Near-infrared fluorescence imaging in colorectal cancer and its metastases

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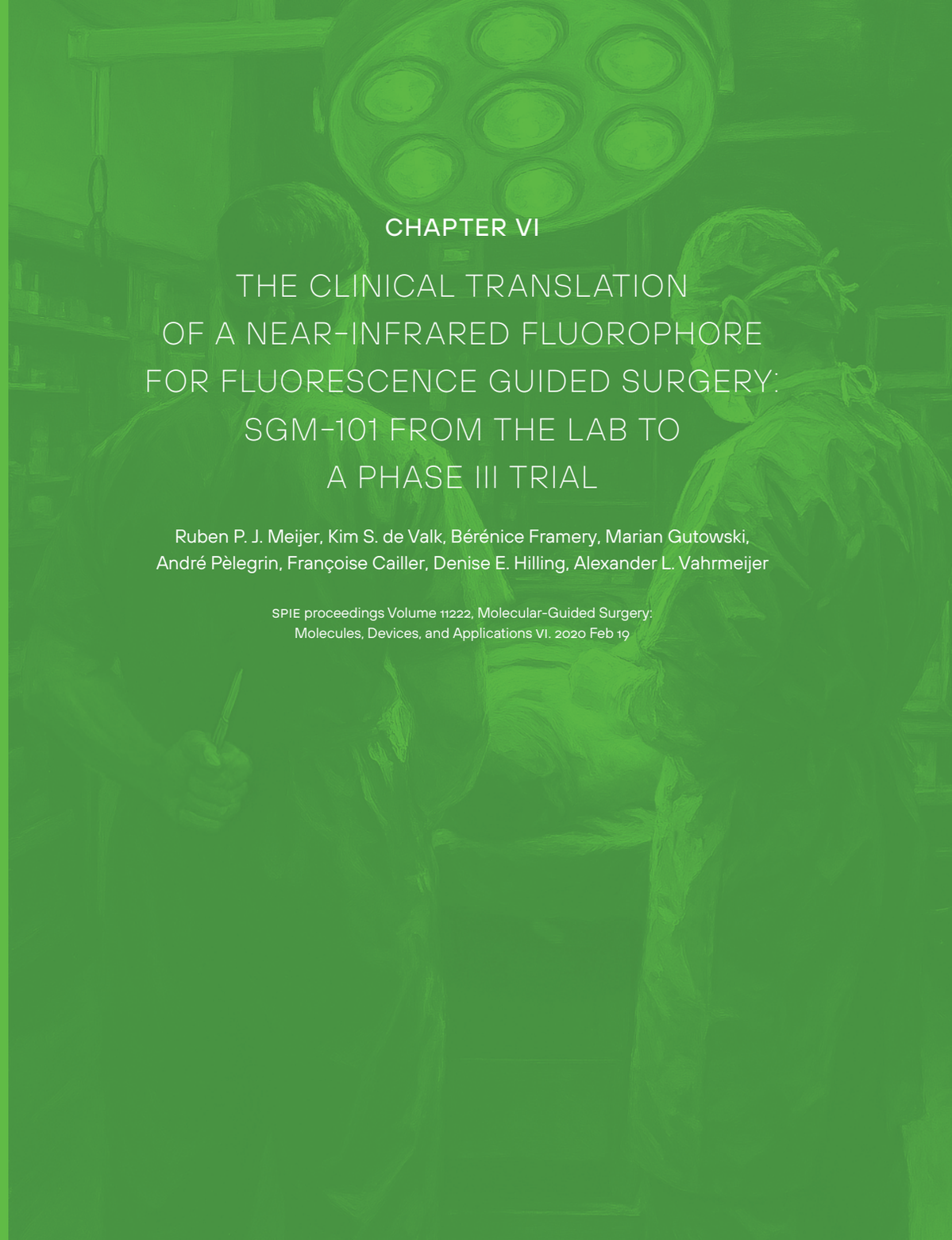
PART 2

