



¹⁸F-fluorodeoxyglucose positron emission tomography for intrahepatic cholangiocarcinoma N- and M-staging: should guidelines recommend it at last?

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We really appreciated Lin *et al.*'s "*The influence of ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography on the N- and M-staging and subsequent clinical management of intrahepatic cholangiocarcinoma*" in *HepatoBiliary Surgery and Nutrition* (1). A 291-patient population affected by intrahepatic cholangiocarcinoma (ICC) was retrospectively analyzed with the aim of assessing the accuracy of preoperative staging and treatment reallocation by ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography (¹⁸F-FDG PET/CT) (1). Through a comparison of conventional imaging examinations [computed tomography (CT) and/or magnetic resonance imaging (MRI)] with ¹⁸F-FDG PET/CT, the latter recorded a higher diagnostic accuracy as concerned both lymph node (LNM) and distant metastases (DM) (1). In particular, authors highlighted more significant results in terms of sensitivity (LNM: 83% *vs.* 70.5%; DM: 87.8% *vs.* 67.6%) and diagnostic accuracy (LNM: 86.3% *vs.* 73.2%; DM: 93.5% *vs.* 89.3%) for both types of metastases, in addition to more outstanding specificity (88.3% *vs.* 74.9%) just in LNM (1). Overall, through inclusion of ¹⁸F-FDG

PET/CT, the rate of diagnostic accuracy in preoperative staging increased from 60.1% to 71.8% (1). Furthermore, treatment strategies for 5.8% cases changed to the point of avoiding unnecessary surgery (1). Therefore, authors came to the conclusion that the use of ¹⁸F-FDG PET/CT should be recommended in preoperative staging, due to the high rate of metastases for ICC (1).

Recently, Gavriilidis *et al.* analyzed the quality of 13 guidelines on the management of cholangiocarcinoma using the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument and concluded that it was generally poor and based on relatively low-quality evidence (2). Although authors' conclusions appear to be of significant importance, above mentioned guidelines remain the national and international point of reference in treating cholangiocarcinoma, nowadays. As recently Fong *et al.* have pointed out, such guidelines disagree in terms of PET in preoperative ICC staging (3). As a matter of fact, National Comprehensive Cancer Network (NCCN), British Society of Gastroenterology (BSG), European Association for the Study of the Liver (EASL)/International Liver Cancer

Association (ILCA), Japanese Society of Hepato-Biliary-Pancreatic Surgery (JSHBPS), Italian Cholangiocarcinoma Working Group** and European Society for Medical Oncology (ESMO) guidelines underline the potential role of PET in ICC staging while not routinely recommending it due to the lack of adequate validation (3-8).

Evidence regarding the real benefit of ¹⁸F-FDG PET in ICC staging is lacking. In current scientific literature, the most relevant information stem from some recent meta-analyses (9-11). In 2018, Hu *et al.* analyzed 18 studies (totaling 1,037 patients) in which preoperative staging of cholangiocarcinoma was performed using ¹⁸F-FDG PET in addition to conventional imaging examinations (9). Study results showed that ¹⁸F-FDG PET had good diagnostic accuracy for both LNM [pooled diagnostic odds ratio (OR): 11.34 and summary receiver operating characteristic (SROC)/area under the curve (AUC): 0.8584] and DM (pooled diagnostic OR: 47.68 and SROC/AUC: 0.9717) in particular (9). In 2019, Lamarca *et al.* introduced a similar meta-analysis focusing on methodology and scope but led to more extensive and detailed results (10). According to a 46-study meta-analysis (totaling 2,125 patients) use of ¹⁸F-FDG-PET should be endorsed for LNM (pooled diagnostic OR: 11.358 and SROC/AUC: 0.8519) and DM (pooled diagnostic OR: 44.42 and SROC/AUC: 0.9253) diagnosis (10). Overall, the pooled rate of treatment change (random effects model) recorded 15% (95% CI: 11–20%) (10). Finally, in 2020 Huang *et al.*'s meta-analysis (32 studies, totaling 1,626 patients) aimed at comparing MRI with ¹⁸F-FDG PET/CT, in order to evaluate diagnostic and staging accuracy in the cholangiocarcinoma (11). Overall, compared with MRI, ¹⁸F-FDG PET/CT seemed to be more effective in assessing LNM in patients with cholangiocarcinoma (pooled diagnostic OR: 3.83 and SROC/AUC: 0.69 for MRI *vs.* pooled diagnostic OR: 11.90 and SROC/AUC: 0.77 for ¹⁸F-FDG PET/CT), although negative results should not serve as exclusion criteria of lymph node dissection (11). Moreover, results showed that ¹⁸F-FDG PET/CT imaging is beneficial to diagnosing DM (pooled diagnostic OR is not available and SROC/AUC is 0.90), although it remains useless to rule out metastatic lesions, meaning that some

patients affected by DM might be misdiagnosed as negative ones (11). In all three of the aforementioned meta-analyses, the relevant results observed in the pooled population were confirmed in ICC subgroup (9-11). However, the studies were marked by significant heterogeneity, including but not limited to study design (9-11).

On this background, data suffice to include ¹⁸F-FDG-PET into patient pathway, especially for N- an M-staging, when identification of occult disease sites would justify a change in patient treatment (e.g., surgery/local therapies) (10).

Starting from January 2020, multidisciplinary team for pancreatobiliary diseases at our institution (Azienda USL-IRCCS di Reggio Emilia, Italy) decided to introduce ¹⁸F-FDG-PET, in addition to conventional imaging examinations (abdomen CT and/or MRI), for staging patients affected by resectable ICC (as defined in radiological review performed by a radiologist skilled in hepato-biliary-pancreatic disorders) for the purpose of ruling out non-regional LNM or DM, that could modify therapeutic indication. From January 2020 to June 2022, 9 cases of pathologically proven ICC were discussed. In conventional imaging examinations, 5 patients were diagnosed as already affected by DM, while in 4 patients resectable ICC was diagnosed, and 2 of them showed DM (peritoneal carcinomatosis) and non-regional LNM (para-aortic and mediastinal LN), respectively, through ¹⁸F-FDG-PET. Therefore, based on ¹⁸F-FDG-PET results, multidisciplinary team decided to shift from surgical therapy to systemic one.

In conclusion, ICC is a highly aggressive disease marked by a post-operative poor prognosis (5-year overall survival after R0 resection is 15–40% and 80% patients develop intrahepatic recurrences) (12). Surgical resection with negative resection margins remains the gold standard treatment (12). To sum up, a correct preoperative staging of disease seems paramount to avoid unnecessary surgery. The most common imaging methods used to diagnose and stage ICC include ultrasound (US), CT and MRI/magnetic resonance cholangiopancreatography (MRCP) (13,14). To date, main international guidelines have never recommended ¹⁸F-FDG-PET in ICC staging (3-8). Despite lack of robust evidence, ¹⁸F-FDG-PET diagnostic accuracy

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in LNM and DM seems to be meaningful and capable of changing ICC patients' management after "standard" staging with CT and/or MRI alone (1,10). Therefore, we would like to suggest ¹⁸F-DG-PET in refining the staging of ICC patients, whom conventional imaging examinations have already identified as resectable ones without non-regional LNM and DM.

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Footnote

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