# Surgical treatment of colorectal cancer liver metastases

# Dainius Šimčikas,

Marius Paškonis,

Vitalijus Sokolovas,

## Eligijus Poškus,

## **Kęstutis Strupas**

Center of Abdominal Surgery, Clinic of Gastroenterology, Nephrology, Urology and Abdominal Surgery, Vilnius University Hospital Santariskiu Clinics, Vilnius, Lithuania **Background.** Colorectal cancer is a major health problem. Approximately 25% of the patients present with liver metastases at initial diagnosis and more than 50% develop metastases in the course of illness. Over the last few decades, with improvements in therapy, the management of colorectal liver metastases has changed dramatically.

In this review, we explore various current modalities of care, with surgical treatment ahead, for patients with colorectal liver metastases and present a brief report about the Vilnius University Hospital Santariskiu Clinics experience in the surgical treatment of metastatic liver disease.

Methods. The Medline / PubMed literature database was searched for articles on the topics of colorectal liver metastases, including criteria of surgical resectability, chemo-therapy, adjunctive and locoregional therapies. Also, results of the surgical treatment of liver metastases at the Vilnius University Hospital Santariskiu Clinics were analysed.

**Results.** Globally, surgical liver resection for colorectal liver metastases remains the only regular curative treatment with the 5-year survival rates reported as 20–50%. With improvements in therapy, resectability criteria are expanding. Hepatic metastases are primarily resectable in 15–25% cases only. Up to 25% of patients with initially non-resectable metastases become amenable to a potentially curative operation after interdisciplinary treatment involving preoperative chemotherapy, portal vein embolization or ligation, few-stage hepatectomy, and / or locally ablative procedures.

We observed good and optimistic survival results in the Vilnius University Hospital Santariskiu Clinics patient population after liver resection: 1-, 2- and 3-year survival was 86.9%, 63.5% and 42.3%, respectively.

**Conclusions.** Over the last ten years, liver surgery has changed dramatically. A thorough selection of patients with colorectal liver metastases in a multidisciplinary team may improve treatment results significantly. Surgical treatment results for liver metastases at the Vilnius University Hospital Santariskiu Clinics are good.

Key words: colorectal liver metastases, liver resection, ablation, chemotherapy, portal vein embolisation

## INTRODUCTION

Colorectal cancer (CRC) is a major health problem. Nearly one million new cases are diagnosed worldwide annually (1). It is the third most frequent cancer and the second leading cause of cancer-related deaths in the European Union (2) and in the United States (3). Metastases are the most common neoplasms in an adult liver; however, their true prevalence is unknow. Liver is the most common site of CRC metastases which extremely worsen the prognosis. Approximately 25% present with metastases at the initial diagnosis and more than 50% of patients with colorectal cancer will develop metastases in the course of illness (4, 5).

Over the last few decades, the management of colorectal liver metastases (CLM) has changed dramatically. Without treatment, the median survival of patients with CLM is 5–10 months (5). Improvements in the diagnostics and

Correspondence to: Dainius Šimčikas, Bitininkų 1C-57, Vilnius, Lithuania. E-mail: dsimcikas@yahoo.com

medical, surgical, locoregional adjunctive therapies offer a better patient care and survival. Improvements in therapy present increasing challenges to clinical practitioners on the issue of CLM optimal management. Patients require a comprehensive multimodality treatment approach, but surgical resection does remain the mainstay and the only regularly curative treatment, with the 5-year survival rates reported as 20-50% (1,6).

The purpose of this review was to explore various disciplines and modalities of care, with surgical treatment ahead, for patients with CLM. The Medline / PubMed literature database was searched for articles concerning "colorectal liver metastases" "surgical treatment", "liver resection", "portal vein embolization", "radiofrequency ablation" and "chemotherapy", published up to August 2010. Special attention was paid to systematic reviews, evidence-based guidelines, meta-analyses and randomized controlled trials. We also present a brief report of our single-center experience in the surgical treatment of CLM as part of multidisciplinary approach.

## TREATMENT OF LIVER METASTASES

The treatment of metastatic CRC has one of two goals, depending on the patient's clinical condition. Palliative thera-

Table 1. Treatment goals and methods of colorectal liver metastases

py aims to prolong survival while preserving or improving the quality of life, whereas organ metastases, usually hepatic, can be resected with curative intent (7). Different treatment methods are listed in Table 1. When possible, surgical resection is the standard of care for liver metastases as it is the only treatment that offers the chance of cure. The reported 5-year survival rates achieved after the resection of isolated hepatic metastases range from 25 to 50% (Table 2) (8–11).

