a study with 45 patients documented that the 3-year survival rate after percutaneous RFA for recurrent HCCs after hepatectomy was 54%^[52]. Lu *et al.*^[54] also reported on the long-term survival results of 72 patients who underwent percutaneous microwave ablation ($n = 33$) and RFA ($n = 39$). The overall survival rates at 3 years and 5 years after thermal ablation were 43% and 18%, respectively. In another study, the 3-year survival rate after percutaneous RFA for recurrent HCCs after hepatectomy was 44%^[55].

Repeat hepatectomy may promise complete resection of intrahepatic recurrences, and any extrahepatic lesions in the abdominal cavity can also be explored. However, this operation is more difficult to perform than an initial hepatectomy, and it results in increased risks of postoperative morbidity and mortality^[38,41]. In prior reports on repeat hepatectomy for recurrent HCCs, the 3-year and 5-year survival rates were 56% to 83% and 40% to 52%, respectively^[38,39,41,56,57]. A recent study of RFA for recurrent HCCs after hepatectomy in 102 patients demonstrated comparable long-term survival results (65.7% and 51.6% at 3 and 5 year, respectively)^[53]. This study also showed that the primary effectiveness rate was 93.3% (111 of 119) and the cumulative rate of local tumor progression at 5 years was 11.9%. In this study, liver abscess is the only complication, which can be related with bilioenteric anastomoses following surgical procedures^[58]. When percutaneous RFA is performed for recurrent HCCs abutting the gastrointestinal tract, bowel perforation frequently occurred due to postoperative adhesion^[59,60]. Figure 2 shown a successful RFA of intrahepatic recurrent HCC in a 49-year-old man.

In three studies with large populations, long-term survival of patients with HCCs treated with percutaneous RFA as a first-line treatment depended upon the Child-Pugh class, serum α -fetoprotein (AFP) level, age, tumor size, and multiplicity of tumors^[61-63]. In addition, several prior reports suggested various prognostic factors after surgical resection for HCCs^[24,29,64-66]. Among them, histopathologic grading of resected HCCs, tumor size, Child-Pugh class, fibrosis staging of the liver, serum AFP level, and microvascular invasion were generally considered to be prognostic predictors. However, in a recent study of RFA for recurrent HCCs after hepatectomy by Choi *et al.*^[53] serum AFP level before RFA and resected tumor size were independent significant predictive factors of long-term survival. Lu *et al.*^[54] reported that the pre-ablation serum AFP level was the only prognostic predictor.

CONCLUSION

For the treatment of multifocal HCCs and recurrent HCC, RFA can be complementary to hepatectomy. In fact, most patients with HCCs received multimodal approaches to treatment that included hepatectomy, TACE, RFA, ethanol ablation, microwave ablation, radiation therapy, or systemic chemotherapy, either in sequence or combination^[35,67]. Aggressive combination treatment by concurrent RFA and hepatic resection may enhance the chance of curative treatments for patients with multifocal tumors that are traditionally considered unresectable. However, further investigation should compare the outcome of hepatectomy plus RFA with that of hepatectomy alone to see whether the survival results are truly comparable^[16]. For recurrent HCCs in patients who were not eligible for repeat hepatectomy, RFA should be considered. However, it remains unclear whether percutaneous RFA can replace repeat hepatectomy as the standard treatment for small, resectable, recurrent HCCs. For this issue, randomized controlled trials that compare RFA and repeat hepatectomy would be needed.

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Metachronous cancer of gallbladder and pancreas with pancreatobiliary maljunction

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pancreas during the long-term follow-up of patients with pancreatobiliary maljunction, especially after they have undergone a choledochojunostomy.

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Abstract

Pancreatobiliary maljunction is a congenital anomaly in which the junction between the pancreatic duct and the common bile duct is located outside the sphincter of Oddi. It is well known that pancreatobiliary maljunction is frequently associated with carcinoma of the biliary tract. We report a case of metachronous cancer of the gallbladder and pancreas associated with pancreatobiliary maljunction and cystic dilatation of common bile duct in a 68-year-old Tunisian woman who underwent a cholecystectomy for acute cholecystitis. The pancreatic tumor was an adenosquamous carcinoma. Pancreatobiliary maljunction allows for pancreatobiliary or biliopancreatic reflux which may induce biliary tract carcinoma. Few cases of multifocal cancer associated with this anomaly have been reported. The association with pancreatic carcinoma remains rare. Close attention should be given to both the biliary tract system and