INTRAOPERATIVE IMAGING USING SGM-101; A TUMOR TARGETED NIR FLUOROPHORE



CHAPTER VI

THE CLINICAL TRANSLATION OF A NEAR-INFRARED FLUOROPHORE FOR FLUORESCENCE GUIDED SURGERY: SGM-101 FROM THE LAB TO A PHASE III TRIAL

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Abstract

Near-infrared (NIR) fluorescence imaging is a promising intraoperative technique for real-time visualization of tumor tissue during surgery. The process of clinical translation of novel fluorescent agents is an essential part in the evolution of NIR fluorescence guided surgery. Poor visualization of tumors during surgery is one of the major challenges surgeons often face in oncologic patients, mainly due to the improved neo-adjuvant treatment patients receive. In these cases, NIR fluorescence imaging with the use of tumor-targeted fluorescent agents can play an essential role and help provide better oncologic results or patient outcomes. However, before this technique can be implemented in standard of care, optimal tumor-targeted fluorescent agents need to be developed and novel fluorescent agents need to undergo a successful process of clinical translation. Here we describe the clinical translation of SGM-101, a fluorescent anti-CEA monoclonal antibody.

Introduction

Surgery is the most important therapy for patients with colon, rectum or pancreas cancer. Complete resection, which is a crucial factor for patient prognosis, is challenging as surgeons have to rely on the visual appearance and palpation of tissue to discriminate between tumor and normal tissue. Consequently, incomplete resection of malignant tissue or unnecessary removal of healthy tissue may occur. This problem may become bigger as open surgery is increasingly replaced by minimal invasive surgery. In these cases, or complex open surgeries, NIR intraoperative imaging techniques can be of added value. Intraoperative NIR fluorescence imaging is an evolving technique that combines the use of a fluorescent agent with a dedicated NIR camera system, to allow real-time visualization of lymph nodes, tumor tissue and/or vital anatomic structures for surgical guidance.[1] Particularly the use of tumor-specific markers coupled to fluorescent imaging moieties show great potential to improve the intraoperative tumor staging and possibly allow more radical tissue resections.

Carcinoembryonic antigen (CEA) is a tumor-specific marker that is highly expressed in several tumors of epithelial origin (such as colorectal and pancreas cancer) while it is minimally expressed in normal tissue. Anti-CEA monoclonal antibodies have been used in more than 100 clinical studies without any toxicity concerns. In addition, it has been shown that it is possible to link an anti-CEA monoclonal antibody to a NIR fluorophore. The compound that will be discussed in this paper is SGM-101, a CEA-specific antibody conjugated to the fluorophore BM104, developed by SurgiMab (Montpellier, France). The hypothesis is that, following preoperative intravenous (IV) administration of SGM-101 in patients with colon, rectum or pancreas cancer, SGM-101 will bind to CEA expressing cancer cells, consequently enhancing malignant tissue with the use of a NIR fluorescence imaging system. Due to this, surgeons will be able to visualize tumors in real-time during surgery and thereby increase the chance of complete resections.

This article gives an overview of the clinical translation of SGM-101, starting with the preclinical work all the way to the currently enrolling phase III studies.

Clinical translation of sgm-101

In the past years SGM-101 has successfully been translated from the preclinical setting to a currently enrolling international phase III study. As one of the first tumor specific fluorescent antibodies, this path towards clinical approval is still new and lacking standardization. The translational route of SGM-101 can serve

as a platform for discussion about standardizing the clinical methodology in fluorescence-guided surgery research.

PRECLINICAL WORK

Preclinical studies are of great importance, as it acts as a preliminary study to determine whether further studies are consequential. Most importantly, they are crucial in the step towards the clinic (i.e. humans) as the preclinical data is needed to validate and determine the toxicity of a novel agent before it gets exposed to humans. The studies provide useful information regarding the toxicology, as well as the initial diagnostic value of a new agent. Once the novel agent has passed the validation process of whether it is useful for further employment, it will undergo the Good Manufacturing Practice (GMP) production and release by a qualified person so that it can be used in humans. The GMP batch will yet again undergo, more extensive, toxicity testing in animals.