For unresectable patients, advances in combination chemotherapy, particularly with targeted biologic agents, have resulted in tumour response rates of up to 50% and a doubling of median survival from 10 to 20 months in patients with metastatic CRC (12, 13). Chemotherapy has also been used to downstage lesions, making about 15% of patients eligible for surgery; however, the majority of liver metastases remain not resectable (14).

A number of local, less invasive treatment approaches, including ablative (e. g., RFA, cryoablation) and embolization (e.g., TACE) therapies have shown promising local control results, but each of these techniques has limitations and variable high recurrence rates (15–17). Radiation therapy is an established palliative modality, but the optimal role of radiation therapy in the treatment of liver tumours has not been well defined (13).

Goal	Method	Combination				
Curative	Surgical liver resection	± Systemic chemotherapy (ChT) (pre-/postoperative) ± Biologics				
		± Ablation				
	Liver transplantation for highly selected patients					
Palliative	Systemic chemotherapy (ChT)	± Biologics				
	Ablation	Usually radiofrequency ablation (RFA)				
	Local chemotherapy	Usually chemoembolisation (TACE)				
	Radiation therapy (RT)	Selective internal radiation therapy (SIRT)				
		Stereotactic body radiation therapy (SBRT)				

Study, year	Number of patients	1-year survival, %	3-year survival, %	5-year survival, %	10-year survival, %	Median survival, months
Foster, 1978	78	_	_	22	_	_
Hughes et al., 1986	607	_	_	33	_	-
Rosen et al., 1992	280	84	47	25	_	-
Scheele et al., 1995	434	85	45	33	20	40
Nordlinger et al., 1996	1568	80	_	28	_	40
Jamison et al., 1997	280	84	_	27	20	33
Fong, 1999	1001	89	57	36	22	42
Minagawa, 2000	235	_	51	38	26	-
Choti, 2002	226	93	57	40	26	46
Belli, 2002	181	91	55	40	_	-
Kato, 2003	585	_	_	33	_	-
Mutsaerts, 2003	102	_	_	29	_	-
Gayowski et al., 1994	204	91	_	32	_	33
Adam et al., 2001	335	91	66	48	30	52

Surgical treatment of colorectal cancer liver metastases



Figure. Clinical groups of patients with colorectal liver metastases (21)

A therapeutic approach that includes all aspects of multidisciplinary and multimodality care is required to select and treat this complex group of patients. For optimal care, multidisciplinary team (MDT) should consist of a diagnostic and interventional radiologist as imaging studies are critical to diagnose and to determine the course of treatment; an oncologist can provide an expert opinion on the best choices of therapy; a gastroenterologist (hepatologist) can guide the use of systemic agents and help manage their side effects; surgeons can help to recognize those who are candidates for resection; pathologists are needed to provide an analysis of tissue samples (18, 19). Therefore, patients with colorectal liver metastases should be treated at centres with experience in liver surgery.

#### **CLINICAL GROUPS**

Hepatic metastases are primarily resectable in only about 15–25% of patients (14, 20). For the remaining 75–85%, resection is contraindicated by the presence of an unfavourable anatomical site or diffuse hepatic metastases, impaired liver function, non-resectable extrahepatic disease, the patient's poor general condition (9). In up to 25% of patients with initially non-resectable metastases, treated with systemic therapy, organ metastases shrink to such an extent that a potentially curative operation can be considered (7). Thus, treatment is chosen depending on the clinical group to which the patient belongs (Figure) (21).

## **OLD RESECTABILITY PARAMETERS**

It is now generally accepted that the contraindications for hepatic resection that were defined in the 1980s are no longer applicable. At that time, such features as the number of metastases (3 to 4), the size of the tumour lesion (less than 5 cm), a mandatory 1-cm tumour-free margin of resection and absence of extrahepatic disease dictated what was "resectable" (9, 22). Nowadays, these factors are no longer considered as absolute contraindications to surgical resection, although they are still harbingers of the risk of recurrence after hepatectomy (23).

## Prognostic scoring systems

Many different prognostic scoring systems are used to predict the patient's risk of recurrence and chances of long-term survival on the basis of preoperatively measured parameters (8, 24, 25). These systems differ with respect to certain individual parameters; however, they share the common feature that a low score is correlated with a low risk of recurrence, while the chance of longterm survival is less than 10% when all risk factors are present. Fong et al. defined 7 parameters as independent predictors of a poor long-term outcome: positive margin, presence of extrahepatic disease, >1 metastasis, preoperative CEA level >200 ng/ml, the largest tumour >5 cm, node-positive primary tumour, occurrence of metastases within 12 months after the initial diagnosis. Authors present one of the most popular clinical risk scores (CRS) which includes 5 clinical criteria (Table 3) (8). Risk scores may be utilized preoperatively as prognostic indicators of long-term outcome and hence be helpful in patient selection, but no prognostic parameter can identify with any certainty the patients who will not benefit from surgical treatment. Recently, Pulitano et al. analysis of 10-year follow-up data has also demonstrated that a positive surgical margin, >3 metastases, tumour size >5 cm are independent negative prognostic factors for survival (26). The most important prognostic factor, according to many studies, is a tumour-free resection margin (27).