INTRODUCTION

It is well known that pancreatobiliary maljunction is frequently associated with carcinoma of the biliary tract^[1]. However, its association with adenocarcinoma of the pancreas remains rare. Furthermore, metachronous cancer of the gallbladder and pancreas associated with pancreatobiliary maljunction and cystic dilatation of common bile duct has never, to our knowledge, been reported. Pancreatobiliary maljunction is a congenital anomaly in which the junction between the pancreatic duct and the common bile duct is located outside the sphincter of Oddi. This anomaly leads to two-way regurgitation of pancreatic juice into the biliary tract or bile into the pancreatic duct because of the lack of a sphincter mechanism. Here we report a case of metachronous cancer of the gallbladder and pancreas associated with pancreatobiliary maljunction

and cystic dilatation of the common bile duct. To date, only four cases of metachronous double cancer of the pancreas and gallbladder associated with pancreaticobiliary maljunction without cystic dilatation of common bile duct have been reported.

CASE REPORT

In April 2004, a 68-year-old Tunisian woman underwent a cholecystectomy for acute cholecystitis. The histological examination revealed moderately differentiated adenocarcinoma of gallbladder classified pT2N1M0. She was referred to our department. On the admission, physical examination and hepatic test were normal. Ultrasonography and computed tomography (CT) showed a bile duct dilatation. Magnetic resonance imaging (MRI) showed a cystic dilatation of common bile duct and revealed that the pancreatic duct was joined to the bile duct 22 mm above the papilla of Vater. The cystic dilatation of the common bile duct was classified as Type I of Todani and the pancreaticobiliary maljunction as variety I of Kumura (Figure 1A and B). The patient underwent a bisegmentectomy IV-V, wide lymph node dissection and resection of all the pathological common bile duct. The common bile duct was transected in the intra pancreatic part which is important to reduce the risk of recurrence in the intra pancreatic part of the bile duct. The post operative course was complicated by an intra peritoneal abscess treated by percutaneous drainage and antibiotics. Histological examination revealed moderately differentiated adenocarcinoma invading the cystic dilatation of common bile duct and lymph nodes (Figure 2A and B). She underwent a postoperative chemotherapy (Cisplatin, 5FU). In January 2008, the serum carcinoembryonic antigen level was 125 ng/mL (NI = 5 ng/mL). On admission, physical examination was unremarkable. The serum CA 19-9 level was 965 U/L, alkaline phosphatase was 90 IU/L and γ -glutamyl transpeptidase was 23 IU/L. Abdominal CT revealed a low-density head pancreatic tumor measuring 40 mm in maximum diameter (Figure 3). In February 2009, she underwent a pancreatoduodenectomy with regional lymph node dissection without resection of the hepaticojejunostomy. The final histological diagnosis was adenosquamous carcinoma of pancreas with two malignant components (one glandular and the other squamous) without regional lymph node metastasis (pT2N0M0) (Figure 4). The patient's postoperative course was complicated by pancreatic fistula treated by percutaneous drainage and antibiotics. She was discharged about 1 mo after the surgery and is still alive without any evidence of recurrence 1 year after the procedure.

DISCUSSION

Pancreaticobiliary maljunction is a congenital anomaly in which the junction between the pancreatic duct and the common bile duct is located outside the sphincter of Oddi; it is an uncommon anomaly, with an incidence of

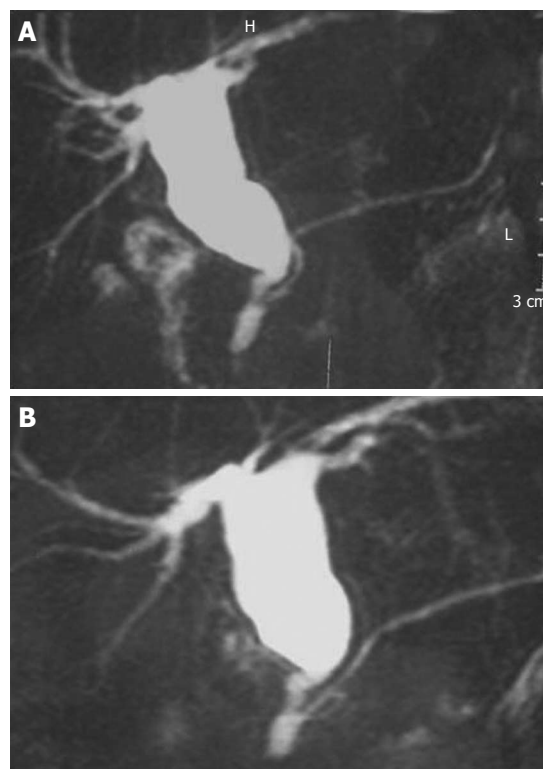


Figure 1 Magnetic resonance imaging. A: Pancreaticobiliary maljunction variety I of Kimura; B: Pancreaticobiliary maljunction with cystic dilatation of common bile duct (Type I of Todani).

