Editorial Commentary

Disappearing colorectal liver metastases: the importance of radiographic-pathologic correlation in oncology care

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The dual centre retrospective study by Chávez-Villa *et al.* assessed the rate of radiologically missed, occult colorectal liver metastases (CRLM) on pathologic evaluation of total hepatectomy specimens (1). Of the 14 patients who underwent liver transplantation for unresectable CRLM, 7 (50%) patients were deemed to have radiographically viable tumours, as defined by fluorodeoxyglucose positron emission tomography (FDG-PET) avidity; the remainder had complete radiographic response. However, on pathologic assessment, 11 (78.6%) were noted to have viable tumours, with a median of two viable tumours, ranging from 0.2 to 6.5 cm in size. Three (21.4%) patients had complete radiological and pathological responses. Additionally, 9 (64.2%) had undiagnosed metastases on the explant pathology, with at least 22 unaccounted viable tumours. Of note, the majority of these patients received at least two lines of chemotherapy, with a median of 1.4 years on systemic chemotherapy, and concomitant targeted therapy. Additionally, five of these patients had hepatic artery infusion pump (HAIP), and six patients had surgical resection, prior to liver transplantation. The median time between diagnosis of CRLM to liver transplantation was 2 years, and 12 (85.7%) patients underwent living donor liver transplantation while the other 2 received a full graft. In 6 patients (42.9%), the primary indication for liver transplantation was liver failure secondary to oncologic treatment. Despite maximal cytotoxic therapy resulting in liver failure, 50% had residual disease on pathology. The mean time between FDG-PET scan and liver transplantation was 2.2 months. This study demonstrated that despite a highly selective population, with extensive time from diagnosis to transplantation, and frequent contemporary pre-treatment and preoperative radiographic assessment using high sensitivity multiphasic computed tomography (CT) or magnetic resonance imaging (MRI) and PET scans, there was still a high rate of undiagnosed or viable tumours on the explant specimens even in the cases where a complete radiological response was reported. This underscores the vital importance of radiological-pathological correlation in patients with liver metastases from colorectal cancer (CRC).

Our living donor liver transplant (LDLT) trial for CRLM at the Toronto General Hospital has now performed a total of 15 transplants, with available FDG-PET CT and pathology reports for evaluation (2). In this trial, patients are continued on chemotherapy up till 6 weeks before their

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transplant and are candidates for LDLT assuming that they do not have extrahepatic disease, the disease downstages and becomes resectable, or there is disease progression on subsequent assessment. All patients in this trial underwent LDLT for the primary indication of unresectable bilobar CRLM, and had a PET scan within 6 months prior to transplant. The systemic therapy regimens, pre-transplant FDG-PET CT reports, and the post-transplant explant pathology are summarized in *Table 1*. Five (33%) patients had insertion of HAIP. Two patients were from out of province and had missing radiographic reports, but the PET scan results were summarized in clinical notes. Overall, radiographic assessment underrepresented the number and viability of tumours seen on pathology. There were two patients where no viable disease was confidently seen on PET, whom on pathology still had significant residual disease. This further validates the findings of Chávez-Villa *et al.* (1) in a more homogenous population, reinforcing the lack of complete radiographic-pathologic correlation post-treatment in patients with CRLM.

High-resolution diagnostic and molecular imaging including CT, MRI, and PET scans provide a central role in the early detection, diagnosis, staging, and management of neoplasms (3). However, histopathology in the form of biopsies or surgical specimens are the gold standard tool to validate imaging results and best diagnose or characterize tumours (4). For instance, treatment of breast and prostate cancers heavily rely on the synergy of anatomical imaging and immunohistochemical pathologic analysis (5,6). Advances in molecular imaging such as PET-radiolabelled molecules may increase prediction and prognosis capabilities, improving radiographic-pathologic correlation (7). Currently however, the combination of imaging and pathology plays a crucial, commensal role in the provision of personalized oncologic care.

Most patients with CRLM will receive chemotherapy, especially in the context of multiple lesions and bilateral disease (8). Preoperative chemotherapy can result in radiographic disappearance of disease, i.e., disappearing CRLM (dCRLM). This provides for a therapeutic dilemma, as up to 83% of patients can have residual active cancer on pathologic evaluation, which in turn leads to high rate of disease recurrence or progression (9). However, "blind" resections do not guarantee that diseased sites will be removed and can result in increased morbidity and mortality. Consequently, there are inconsistencies in the management decisions around dCRLM (10). Some studies demonstrated that after chemotherapy, MRI or contrast-enhanced intraoperative ultrasound may enhance detection accuracy for assessing dCRLM (11), with improved prognosis in patients with initially unresectable CRLM who underwent curative resection following preoperative chemotherapy. In this new era where liver transplantation has demonstrated better oncological outcomes than systemic chemotherapy alone in the randomized Transmet trial (12); in our opinion, patients with initially unresectable liver metastases that become resectable, with missing metastases (and no plan to resect those) should be considered for liver transplantation. It is important therefore, to assess patients and scans at the time of diagnosis.

Major pathologic response following neoadjuvant therapy has been demonstrated to have an important role in oncologic survival outcomes. For instance, in patients with non-small cell lung cancer, the use of neoadjuvant chemoradiation followed by lobectomy, with demonstrated pathologic complete response has demonstrated greater overall survival, compared to non-pathologic complete response (P<0.001) (13). This has further been highlighted in the recent randomized phase 3 trial (NADINA) comparing patients with resectable stage III melanoma, who underwent neoadjuvant ipilimumab plus nivolumab followed by surgery and response-driven adjuvant therapy versus surgery and adjuvant nivolumab (14). In this trial, 59% of patients had major pathologic response, and the estimated recurrence-free survival was 95.1% in the patients who had major pathologic response, compared to 57% in the patients who were limited response (>50% residual viable tumour) (14). Similarly, in patients with hepatocellular carcinoma who underwent neoadjuvant immunotherapy, 33 (32%) of patients demonstrated major pathologic response, and radiological overall response was associated with major pathologic response 23/31 (74%), but 10/33 (30%) of pathologic response was not predicted by radiologic response (15). This highlights the importance of pathologic response in survival outcomes of various malignancies.