Table 3. Clinical risk score (CRS): prognostic scoring system for CLM. One point is assigned for each positive criterion. Sum of points is CRS (8)

#### Clinical risk score (CRS)

- Node-positive primary tumour
- Occurrence of metastases within 12 months after colon resection
- The largest tumour >5 cm
- >1 metastasis
- Preoperative carcinoembryonic antigen level >200 ng/ml

#### NEW RESECTABILITY PARAMETERS

Recently the diagnostic assessment has become markedly more sensitive through the use of modern computed tomography (CT), magnetic resonance imaging (MRI) and PET-CT imaging (28). There have also been technical improvements in surgical dissecting techniques and the development of potent systemic chemotherapy protocols in the treatment of CLM (29). Surgeons and all MDT related to these factors and the improvement in postoperative care have a more liberal definition of what is resectable. The criteria for resectability have been expanded to include any patient in whom all disease can be removed with a negative margin (R0) and who has an adequate hepatic remnant. Specifically, instead of resectability being defined by what is removed, decisions concerning resectability now center around what will remain after resection, with a particular focus on the volume and function of the residual liver (22, 30).

In general, 20–25% of the total liver volume appears to be the minimum safe volume that can be left following an extended resection in patients with a normal liver parenchyma. An anticipated future liver remnant (FLR) volume below 25% of the total liver volume leads to an increased risk of postoperative morbidity and mortality (31, 32). However, FLR must be greater in patients who have received intensive chemotherapy or in cases of fatty liver, liver fibrosis or diabetes (30–50% FLR) and in patients with cirrhosis (50–70% FLR) (22, 33). A recent systematic review and meta-analysis have shown that patients with steatosis had an up to twofold higher risk of complications, including hepatic insufficiency, after major liver resection, and those with excessive steatosis had an almost threefold higher risk of death (34). Preoperative volumetry is indicated when a major hepatic resection is planned. CT or MRI can now provide an accurate, reproducible method for preoperatively measuring the FLR volume (35). Nowadays, new liver function tests, such as LiMAx, significantly improve the preoperative evaluation of residual liver function for predicting the postoperative outcome in liver surgery (36).

To conclude, CLM resectability is defined by the following criteria:

1. Comorbidity and the general operability of the patient.

2. Ability to obtain margin-negative (R0) resection of both intra- and extrahepatic disease.

3. Feasibility to preserve a sufficient liver volume after resection (FLR), consisting of at least two contiguous hepatic segments with an adequate vascular inflow, outflow and biliary drainage.

4. Experience of the surgeon and the centre!

With expanding the indications for liver resection, contraindications have naturally narrowed down. A comparison between old and current contraindications is demonstrated in Table 4 (9, 22).

Table 4.	Old and	current	contraind	ications	for live	r resection	(9	, 22	)
----------	---------	---------	-----------	----------	----------	-------------	----	------	---

	Old (y. 1986)	New
1	≥4 metastases	Parenchymal involvement ≥75%
2	Large size of metastases	Involved 3 hepatic veins and ≥7 segments
3	Inability to achieve a clear resection margin of ≥1cm	Hepatic insufficiency, Child B or C cirrhosis
4	Extrahepatic metastatic disease	Non-resectable extrahepatic tumour manifestation
5	Severe accompanying diseases	Severe accompanying diseases

# INCREASING THE NUMBER OF CANDIDATES FOR LIVER RESECTION

There are three broad strategies to increase the number of patients with resectable disease: increasing hepatic reserve, combining resection with local therapies (e.g., ablation), decreasing tumour size by preoperative chemotherapy (22).

#### I. Increasing hepatic reserve

Portal vein obstructive procedures (embolization (PVE) or ligation (PVL)) and few-stage liver resection (2- or 3-stage) have enabled surgeons to increase FLR volume and to remove more disease (37).