3.2% in patients undergoing ERCP or operative cholangio-pancreatography^[2]. This anomaly allows pancreatobiliary or biliopancreatic reflux. Refluxed proteolytic pancreatic enzymes are activated in the biliary tract and may induce biliary tract carcinoma.

After a meal, the bile duct pressure is raised by contraction of the gallbladder and regurgitation occurs in the opposite direction with bile flowing into the pancreatic duct. The reflux of bile may activate pancreatic enzymes which may cause chronic inflammation and metaplastic epithelial change in the pancreatic duct and pancreatic cancer may eventually develop^[3]. In our patient, the cystic dilatation of the common bile duct was classified as Type I of Todani and the pancreaticobiliary maljunction as variety I of Kimura; this variety account for only 5% of pancreaticobiliary maljunction^[2]. The pancreatic cancer was found 4 years after the resection of her gallbladder and excision of the cystic dilatation of the common bile duct. Therefore, it seems that the inflammatory changes in the pancreas had been present for many years with the tendency for carcinogenesis^[3-5]. There have been 27 reported cases of pancreatic cancer in patients who had pancreaticobiliary maljunction. Multifocal cancer of the biliary tree and pancreas associated with pancreaticobiliary maljunction has been reported in 7 patients (two cases were triple cancer of the gallbladder, the bile duct and the pancreas)^[4-6] and six of them were women. In the seven patients, the cancer of the gallbladder occurred previously

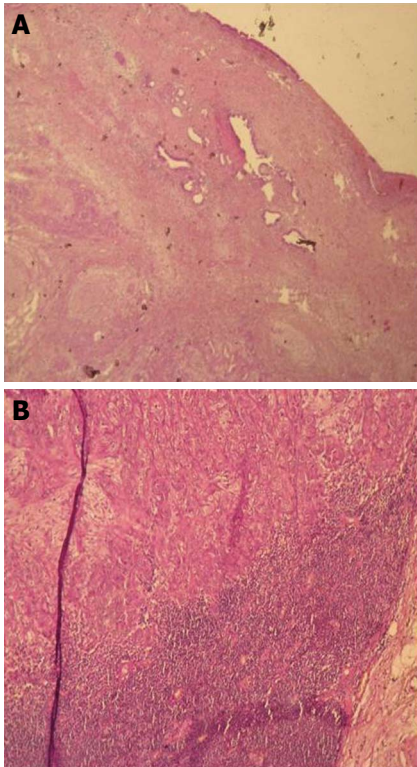


Figure 2 Histological examination. A: Involvement of the cystic dilatation of common bile duct by the adenocarcinoma of gallbladder; B: Lymph node involvement by the adenocarcinoma of gallbladder.

or synchronously with the pancreatic cancer^[7]. Gallbladder cancer was more frequent than bile duct cancer^[7]. Three patients had bile duct dilatation and none presented a choledochal cyst. Our patient had double cancer of gallbladder and pancreas associated with a choledochal cyst.

The histological diagnosis on examination of the surgical specimen was adenosquamous carcinoma which has two associated carcinomatous components: glandular and squamous. It is rare, accounting for 3%-4% of all pancreatic carcinoma^[8]. Adenosquamous carcinoma of the pancreas has a poor prognosis because of systemic metastases in the liver and peritoneal dissemination. In addition, tumor recurrence occurs frequently early after tumor resection^[8].

CONCLUSION

Pancreatic carcinoma associated with pancreaticobiliary maljunction is rare. The relationship between pancreatic carcinoma and pancreaticobiliary maljunction is clear. Therefore, close attention should be paid to both the biliary tract system and the pancreas during the long-term follow-up of patients with pancreaticobiliary maljunction following a choledochojejunostomy.

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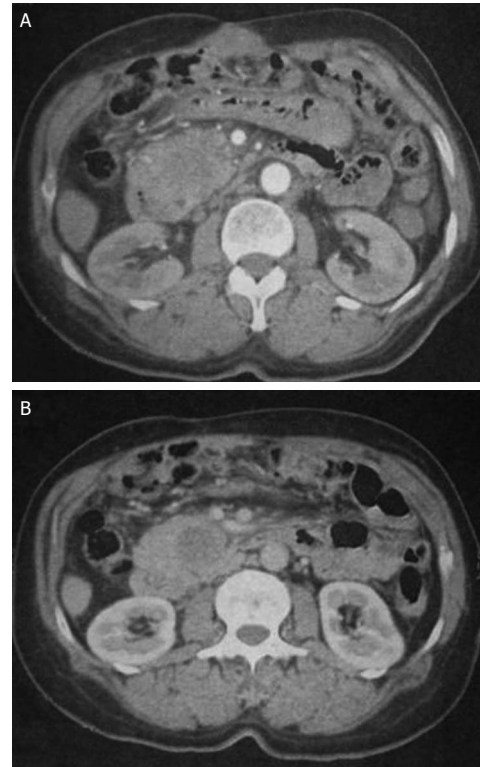


Figure 3 Abdominal CT: low-density mass in the pancreatic head. A: Arterial phase; B: Portal phase. CT: Computed tomography.