The preclinical work of SGM-101 has demonstrated SGM-101's efficacy in binding CEA *in vitro* and *in vivo* in human CEA expressing mouse models. Stability testing showed no amounts of the dye used for SGM-101 released after up to 96 hours of incubation. Furthermore, biodistribution studies showed high values of SGM-101 at the tumor site and almost none in normal tissue. Moreover, the injection of SGM-101 was well tolerated in all mouse models, Wistar rats and beagle dogs during the *in vivo* pharmacology studies. The lowest NOAEL (no observed adverse effect level) was determined in dogs at 5 mg/kg per day (which corresponds to a 15-fold the intended maximum clinical dose).[2]

The final preclinical study of SGM-101 showed the detection of tumor nodules in three different colon cancer models. Positive predictive values ranged from 90.24 (nodules <1 mg) to 99.04% (nodules >10mg). Free BM105 dye (BM104 with an activated ester for conjugation to the antibody) and an irrelevant conjugate did not induce any NIR fluorescence.[3]

These preclinical data formed the solid base for conducting the first clinical studies with SGM-101 in CEA-expressing tumors.

FIRST-IN-HUMAN

After completion of the preclinical studies and approval by the medical ethics committee, the first major step in the clinic could be performed, which is the exposure of the agent in humans. First-in-human studies with novel fluorescent agents can be performed in either healthy volunteers or in a selected group of the target patient population. SGM-101 was first injected in 18 patients with peritoneal metastasized cancer. All doses, including the maximal dose of 15 mg, were well tolerated; no dose-limiting toxicity has been recorded during the dose escalation phase and none of the adverse events observed have been considered related to the investigational medicinal product.

COLORECTAL CANCER

After first-in-human studies it is important to determine the right dose and dosing interval, respecting the maximum dose tested in previous studies. Nowadays, the only quantitative endpoint for (tumor) visibility using NIR fluorescence is the tumor-to-background ratio (TBR). Nevertheless, there is no consensus about the cut-off points for a sufficient TBR.

Boogerd *et al.* included 26 patients in a multicenter trial, to assess the safety, tolerability and feasibility of SGM-101 in detecting colorectal cancer. SGM-101 did not cause any treatment-related adverse events and showed good intraoperative results (Figure 1). A mean intraoperative TBR of 1.6 was found and the surgeons changed their initial surgical plan, based on SGM-101 NIR assessment, in 6 patients. They reported a sensitivity of 98%, specificity of 62% and accuracy of 84%.[4]

In order to find the optimal dose and dosing time to surgery the study by Boogerd *et al.* got expanded by de Valk *et al.* (Unpublished data). The optimal dose of 10 mg, 4 days prior to surgery, was determined in 36 patients. Moreover, comparable intraoperative results were found.