Portal vein obstructive procedures: PVE or PVL. In some cases, the resection of one or more hepatic metastases is technically feasible, yet cannot be performed because the FLR volume would be too small. To minimize the risk of postoperative hepatic insufficiency, ipsilateral hepatic atrophy and contralateral hepatic hypertrophy can be induced preoperatively by selective embolization of the hepatic portal vein (9). PVE was first described in 1990 by Makuuchi as a means to hypertrophy the FLR prior to liver resection (38). Currently, percutaneous transhepatic technique with various embolic agents is the procedure most commonly used for PVE (39). If liver regeneration is adequate, FLR increase may be seen 4-6 weeks after the procedure. To decide whether PVE is necessary, an estimation of the remaining liver volume has to be performed. PVE should always be considered when the residual hepatic volume would be less than 25% of the normal function liver, less than 30% in patients with steatohepatitis or steatosis due to chemotherapy (or other etiology) and less than 40% in patients with severe fibrosis or cirrhosis (9, 23, 30). Also, at least two contiguous hepatic segments must be free of metastases. As long as the liver is not cirrhotic, PVE results in a 40-60% hypertrophy of the contralateral hepatic lobe. PVL is as effective as PVE in inducing contralateral liver hypertrophy. Both can be performed simultaneously at the surgery for the primary CRC tumour (39, 40). PVE and PVL have achieved a significant improvement in the outcome of major hepatectomy and have expanded the candidate pool of liver resection.

Some new techniques, such as PVE with stem cell administration, have shown a promising clinical future. In patients requiring resection, the expansion of liver volume after PVE may be substantially lower and the time to surgery may be unacceptably long (observed to be up to 150 days) (32). Evidence suggests that hematopoietic stem cells participate in hepatic regeneration (41) and are helpful to further augment and accelerate hepatic proliferation. Furst et al. prospectively evaluated the effectiveness of portal vein embolization (PVE) and autologous CD133+ bone marrow stem cell (BMSC) administration to the liver, compared with PVE alone, to augment hepatic regeneration in patients with large hepatic malignancies. Despite the small number of patients (13 patients) and the lack of a randomized reference group, they found more than a twofold higher mean daily hepatic growth rate in patients treated with PVE and BMSCs compared with patients who underwent PVE alone (9.5 mL/d  $\pm$  4.3 vs 4.1 mL/d  $\pm$  1.9) (P = 0.03). This resulted in a reduction of the time to surgery by an average of 18 days (27 days  $\pm$  11 vs 45 days  $\pm$  21) (P = 0.057). Data suggested that the concept of PVE with CD133+ BMSC administration to the liver bears the potential to accelerate and augment the proliferation of the FLR volume more than does PVE alone in preparation for extensive liver resection. The modality seems to be safe and suitable for clinical routine. Recent progress in stem cell research and cell transplantation spurs our attempts to augment preoperative liver regeneration and shorten the time to a sufficient expansion of the FLR volume (32).

*Few-stage hepatic resection.* A further way of enabling curative resection of patients with multiple bilobar liver metastases of CRC is the so-called few-stage (usually 2-stage) hepatic resection (42). This technique is suitable for patients with bilateral hepatic metastases who can undergo neither complete tumour resection nor tumour resection combined with a local ablative procedure because of the risk of postoperative hepatic insufficiency (9). In the staged resection, one lobe of the liver is usually cleared of tumour or resected initially. Then, after a period of recovery (usually around 3–4 weeks), the contralateral side is dealt with. In this time, regeneration and recovery of the initially treated lobe should occur.

A two-stage hepatectomy has become a viable option for the patients that were previously considered "unresectable" for multiple bilateral hepatic metastases, especially with the improvements in modern-day chemotherapy (23). A two-stage hepatectomy should only be performed with a curative intent, and the application of this strategy must be carefully considered to avoid posthepatectomy liver failure (22).

## II. Combining resection with local therapies

*Resection with ablation.* Ablation of liver tumour was developed originally as an alternative option to surgical resection for unresectable lesions (43). Combining hepatic resection with ablation can expand the number of patients who may be candidates for liver directed surgical therapy, particularly as larger lesions, which are less effectively treated with ablation, can be resected and small lesions can be ablated (22, 44).

The term "tumour ablation" is defined as a direct local application of chemical(s) or thermal energy to achieve tumour destruction. It can be performed percutaneously, laparoscopically, or at open surgery, and is currently used for tumours up to 5 cm in diameter. There are various modalities of ablation therapy currently used or under development (Table 5) (43).