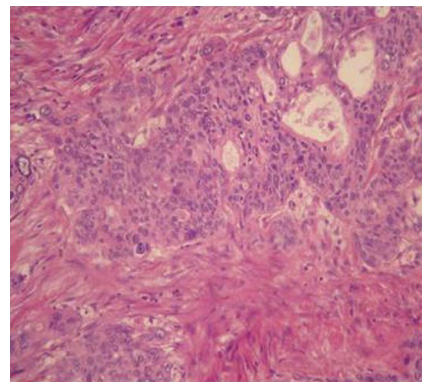


Figure 4 (He × 250): Microscopic findings: two components of the pancreatic carcinoma, the squamous one and the glandular one.

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Laparoscopic splenectomy for splenic hamartoma: Case management and clinical consequences

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Abstract

Splenic hamartoma is a rare benign tumor, and although minimally invasive surgery may be suitable for this condition, there have only been 2 previous reports of laparoscopic surgery. Here we report the third case of splenic hamartoma managed by laparoscopic splenectomy. A 37-year-old male was incidentally diagnosed by abdominal ultrasonography with a hypoechoic mass measuring 2.5 cm × 2.4 cm in the spleen. Color Doppler sonography showed multiple flow signals within the mass and contrast-enhanced computed tomography revealed strong enhancement of the lesion. On T1- and T2-weighted magnetic resonance images, the splenic mass was demonstrated as isointense and hyperintense respectively. Although a malignant tumor could not be ruled out, a hand-assisted laparoscopic splenectomy was performed because the splenic mass was limited

in size and had not invaded adjacent organs. The pathological diagnosis was splenic hamartoma. The postoperative course was uneventful and the patient was discharged by the seventh postoperative day. Although splenic hamartomas have some specific imaging features, more reports and analyses of these cases are required to increase the reliability of the diagnosis and management. Hand-assisted laparoscopic splenectomy may play a pivotal role in the postoperative diagnosis and management of this condition.

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Key words: Splenic hamartoma; Splenoma; Splenic tumor; Laparoscopic splenectomy; Splenectomy

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INTRODUCTION

Splenic tumors are relatively uncommon. Among them, lymphomatous tumors of the spleen are the most common with other tumors including angiosarcomas, plasmacytomas, primary malignant fibrous histiocytomas, and metastatic disease to the spleen often associated with diffuse carcinomatous dissemination. Benign splenic tumors are exceedingly rare with an incidence of 7 in 100 000 autopsy specimens^[1] and most are either cysts or hemangiomas.

Splenic hamartoma is an extremely rare benign tumor with an incidence of 3 in 200 000 splenectomies^[2]. Although splenic hamartomas are benign and usually asymptomatic^[2], it is important that they are not mistaken for malignant lesions which can sometimes occur due to diagnostic difficulties. Splenectomy has traditionally been performed through a generous laparotomy incision, requiring complete mobilization of the spleen for removal. Recently, laparoscopic surgery has become the standard technique for the surgical treatment of many disorders including malignant diseases. Although minimally invasive surgery may be suitable for splenic hamartomas, to the best of our knowledge, there have been only 2 previous reports of laparoscopic surgery for splenic hamartoma. Here we report a third case of splenic hamartoma that underwent laparoscopic splenectomy.

CASE REPORT

A 37-year-old Japanese male was incidentally diagnosed with a splenic mass by abdominal ultrasonography (US) and visited our hospital for further investigation. On physical examination, he was afebrile with normal vital signs and no weight loss. The laboratory findings on admission were unremarkable: red blood cell count $460 \times 10^4/\text{mm}^3$ (normal range $370\text{--}490 \times 10^4/\text{mm}^3$); white blood cell count $4.7 \times 10^3/\text{mm}^3$ (normal range $4.0\text{--}8.0 \times 10^3/\text{mm}^3$); and platelet count $25.3 \times 10^4/\text{mm}^3$ (normal range $14.5\text{--}34.0 \times 10^4/\text{mm}^3$). Total protein, alanine aminotransferase, aspartate aminotransferase, total bilirubin and serum creatinine levels were all within normal limits, as were serum carcinoembryonic antigen and cancer antigen 19-9.