PERITONEAL METASTASES

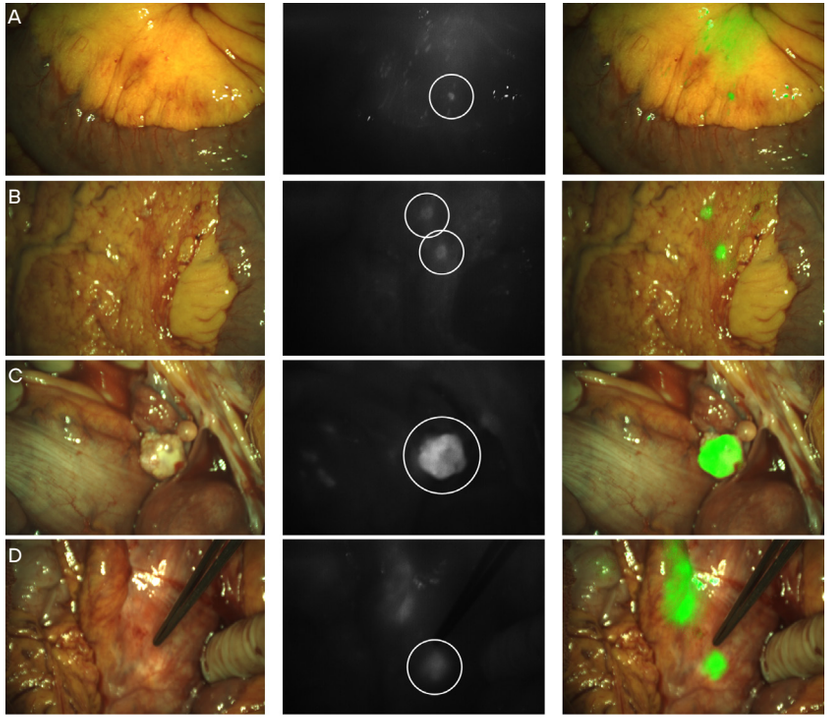
An exploratory multicenter pilot study was performed in 14 patients with peritoneal metastasized colorectal cancer who were scheduled for hyperthermic intraperitoneal chemotherapy (HIPEC).[5] Due to too extensive disease, two patients only underwent explorative laparotomy, without HIPEC.

In the remaining 12 patients, a total of 103 lesions were resected. Sixty-five of the 66 malignant lesions were fluorescent (true positive) and 23 of the 37 benign lesions showed no fluorescence (true negative), resulting in a sensitivity of 98.5% and a specificity of 62.2%. The study demonstrated a positive predictive value of 82.3%, a negative predictive value of 95.8% and an accuracy of SGM-101 of 85.4%.

The peritoneal cancer index (PCI) changed in 7 out of 12 patients due to fluorescence imaging. In six patients the PCI increased under fluorescence, which was accurate in four, confirmed by histopathological analysis. In those four patients the score increased with 1 or 2 points, but did not result in termination of the surgical procedure. According to Dutch guidelines, a planned surgical procedure is terminated when a PCI of more than 20 is determined or more than 5 regions are affected. The one case with a decrease in PCI (PCI 5 to 4) due to fluorescence was correct, but definitive pathological analysis concluded a PCI of 3.

Although the detection of extra tumor tissue might not influence the PCI or alter the surgery, SGM-101 still showed additional benefit in 5 out of 12 patients. Detection of those extra lesions still resulted in a more complete cytoreduction, which might be beneficial on the oncologic outcome.

FIGURE 1 Intraoperative images from NIR detected additional lesions.
All lesions were undetected or not suspicious for malignancy in white light, but detected by NIR fluorescence and confirmed malignant by histopathological analysis. (A) Fluorescent hotspot in the bowel mesentery. (B) Two small tumor hotspots in the omentum. (C) Intense fluorescent signal in the right ovary. (D) Retroperitoneal lymph nodes, visible below a layer of overlying tissue.



LIVER METASTASES

In total, 11 patients with liver metastases were included (Unpublished data, Meijer *et al.*). Eight patients had liver metastases from colorectal origin and three patients from pancreatic origin. In those 11 patients all malignant lesions were fluorescent. This study showed no additional lesions or alterations due to SGM-101. Nevertheless, these results are promising since all malignant liver lesions were fluorescent and only a very limited number of patients were studied for the visualization of liver metastases with SGM-101. One possible benefit of SGM-101 might be lowering the number of positive resection margins in liver matastasectomies, since recent reports still show 28% resection margin positivity.[6]

PANCREATIC CANCER

Twelve patients were included in the first study using SGM-101 for pancreatic cancer.[7] *In vivo* results showed a mean TBR of 1.6 and *ex vivo* with the Pearl imager (LI-COR, Lincoln, USA) a mean TBR of 3.2 was measured. Only 7 tumors were resected and six were confirmed as adenocarcinomas. One lesion was deemed false-positive since pathological assessment showed a premalignant lesion (intraductal papillary mucinous neoplasm with low-grade dysplasia). In the remaining patients the surgical procedure was abandoned due to irresectability or metastases.