More recently, RFA has been adopted as the most commonly applied ablation method, probably because of a smaller size of equipment, speed of use, lower cost, and fewer hepatic parenchymal complications (22). Other local ablative approaches have also been applied to liver metastases, including high-intensity ultrasound ablation or laser thermotherapy, but these have not gained widespread acceptance (45). The ideal diameter of an ablation is 2 cm larger than the diameter of the tumour as this ensures that

1. Chemical ablation		Injections of ethanol or acetic acid	
2. Thermal ablation	a) Cryosurgical	Cryogens: liquid nitrogen, argon, NO <sub>2</sub>	
	b) Coagulative	radiofrequency (RFA)	
		microwave (MWA)	
	laser thermotherapy		
	high-intensity ultrasound		

Table 5. Ablation therapies (43)

all microscopic invasions around the metastasis have been destroyed (43). Tumours  $\leq 4$  cm in diameter can typically be ablated with a single placement of the electrode, and larger tumours require multiple deployments and ablations (22). Complications after RFA included bleeding, fever, pain, biliary fistulae, and hepatic abscess (46). Local recurrence following RFA is highly dependent on tumour size as well as location within the liver. In a retrospective series comparing 418 patients treated by resection only, RFA and resection, and RFA alone, recurrences were lowest with resection only (52%, 64% and 84%, respectively) (47). However, the reasons why patients receive RFA instead of resection are usually based on a more extensive disease that cannot be encompassed by resection.

A recent retrospective study compared hepatic resection (44 patients) with RFA (25 patients) for solitary CLM. The 5-year overall survival rate after resection was higher than after RFA (50.1% and 25.5%, respectively) (48). Also, a literature review indicated that RFA along with chemotherapy showed a better survival after RFA alone (30, 49). While prospective data are still needed to assess the comparability of RFA versus resection, RFA should continue to be used in combination with resection as a means to achieve a complete extirpation or destruction of all tumour-bearing liver in otherwise unresectable patients (22).

## III. Decreasing tumour size with preoperative chemotherapy ("down-staging")

In patients with initially unresectable CLM, preoperative chemotherapy is indicated. About 20% of metastases respond to treatment with 5-fluorouracil (5-FU) and folic acid. Combination therapies that include oxaliplatin and irinotecan rise response rates up to 60% (50). This superior efficacy of chemotherapy agents can downsize tumours to resectable and downstage 15% to 40% of patients (10). The first major clinical series of this type was reported by Bismuth et al.: the 5-year-survival was 40%, i. e. comparable with that of patients with primarily resectable hepatic metastases (51). While receiving chemotherapy, these patients should be regularly evaluated for resectability, and the operation should be performed as soon as a R0 resection becomes possible (7), because hepatic toxicity following preoperative chemotherapy, including steatosis, sinusoidal dilation and steatohepatitis, has been reported in many studies (52). These changes are associated with significantly more frequent perioperative complications, including mortality (53).

## EXPERIENCE OF VILNIUS UNIVERSITY HOSPI-TAL SANTARISKIU CLINICS IN 2003–2009

Between January 2003 and December 2009, at the Vilnius University Hospital Santariskiu Clinics, 31 patients (17 female and 14 male) underwent liver resection for liver metastases; 25 operations (80.65%) were performed for CRC MTS. The mean age of 31 patient population was  $62.32 \pm 9.79$  (range, 43–78) years. The mean size of the tumour was 6.4 (range, 2.6-15) cm. In 24 cases (77.42%), less than four liver segments were removed, and 7 patients (22.58%) underwent hemihepatectomy or removal of more than 4 liver segments. All liver metastases were not resectable by straightforward resection, and portal vein obstructive procedures were performed in two cases: one percutaneous PVE and one PVL intraoperatively. There were 4 early postoperative complications in 3 patients (9.67%): 2 biliary fistulas, 1 bleeding to abdominal cavity, 1 liver failure. The mean time of hospitalization was 12 (range, 6-34) days.

#### Analysis of survival

In all patiens operated on for liver metastases (n = 31), the median survival was 29 months, and the overall survival after 1, 2 and 3 years was 82.9, 64.5 and 48.4%, respectively. In the subgroup of patiens treated for CLM (n = 25), the median survival was also 29 months. The overall survival after 1, 2 and 3 years was 86.9, 63.5 and 42.3%, respectively. Even if the population of our patients with CLM (n = 25) is not comparable with those published by other authors, we observed optimistic survival results in our cases (Table 6) (10, 11).