Abdominal US showed a distinct, round and hypoechoic mass measuring $2.5 \text{ cm} \times 2.4 \text{ cm}$ in the spleen (Figure 1A). Color Doppler sonography showed blood flow signals along the edge of the mass and slight signals within the mass (Figure 1B). Computed tomography (CT) images before the administration of contrast material showed a slightly hypodense lesion relative to the normal splenic parenchyma, measuring $2.4 \text{ cm} \times 2.3 \text{ cm}$ within the spleen (Figure 1C). Following a bolus injection of intravenous contrast material, the mass was strongly enhanced during the early and late hepatic artery phase (Figure 1D) and 3 min after the administration of contrast, the mass showed isodensity. The lesion was a homogenous mass with no calcification or cystic lesions observed. Magnetic resonance imaging (MRI) showed isointensity in the T1-weighted image and heterogeneous hyperintensity in the T2-weighted image (Figure 2). The lesion showed diffuse enhancement on gadolinium-enhanced MRI. Positron emission tomography (PET) using ^{18}F -fluoro-2-deoxy-d-glucose (FDG) with CT showed no abnormal accumulation of FDG. Esophagogastroduodenoscopy and colonoscopy showed no significant lesion.

Although the diagnosis of a malignant tumor was not excluded completely, a hand-assisted laparoscopic

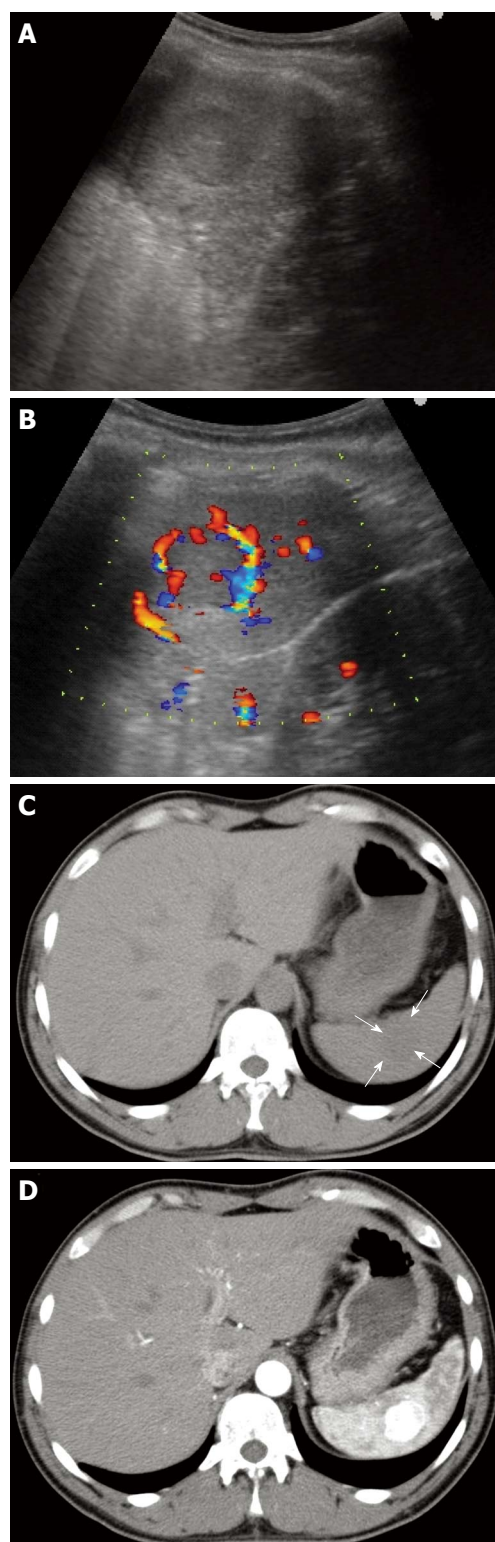


Figure 1 Ultrasonography and computed tomography (CT) of the splenic lesion. A: Gray-scale ultrasonography shows a homogenous and hypoechoic mass at the mid-portion of the spleen; B: Color Doppler sonography shows multiple color circular flow signals within the mass; C: CT shows a slightly lower-density mass in the spleen (arrows); D: The mass demonstrated strong enhancement after the intravenous administration of contrast material.

splenectomy was performed because the splenic mass was limited in size and had not invaded adjacent organs. The patient was placed on the operating table in a right