Future perspectives

The abovementioned results offer a great basis for new projects, both confirming the previous results in phase III studies, as well as extending them to new oncological fields. During the preparation of phase III studies in fluorescence-guided surgery, new challenges emerge. One of the biggest challenges is choosing proper endpoints, in the constantly changing field of oncology. Not only the procedures themselves change (i.e. robot-assisted surgery), but also other treatment strategies, like (neo)adjuvant therapy are subject to change. With this perspective, multiple follow-up studies are being executed with SGM-101.

PHASE III

Currently two large phase III studies are enrolling colorectal cancer patients; 1) "The performance of SGM-101 for the delineation of primary, recurrent and metastatic colorectal cancer (SGM-CLIN03; EudraCT# 2018-000151-40 and IND# 134725)" and 2) "SGM-101 in Locally Advanced and Recurrent Rectal Cancer (SGM-LARRC; EudraCT# 2019-001748-23)".

SGM-CLIN03 is an international, semi-blinded, randomized, controlled clinical study including patients with different advanced staged colorectal cancer (T4 colon, T3/4 rectal, peritoneal metastasized and recurrent colorectal cancer). In total 300 patients will be randomized (4:1 for SGM-101:placebo) in 10 centers in Germany, Italy, the Netherlands and the United States. The primary objective is to show benefit in terms of additional resections only identified by fluorescence and confirmed malignant by histopathological analysis.

SGM-LARRC is a Dutch national multicenter study, supported by the Dutch Cancer Society (KWF), including patients with locally advanced or recurrent rectal cancer in parallel arms. In these patients, clear resection margins are key in terms of overall and disease-free survival. Despite the introduction of neoadjuvant therapy, a positive resection margin is found in 25% of the locally advanced and 50% of the recurrent rectal cancer cases.[8-14] Therefore, the primary endpoint is based on the clinical benefit of fluorescence-guided surgery combined with SGM-101 as the intraoperative imaging agent. The corresponding endpoint is the rate of patients with R0 resections.

LUNG CANCER

In addition, new areas for the use of SGM-101 are being explored. This has led to the development of two studies in lung cancer; "SGM-101 in colorectal lung metastases (SGM-CLM; EudraCT# 2019-002044-24)" and "SGM-101 in primary lung cancer (SGM-CLIN06; IND# 145137)".

Despite novel therapeutic developments curative surgery is still an important treatment option for patients with colorectal lung metastases. Complete resection (R0) is crucial, leading to 46% 5-year overall survival versus 20% in the R1 group. Unfortunately, one in 10 patients will belong to the R1 group.[15] SGM-CLM will enroll patients scheduled for the resection of colorectal lung metastasis in multiple Dutch hospitals. In this feasibility study a maximum of 15 patients will be included in different dosing groups. The primary endpoint will be the concordance between the pathology result with respect to the presence of malignancy and the intraoperative fluorescence assessment. This multicenter Dutch study is expected to start enrolling patients in mid-2020.

Up to 72% of the lung and pleural malignancies express CEA, therefore making it an interesting application for SGM-101.[16] As a proof of concept, SGM-CLIN06 will aim to include 10 to 20 patients in a single-center study, to determine the sensitivity of SGM-101 in the detection of lung nodules. Inclusion is expected to start in the first half of 2020, at the University of Pennsylvania (Philadelphia, USA).

Conclusion

SGM-101 is the first fluorescent agent being tested in phase III studies for colorectal cancer. The promising results in primary, recurrent and metastasized colorectal cancer formed the base for this important step. Moreover, the use of standardized methodology in the field of fluorescence-guided surgery will be of added value for regulatory approval.

REFERENCES

1 Vahrmeijer AL, Hutteman M, van der Vorst JR, van de Velde CJ, Frangioni JV. Image-guided cancer surgery using near-infrared fluorescence. Nat Rev Clin Oncol. 2013;10(9):507-18.