## CONCLUSIONS

1. Over the last ten years, liver surgery has changed dramatically.

2. A thorough patient selection in MDT may improve the results significantly.

3. CLM treatment results at the Vilnius University Hospital Santariskiu Clinics are adequate.

Study, year	Number of patients	1-year survival, %	3-year survival, %	5-year survival, %	10-year survival, %	Median survival, months
Foster, 1978	78	_	-	22	-	-
Hughes et al., 1986	607	_	-	33	-	_
Rosen et al., 1992	280	84	47	25	-	_
Scheele et al., 1995	434	85	45	33	20	40
Nordlinger et al., 1996	1568	80	-	28	-	40
Jamison et al., 1997	280	84	-	27	20	33
Fong, 1999	1001	89	57	36	22	42
Minagawa, 2000	235	_	51	38	26	-
Choti, 2002	226	93	57	40	26	46
Belli, 2002	181	91	55	40	_	_
Kato, 2003	585	_	_	33	_	_
Mutsaerts, 2003	102	_	_	29	_	_
Gayowski et al., 1994	204	91	_	32	_	33
Adam et al., 2001	335	91	66	48	30	52
VUH SC, 2009	25	86.9	42.3	-	_	29

Table 6. Results of hepatic resections for colorectal liver metastases at Vilnius University Hospital Santariskiu Clinics compared with global studies

#### ACKNOWLEDGEMENTS

We are grateful to students Juras Kišonas and Marius Petrulionis for help in collecting data on the experience of the Vilnius University Hospital Santariskiu Clinics

> Received 12 October 2011 Accepted 21 November 2011

#### References

- Nordlinger B, Sorbye H, Glimelius B, Poston GJ, Schlag PM, Rougier P et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008; 371(9617): 1007–16.
- 2. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol. 2007; 18(3): 581–92.
- Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009; 59(4): 225–49.
- Van Cutsem E, Oliveira J. Advanced colorectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol. 2009; 20 Suppl 4: 61–3.
- Smith MD, McCall JL. Systematic review of tumour number and outcome after radical treatment of colorectal liver metastases. Br J Surg. 2009; 96(10): 1101–13.
- Wei AC, Greig PD, Grant D, Taylor B, Langer B, Gallinger S. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006; 13(5): 668–76.
- Schmiegel W, Pox C, Arnold D, Porschen R, Rodel C, Reinacher-Schick A. Colorectal carcinoma: the mana-

gement of polyps, (neo)adjuvant therapy, and the treatment of metastases. Dtsch Arztebl Int. 2009; 106(51– 52): 843–8.

- Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999; 230(3): 309–18; discussion 318–21.
- Neumann UP, Seehofer D, Neuhaus P. The surgical treatment of hepatic metastases in colorectal carcinoma. Dtsch Arztebl Int. 2010; 107(19): 335–42.
- Ito K, Govindarajan A, Ito H, Fong Y. Surgical treatment of hepatic colorectal metastasis: evolving role in the setting of improving systemic therapies and ablative treatments in the 21st century. Cancer J. 2010; 16(2): 103–10.
- Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD 3rd, Dorfman GS et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010; 28(3): 493–508.
- Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol. 2005; 23(20): 4553–60.
- Dawood O, Mahadevan A, Goodman KA. Stereotactic body radiation therapy for liver metastases. Eur J Cancer. 2009; 45(17): 2947–59.
- Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004; 240(4): 644–57; discussion 657–48.
- Kemeny N. Management of liver metastases from colorectal cancer. Oncology (Williston Park) 2006; 20(10): 1161–76, 1179; discussion 1179–80, 1185–6.

- Garrean S, Hering J, Saied A, Helton WS, Espat NJ. Radiofrequency ablation of primary and metastatic liver tumours: a critical review of the literature. Am J Surg. 2008; 195(4): 508–20.
- Vogl TJ, Zangos S, Eichler K, Yakoub D, Nabil M. Colorectal liver metastases: regional chemotherapy via transarterial chemoembolization (TACE) and hepatic chemoperfusion: an update. Eur Radiol. 2007; 17(4): 1025–34.
- Garden OJ, Rees M, Poston GJ, Mirza D, Saunders M, Ledermann J et al. Guidelines for resection of colorectal cancer liver metastases. Gut. 2006; 55 Suppl 3: iii1–8.
- Gish RG, Marrero JA, Benson AB. A multidisciplinary approach to the management of hepatocellular carcinoma. Gastroenterol Hepatol (NY). 2010; 6(3 Suppl 6): 1–16.
- Gurusamy KS, Ramamoorthy R, Imber C, Davidson BR. Surgical resection versus non-surgical treatment for hepatic node positive patients with colorectal liver metastases. Cochrane Database Syst Rev. (1): CD006797.
- Nordlinger B, Van Cutsem E, Gruenberger T, Glimelius B, Poston G, Rougier P et al. Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel. Ann Oncol. 2009; 20(6): 985–92.
- Pawlik TM, Schulick RD, Choti MA. Expanding criteria for resectability of colorectal liver metastases. Oncologist. 2008; 13(1): 51–64.
- Abdel-Misih SR, Schmidt CR, Bloomston PM. Update and review of the multidisciplinary management of stage IV colorectal cancer with liver metastases. World J Surg Oncol. 2009; 7: 72.
- Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996; 77(7): 1254–62.
- Scheele J, Stang R, Altendorf-Hofmann A, Paul M. Resection of colorectal liver metastases. World J Surg. 1995; 19(1): 59–71.
- Pulitano C, Castillo F, Aldrighetti L, Bodingbauer M, Parks RW, Ferla G et al. What defines 'cure' after liver resection for colorectal metastases? Results after 10 years of follow-up. HPB (Oxford). 2010; 12(4): 244–9.
- Pawlik TM, Vauthey JN. Surgical margins during hepatic surgery for colorectal liver metastases: complete resection not millimeters defines outcome. Ann Surg Oncol. 2008; 15(3): 677–9.
- Kong G, Jackson C, Koh DM, Lewington V, Sharma B, Brown G et al. The use of 18F-FDG PET/CT in colorectal liver metastases – comparison with CT and liver MRI. Eur J Nucl Med Mol Imaging. 2008; 35(7): 1323–9.

- Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007; 25(12): 1539– 44.
- Kemeny N. The management of resectable and unresectable liver metastases from colorectal cancer. Curr Opin Oncol. 2010; 22(4): 364–73.
- Hemming AW, Reed AI, Howard RJ, Fujita S, Hochwald SN, Caridi JG et al. Preoperative portal vein embolization for extended hepatectomy. Ann Surg. 2003; 237(5): 686–91; discussion 691–83.
- 32. Furst G, Schulte am Esch J, Poll LW, Hosch SB, Fritz LB, Klein M et al. Portal vein embolization and autologous CD133+ bone marrow stem cells for liver regeneration: initial experience. Radiology. 2007; 243(1): 171–9.
- Grundmann RT, Hermanek P, Merkel S, Germer CT, Hauss J, Henne-Bruns D et al. [Diagnosis and treatment of colorectal liver metastases – workflow]. Zentralbl Chir. 2008; 133(3): 267–84.
- de Meijer VE, Kalish BT, Puder M, Ijzermans JN. Systematic review and meta-analysis of steatosis as a risk factor in major hepatic resection. Br J Surg. 2010; 97(9): 1331–9.
- Abdalla EK, Barnett CC, Doherty D, Curley SA, Vauthey JN. Extended hepatectomy in patients with hepatobiliary malignancies with and without preoperative portal vein embolization. Arch Surg. 2002; 137(6): 675–80.
- Stockmann M, Lock JF, Malinowski M, Niehues SM, Seehofer D, Neuhaus P. The LiMAx test: a new liver function test for predicting postoperative outcome in liver surgery. HPB (Oxford). 2010; 12(2): 139–46.
- 37. Adam R, Miller R, Pitombo M, Wicherts DA, de Haas RJ, Bitsakou G et al. Two-stage hepatectomy approach for initially unresectable colorectal hepatic metastases. Surg Oncol Clin N Am. 2007; 16(3): 525–36, viii.
- Makuuchi M, Thai BL, Takayasu K, Takayama T, Kosuge T, Gunven P et al. Preoperative portal embolization to increase safety of major hepatectomy for hilar bile duct carcinoma: a preliminary report. Surgery. 1990; 107(5): 521–7.
- Liu H, Zhu S. Present status and future perspectives of preoperative portal vein embolization. Am J Surg. 2009; 197(5): 686–90.
- Selzner N, Pestalozzi BC, Kadry Z, Selzner M, Wildermuth S, Clavien PA. Downstaging colorectal liver metastases by concomitant unilateral portal vein ligation and selective intra-arterial chemotherapy. Br J Surg. 2006; 93(5): 587–92.
- 41. Alison MR, Poulsom R, Jeffery R, Dhillon AP, Quaglia A, Jacob J et al. Hepatocytes from non-hepatic adult stem cells. Nature 2000; 406(6793): 257.