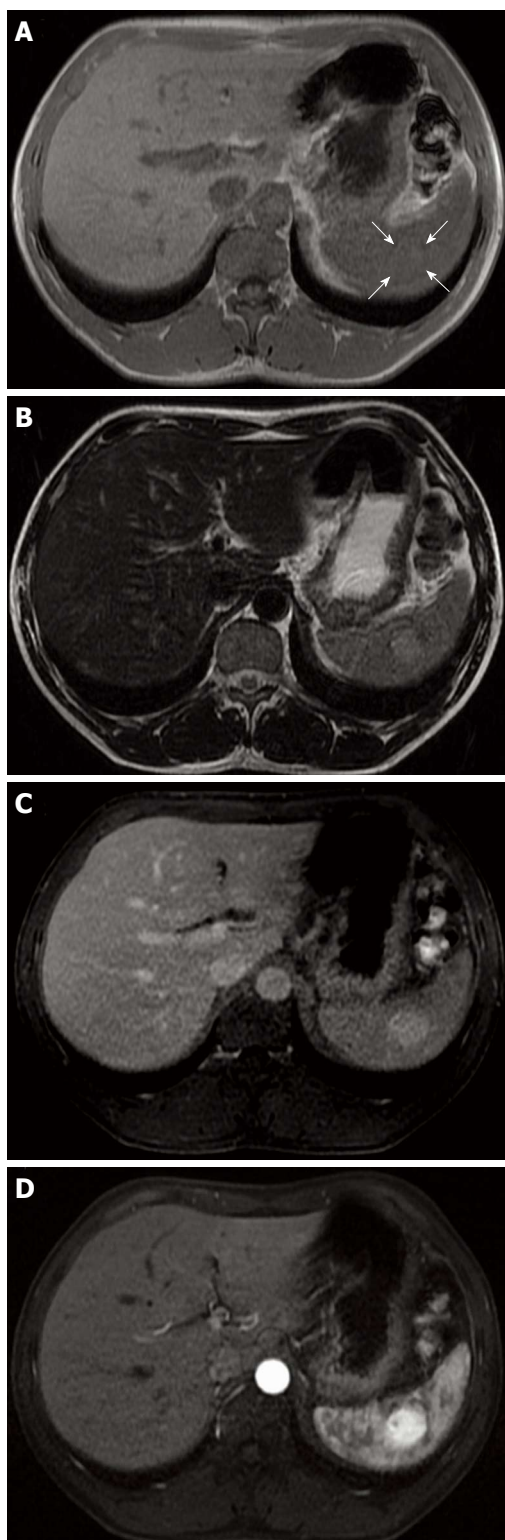


Figure 2 Magnetic resonance imaging (MRI) of the splenic lesion. A: T1-weighted MRI shows the isointense mass (arrows); B: The mass is mildly hyperintense in the T2-weighted MRI; C: The early phase of dynamic MRI shows diffuse heterogeneous enhancement of the mass; D: The mass becomes more enhanced during the delayed phase.

semilateral decubitus position with the left arm tucked above the head. An incision measuring 7.5 cm, large enough for the surgeon's hand and forearm, was made



Figure 3 Macroscopic appearance of the resected spleen showing a circumscribed mass measuring 2.5 cm × 2.4 cm in diameter (arrows).

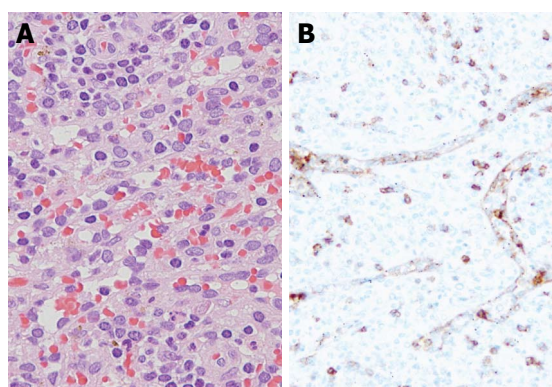


Figure 4 Pathology of the splenic lesion. A: Microscopically, the mass is composed of predominantly a red pulp splenic sinusoidal structure accompanied by lymphocytes and macrophages. Atypical cells or mitosis were not observed; B: The endothelial cells lining the sinusoidal structure are immunoreactive for CD8.

in the upper midline of the abdomen and three ports were used. The splenic artery at the tail of the pancreas was double ligated with absorbable suture. After mobilization of the spleen, the splenic vein at the splenic hilum was finally ligated and the resected spleen, contained in a plastic bag, was extracted through the upper midline incision. The total operation time and estimated intraoperative blood loss were 100 min and 20 mL respectively. The patient's postoperative course was uneventful and he was discharged on the seventh postoperative day.

The resected spleen weighed 110 g and measured 8.0 cm × 5.0 cm × 4.5 cm. The mass was noted deep inside the spleen near the hilum. Gross examination of the cut surface showed a dark-red, solid, well-circumscribed and firm lesion measuring 2.5 cm × 2.4 cm × 2.4 cm (Figure 3). There were no cystic lesions within the tumor.