2 Framery B, Gutowski M, Dumas K, Evrard A, Muller N, Dubois V, *et al.* Toxicity and pharmacokinetic profile of SGM-101, a fluorescent anti-CEA chimeric antibody for fluorescence imaging of tumors in patients. Toxicol Rep. 2019;6:409-15.

3 Gutowski M, Framery B, Boonstra MC, Garambois V, Quenet F, Dumas K, *et al.* SGM-101: An innovative near-infrared dye-antibody conjugate that targets CEA for fluorescence-guided surgery. Surg Oncol. 2017;26(2):153-62.

4 Boogerd LSF, Hoogstins CES, Schaap DP, Kusters M, Handgraaf HJM, van der Valk MJM, *et al.* Safety and effectiveness of SGM-101, a fluorescent antibody targeting carcinoembryonic antigen, for intraoperative detection of colorectal cancer: a dose-escalation pilot study. Lancet Gastroenterol Hepatol. 2018;3(3):181-91.

5 Schaap DP, de Valk KS, Deken MM, Meijer RPJ, Burggraaf J, Vahrmeijer AL, *et al.* Carcinoembryonic antigen-specific, fluorescent image-guided cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer. Br J Surg. 2020.

6 Fretland AA, Dagenborg VJ, Bjornelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW, *et al.* Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Ann Surg. 2018;267(2):199-207.

7 Hoogstins CES, Boogerd LSF, Sibinga Mulder BG, Mieog JSD, Swijnenburg RJ, van de Velde CJH, *et al.* Image-Guided Surgery in Patients with Pancreatic Cancer: First Results of a Clinical Trial Using SGM-101, a Novel Carcinoembryonic Antigen-Targeting, Near-Infrared Fluorescent Agent. Ann Surg Oncol. 2018;25(11):3350-7.

8 Debove C, Maggiori L, Chau A, Kanso F, Ferron M, Panis Y. Risk factors for circumferential R1 resection after neoadjuvant radiochemotherapy and laparoscopic total mesorectal excision: a study in 233 consecutive patients with mid or low rectal cancer. Int J Colorectal Dis. 2015;30(2):197-203.

9 Gebhardt C, Meyer W, Ruckriegel S, Meier U. Multivisceral resection of advanced colorectal carcinoma. Langenbecks Arch Surg. 1999;384(2):194-9.

10 Frykholm GJ, Pahlman L, Glimelius B. Combined chemo- and radiotherapy vs. radiotherapy alone in the treatment of primary, nonresectable adenocarcinoma of the rectum. Int J Radiat Oncol Biol Phys. 2001;50(2):427-34.

11 Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers GJ, Daniels-Gooszen AW, *et al.* Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008;15(7):1937-47.

12 Dresen RC, Kusters M, Daniels-Gooszen AW, Cappendijk VC, Nieuwenhuijzen GA, Kessels AG, *et al.* Absence of tumor invasion into pelvic structures in locally recurrent rectal cancer: prediction with preoperative MR imaging. Radiology. 2010;256(1):143-50.

13 Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol. 2007;14(2):447-54.

14 Heriot AG, Byrne CM, Lee P, Dobbs B, Tilney H, Solomon MJ, *et al.* Extended radical resection: the choice for locally recurrent rectal cancer. Dis Colon Rectum. 2008;51(3):284-91.

15 Casiraghi M, De Pas T, Maisonneuve P, Brambilla D, Ciprandi B, Galetta D, *et al.* A 10-year single-center experience on 708 lung metastasectomies: the evidence of the "international registry of lung metastases". J Thorac Oncol. 2011;6(8):1373-8.

16 Wang J, Ma Y, Zhu ZH, Situ DR, Hu Y, Rong TH. Expression and prognostic relevance of tumor carcinoembryonic antigen in stage IB non-small cell lung cancer. J Thorac Dis. 2012;4(5):490-6.