- 42. Jaeck D, Oussoultzoglou E, Rosso E, Greget M, Weber JC, Bachellier P. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg. 2004; 240(6): 1037–49; discussion 1049–51.
- Padma S, Martinie JB, Iannitti DA. Liver tumour ablation: percutaneous and open approaches. J Surg Oncol. 2009; 100(8): 619–34.
- 44. Elias D, Goharin A, El Otmany A, Taieb J, Duvillard P, Lasser P et al. Usefulness of intraoperative radiofrequency thermoablation of liver tumours associated or not with hepatectomy. Eur J Surg Oncol. 2000; 26(8): 763–9.
- Christophi C, Nikfarjam M, Malcontenti-Wilson C, Muralidharan V. Long-term survival of patients with unresectable colorectal liver metastases treated by percutaneous interstitial laser thermotherapy. World J Surg. 2004; 28(10): 987–94.
- Pawlik TM, Izzo F, Cohen DS, Morris JS, Curley SA. Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol. 2003; 10(9): 1059–69.
- 47. Abdalla EK, Vauthey JN, Ellis LM, Ellis V, Pollock R, Broglio KR et al. Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection / ablation for colorectal liver metastases. Ann Surg. 2004; 239(6): 818–25; discussion 825–17.
- Hur H, Ko YT, Min BS, Kim KS, Choi JS, Sohn SK et al. Comparative study of resection and radiofrequency ablation in the treatment of solitary colorectal liver metastases. Am J Surg. 2009; 197(6): 728–36.
- Stang A, Fischbach R, Teichmann W, Bokemeyer C, Braumann D. A systematic review on the clinical benefit and role of radiofrequency ablation as treatment of colorectal liver metastases. Eur J Cancer. 2009; 45(10): 174856.
- Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. Lancet. 2000; 355(9209): 1041–7.
- Bismuth H, Adam R, Levi F, Farabos C, Waechter F, Castaing D et al. Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg. 1996; 224(4): 509–20; discussion 520–2.
- Kooby DA, Fong Y, Suriawinata A, Gonen M, Allen PJ, Klimstra DS et al. Impact of steatosis on perioperative outcome following hepatic resection. J Gastrointest Surg. 2003; 7(8): 1034–44.
- 53. Vauthey JN, Pawlik TM, Ribero D, Wu TT, Zorzi D, Hoff PM et al. Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol. 2006; 24(13): 2065–72.

## Kęstutis Strupas, Dainius Šimčikas, Vitalijus Sokolovas, Eligijus Poškus

# KOLOREKTALINIO VĖŽIO KEPENŲ METASTAZIŲ CHIRURGINIS GYDYMAS

#### Santrauka

Įvadas. Storosios ir tiesiosios žarnos vėžys yra didžiulė sveikatos problema. Pirminės diagnozės metu apie 25 % pacientų kepenyse nustatoma metastazių ir daugiau nei 50 % pacientų jos atsiranda ligos metu. Per pastaruosius kelis dešimtmečius gerėjant gydymo galimybėms, metastazių kepenyse diagnostika ir gydymas smarkiai pasikeitė. Šioje apžvalgoje ypatingą dėmesį skirdami chirurginiam gydymui aptariame įvairias šiuolaikines kolorektalinių kepenų metastazių gydymo galimybes, trumpai pateikiame Vilniaus universiteto ligoninės Santariškių klinikų rezultatus gydant kepenų metastazinę ligą.

Metodai. MEDLINE / PubMed literatūros duomenų bazėje buvo atrinkti straipsniai storosios ir tiesiosios žarnos vėžio metastazių kepenyse tema. Daug dėmesio skirta straipsniams rezektabilumo, chemoterapijos ir lokalių bei regioninių gydymo būdų temomis, taip pat išanalizuoti Vilniaus universiteto ligoninės Santariškių klinikų kepenų metastazių chirurginio gydymo rezultatai.

Rezultatai. Visame pasaulyje chirurginė kepenų rezekcija dėl kolorektalinių metastazių tėra vienintelis gydymo būdas; penkerių metų išgyvenamumo rezultatai sudaro 20–50 %. Gerėjant gydymo galimybėms plečiasi rezektabilumo kriterijai. Nustačius kepenų metastazes, jos būna rezektabilios tik 15–25 % pacientų. Kai metastazių negalima pašalinti iškart, iki 25 % pacientų jos tampa rezektabilios po tarpdisciplininio gydymo priešoperacine chemoterapija, vartų venos embolizacijos ar ligavimo, keleto etapų kepenų rezekcijų ir / ar abliacijos procedūrų.

Nustatėme, kad Vilniaus universiteto ligoninės Santariškių klinikų pacientų po kepenų rezekcijų išgyvenamumo rezultatai yra geri ir optimistiški: 1, 2 ir 3 metų išgyvenamumas buvo atitinkamai 86,9, 63,5 ir 42,3 %.

Išvados. Per pastaruosius dešimt metų kepenų chirurgija ženkliai pasikeitė. Kruopšti pacientų atranka daugiadisciplininėje komandoje gali gerokai pagerinti gydymo rezultatus. Vilniaus universiteto ligoninės Santariškių klinikų kepenų metastazių chirurginio gydymo rezultatai yra geri.

Raktažodžiai: kolorektalinio vėžio kepenų metastazės, kepenų rezekcija, abliacija, chemoterapija, vartų venos embolizacija