Microscopically, the splenic tumor showed expansive growth, compressing the surrounding splenic tissue without a capsule. The tumor consisted of disorganized vascular channels lined by slightly plump endothelial cells without atypia, mixed with intervening splenic red pulp-like stroma without fibrous trabeculae and white pulp (Figure 4A). Immunohistochemical staining

Table 1 Imaging comparisons between splenic hamartoma and splenic hemangioma

Modality	Hemangioma	Hamartoma	Our case
US	Hyperechoic (capillary hemangioma) Hypoechoic (cavernous hemangioma) Doppler: Few flow signals	Hypo >> Hyper > Isoechoic Doppler: Multiple flow signals	Hypoechoic Doppler: Multiple flow signals
CT	Hypo-isodense Progressive centripetal prolonged enhancement	Hypo >> Iso > Hyperdense Diffuse heterogeneous enhancement	Hypodense Strong enhancement
MRI	T1: Hypo-isointense T2: Hyper >> Iso > Hypointense Progressive centripetal prolonged enhancement	T1: Iso > Hypointense T2: Hyper > Hypointense Diffuse heterogeneous enhancement	T1: Isointense T2: Hyperintense Diffuse heterogeneous enhancement

CT: Computed tomography; MRI: Magnetic resonance image; T1: T1-weighted image; T2: T2-weighted image; US: Ultrasonography.

was performed and the endothelial cells that lined the vascular channels stained positive for CD8 indicating splenic type endothelium, but negative for CD34 which detects the intervening cord capillaries (Figure 4B). The pathological diagnosis was splenic hamartoma.

DISCUSSION

Splenic hamartoma is a rare benign tumor with vascular proliferation which is usually diagnosed pathologically after laparotomy, splenectomy or at autopsy^[1,2]. The pathogenesis of splenic hamartoma varies and includes congenital malformation of the splenic red pulp, neoplasia or a reactive lesion to prior trauma^[2,3]. Splenic hamartoma is often called splenoma or nodular hyperplasia because it is composed of an aberrant mixture of the normal tissue components of the spleen^[4]. As the majority of patients are asymptomatic, most splenic hamartomas are found incidentally by modern imaging methods including US or CT scans^[3,4], as in this case.

Recent advances in imaging modalities have improved the ability to detect asymptomatic splenic masses^[5,6]. However, the differential diagnosis at imaging in respect to more frequent focal lesions of the spleen is still not straightforward. Although splenic hamartoma should be considered as a differential diagnosis for all splenic masses, it is important to distinguish splenic hamartomas from splenic hemangiomas, the most common benign splenic tumor. Table 1 shows some of the differences observed in the US, CT and MRI findings of splenic hamartomas compared to splenic hemangiomas.

The macroscopic type of splenic hemangioma determines the US findings - a capillary hemangioma appears as a hyperechoic nodule whereas a cavernous hemangioma is seen as a heterogeneous hypoechoic mass, sometimes with calcification or multiple cystic areas^[6]. Generally, splenic hamartomas have been described as solid, homogenous masses with various echogenic patterns relative to the normal splenic parenchyma, showing usually a hypoechoic, but occasionally hyperechoic lesion with or without cystic changes in the spleen^[3,4,7]. The color Doppler sonograms of splenic hemangiomas show only a few color echoes which can appear in the tumor immediately after it is compressed by the probe^[8]. On

the other hand, the color Doppler sonographic findings in splenic hamartomas are multiple radial blood-flow signals inside the mass^[9]. However, masses inside the spleen are usually less vascular than the surrounding normal parenchyma because of the high vascularity of the spleen. Chou *et al*^[10] demonstrated that the tumor could be markedly enhanced on color Doppler sonography by the administration of microbubble contrast agents. Thus, US may be an indispensable method for the diagnosis of splenic hamartoma^[7].

CT scans demonstrate that splenic hamartomas are isodense or hypodense masses and show a dense spreading and prolonged enhancement after intravenous administration of contrast material^[11]. T2-weighted MRI shows most splenic hamartomas as heterogeneously hyperintense lesions relative to the spleen and demonstrates diffuse heterogeneous enhancement on early postcontrast images and more uniform enhancement on delayed images^[5,6,12]. Similar findings were noted in our present case. In the case of splenic hemangiomas, dynamic enhanced imaging using either CT or MRI demonstrates a progressive centripetal pattern of enhancement with prolonged uniform enhancement on delayed images^[6,12,13]. In addition, the fusion of images from FDG-PET with those of CT becomes an important tool in assessing patients with a malignant disease or suspected lymphoma to evaluate other malignant sites^[14]. Avila *et al*^[15] first reported the findings of PET-CT in splenic hamartomas which demonstrated a moderate FDG avidity, while our current case showed no abnormal accumulation of FDG.