Management of CRLM relies heavily on the commensal relationship between radiographic imaging and pathologic correlation. This is true particularly as the majority of patients with CRLM will receive perioperative chemotherapy followed by restaging of disease, and the radiographic findings will then guide subsequent management. More recently with the advent of molecular imaging including FDG-PET scans, we can gain greater information for the diagnosis, staging, and management of neoplasms. The highlighted studies demonstrate that despite disappearance of radiographic evidence of disease,

Table 1 Summary of systemic and locoregional therapy, pre-transplant radiographic report, and explant pathology report of patients who underwent LDLT for the primary indication of unresectable CRLM at a single large North American centre

No.	Chemotherapy type, line, number of cycles prior to initial assessment, total cycles pre-transplant	HAIP (yes/no), time from insertion to transplant (months)	Pre-transplant radiographic findings (FDG-PET CT)	Explant pathology
1	FOLFIRI/panitumumab; first; 10 cycles; total: 25 cycles	No	3×; poorly defined calcified masses in liver seg 2/3/4 5.1 cm × 3.3 cm, seg 7/6 3.1 cm × 2.8 cm, and subcapsular seg 5/6 small focus of uptake	3× foci with ~50% treatment effect
2	FOLFIRI/bevacizumab; first; 18 cycles; total: ~60 cycles	Yes; 25.0	3×; dominant lesion seg 7/8 4.1 cm × 1.7 cm, seg 6 4.8 cm × 2.3 cm, seg 2/3 deposit rim mildly increased activity	6× foci with variable treatment effect
3	FOLFIRINOX/panitumumab; first; 12 cycles; total: 21 cycles	Yes; 14.6	3–4× foci mod suspicious for viable mets	6× foci + satellites, 95–100% necrosis/fibrosis
4	FOLFIRI/panitumumab; first; 12 cycles; total: ~20 cycles	No	1× foci seg 4a	2× foci, one viable <50% treatment effect
5	FOLFIRI/bevacizumab; first; 14 cycles; total: 30 cycles	No	~3×; small residual deposits, small lesions seg 6, seg 2/3, small deposit all low-uptake, significant partial response	14× foci, 90–100% necrosis
6	FOLFIRI/bevacizumab; first; 19 cycles; total: 32 cycles	Yes; 19.0	~1×; subtle focus seg 5/6 indeterminate, tiny focus seg 2, previously seen foci decreased or resolved indicating response	11× foci, rare viable cells
7	FOLFOX; second; 12 cycles; total: ~32 cycles	No	1×; cystic lesion in remnant liver	1× foci, <50% necrosis
8	FOLFIRI/bevacizumab; second; 3 cycles; total: ~16 cycles	No	5×; FDG-avid lesions, 2 seg 2/4, seg 2/3, 2 in seg 4B	5× foci, 3 lesions >50% necrosis; 2 lesions <50% necrosis
9	FOLFIRI/bevacizumab; first; 15 cycles; total: ~29 cycles	No	Missing report some metastases	2× foci, ~50% necrosis
10	FOLFIRI/panitumumab/ bevacizumab; first; 43 cycles; total: ~54 cycles	No	Multiple FDG-avid mets, increased FDG accumulation, largest seg 2 3.4 cm, seg 5/6 2.4 cm, no new lesions	8× foci, 6 lesions >50% treatment effect (3/6 + trans-capsular extension), 1 lesion >90% treatment effect, 1 lesion <50% treatment effect
11	FOLFIRI/panitumumab; first; 8 cycles; total: ~31 cycles	Yes; 20.9	3×; seg 3 0.8 cm, seg 3 1 cm, and focus of uptake seg 7	5× foci, <50% necrosis and focal bile duct invasion
12	Capecitabine/irinotecan/ bevacizumab; third; 23 cycles; total: ~30 cycles	No	1×; 1.4 cm × 1.0 cm FDG avid lesion	2× foci, complete necrosis; no viable tumour
13	FOLFIRI/panitumumab; first; 20 cycles; total: ~30 cycles	Yes; 18.5	Missing report 0; no hypermetabolic activity in the liver	Multiple foci, >85% necrosis
14	FOLFIRI/panitumumab; first; 15 cycles; total: 27 cycles	No	0; no suspicious nodules; residual hypodense 1.2 cm lesion not FDG avid	1×, <50% necrosis; MVI (LHV) and PNI
15	FOLFIRI/panitumumab; first; 7 cycles; total: ~37 cycles	No	1×; seg 2.3 foci of uptake	2× foci, <25% necrosis and bile duct invasion

LDLT, living donor liver transplant; CRLM, colorectal liver metastases; HAIP, hepatic artery infusion pump; FDG, fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; FOLFIRI, folinic acid, fluorouracil, and irinotecan; FOLFIRINOX, folinic acid, fluorouracil, irinotecan, and oxaliplatin; FOLFOX, folinic acid, fluorouracil, and oxaliplatin; seg, segment; MVI, macrovascular invasion; LHV, left hepatic vein; PNI, perineural invasion.

this does not necessarily correlate with complete pathologic response. Majority of patients continue to have some viable disease, and if not completely removed can result in progression or "recurrence" of disease. Utilization of both radiographic studies and pathological assessment together plan a mutual role in providing optimal cancer care, especially in diseases such as CRLM, that are heavily reliant also on perioperative therapy.

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Footnote

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