Although there are some specific imaging features of splenic hamartomas, it is difficult to rule out the possibility of a malignant neoplasm based on such imaging studies. The diagnosis must be confirmed by pathological examination. Although there have been some studies about the efficacy and safety of fine needle aspiration biopsy of the spleen, the possibility of bleeding or tumor dissemination makes this technique problematic^[16,17]. Therefore, splenectomy is still necessary for diagnostic and therapeutic purposes. Recently, less invasive treatments have been developed such as laparoscopy-assisted surgery.

The main pathological differential diagnosis for splenic hamartoma is a benign vascular tumor including hemangioma. They also have similar clinical and

Table 2 Characteristics of reported cases of splenic hamartoma treated by laparoscopic splenectomy

Author	Year	Age (yr)	Gender	Tumor size (cm)	Preoperative diagnosis	Number of ports	Operation time (min)	Estimated blood loss (mL)
Yoshizumi <i>et al</i> ^[25]	1997	45	Male	6.0 × 3.8	Benign tumor	4	305	450
Tatekawa <i>et al</i> ^[22]	2007	12	Female	5	Hamartoma	4	ND	ND
Our case	2009	37	Male	2.5 × 2.4	Benign tumor	3	100	20

ND: Not described.

radiological findings. Immunohistochemical staining can be used to distinguish a splenic hamartoma from a capillary hemangioma by their respective staining characteristics^[18,19]. Endothelial cells which are positive for CD8 are a key feature that distinguishes a hamartoma from other vascular lesions of the spleen^[3,19]. The endothelial cells of hemangiomas are CD8-negative and CD34-positive, in contrast to the CD8-positive and CD34-negative endothelial cells of splenic hamartomas^[18,19]. The splenic hamartoma has been classified into two histological types: the white pulp type and the red pulp type, according to the tumor components^[2]. The former is composed entirely of lymphoid tissue while the latter is composed of sinuses and is histologically similar to that of the normal red pulp of the spleen. Most reported cases are the red pulp type, including this present report. Multiple flow signals on color Doppler US and strongly enhanced findings on CT and MRI in our case are thought to be a reflection of the characteristic hypervascularity of the red pulp itself.

Laparoscopic splenectomy is the standard surgical procedure for the management of most cases of idiopathic thrombocytopenic purpura because of the lower operative and perioperative morbidity, compared to open splenectomy^[20,21]. Moreover, laparoscopic splenectomy has become the surgical procedure of choice for not only the management of idiopathic thrombocytopenic purpura but also of some splenic tumors^[14,21-24]. To the best of our knowledge, only three cases of laparoscopic splenectomy for splenic hamartoma, including our present case, have been reported in detail (Table 2)^[22,25]. Hand-assisted laparoscopic surgery allows the surgeon to place one hand into the abdominal cavity, providing a tactile sense and improving the accuracy of manipulation while maintaining the pneumoperitoneum. This facilitates the surgical procedure by allowing identification of dissection planes or the hand to function as a retractor. Moreover, if bleeding occurs, it is easily controlled by compression of the hand on the splenic vascular pedicle or the injury site. In our case, the 7.5 cm incision made in the upper abdominal midline was large enough to allow entry of the surgeon's hand and forearm. The resected spleen can be easily extracted through this incision without the requirement for an additional incision.

In conclusion, although there are some imaging features that are specific to splenic hamartomas, the collection and analysis of more of these cases is necessary to improve the reliability of the diagnosis and management of this condition. Hand-assisted laparoscopic splenectomy may

play a pivotal role in the postoperative diagnosis and management of splenic hamartomas.

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<http://www.gilearn.org/clinical-congress>

January 27-31, 2010

Alpine Liver & Pancreatic Surgery Meeting
Carlo Magno Zeledria Hotel, Madonna di Campiglio, Italy
<http://www.alpshpbmeeting.soton.ac.uk>

February 25, 2010

Multidisciplinary management of acute pancreatitis symptoms
The Royal Society of Medicine, 1 Wimpole Street, London, United Kingdom
<http://www.rsm.ac.uk/academ/pancreatitis10.php>

March 4-7, 2010

2010 Annual Meeting of the Society of Surgical Oncology
Renaissance® St. Louis Grand Hotel, 800 Washington Avenue, St. Louis, Missouri, United States
<http://www.surgonc.org/>

March 25-28, 2010

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The International Liver Congress™ 2010
Vienna, Austria

May 1-5, 2010

2010 American Transplant Congress
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Prague, Czech Republic
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2010 Gastrointestinal Oncology Conference
The Sheraton Philadelphia City Center, Philadelphia, United States
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Australian Gastroenterology Week
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- 16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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