A retrospective analysis of capecitabine-induced imaging hepatic steatosis in metastatic breast cancer: prevalence and resolution

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Background

Capecitabine is a valid monotherapy option in multiple metastatic breast cancer (mBC) subtypes[1].

While previously only isolated cases of capecitabine-related hepatic steatosis have been reported in the literature, including a single case report of capecitabine-induced hepatic steatosis and studies documenting this toxicity with intravenous 5-FU[2,3], its prevalence remains unknown. Traditional monitoring relies primarily on biochemical tests, which may not fully capture hepatic changes.

Our aim was to evaluate the prevalence of capecitabine-related hepatic steatosis and determine whether routinely performed [^{18}F]FDG PET/CT could quantify hepatic changes during capecitabine treatment, including in patients without visually evident steatosis.

Methods and Materials

We conducted a retrospective analysis of patients with mBC treated with capecitabine between 2014 and 2021 at Gustave Roussy Cancer Campus. Clinico-biological variables (age, BMI, metastatic sites, therapy line, dihydropyrimidine dehydrogenase (DPD) testing, biochemical liver tests) at baseline were collected. Baseline [^{18}F]FDG PET/CT, first evaluation (<180 days), and last [^{18}F]FDG PET/CT scans under capecitabine treatment were analyzed to assess hepatic steatosis prevalence. Hepatic steatosis was defined by visual assessment as a decreased liver attenuation relative to spleen and/or increased hepatic vessel visualization on unenhanced CT. Finally, hepatic changes were quantified using standardized uptake values (SUV) on PET images and Hounsfield units (HU) on CT images. Statistical analyses were performed using R software (version 4.4.3).

Results

The study cohort included 183 patients with mBC. Principal characteristics are summarized in **Table 1**. The median age at capecitabine initiation was 67.00 years (IQR: 60.75-71.25), and median BMI was 23.70 kg/m² (IQR: 21.45-27.40). 86.7% of patients received capecitabine as monotherapy. Median treatment duration was 217 days (IQR: 103-405). When available, DPD testing revealed a partial deficit in 8.3%.

DEMOGRAPHICS & TREATMENT	
Age at capecitabine initiation, years (median [IQR])	67.00 [60.75, 71.25]
BMI, kg/m2 (median [IQR])	23.70 [21.45, 27.40]
Cancer subtype (%) Luminal A-B/HER2+/TNBC	70.0/13.3/15.0
Capecitabine monotherapy (%)	86.7
Capecitabine line of treatment (%) 1st/2nd/3rd/≥4th	10.0/31.7/31.7/26.7
Treatment duration, days (median [IQR])	217.00 [103.00, 404.50]
DPD partial deficiency (%) (n=102 tested)	8.3
Total bilirubin, mg/L (median [IQR])	4.50 [3.60, 5.58]
TREATMENT OUTCOMES	
Dose reduction at first evaluation (%)	23.3
Treatment discontinuation due to progression (%)	77.5
BASELINE [^{18}F]FDG PET/CT	
Liver SUVmean (median [IQR])	2.55 [2.27, 2.81]
Liver mean HU (median [IQR])	60.16 [54.83, 65.66]
Metastasis site count (median [IQR])	2.00 [1.00, 3.00]
Metastatic site distribution (%) Bone/Lymph node/Liver/Lung metastases	67.5/33.3/31.7/20.8
Days to first evaluation (median [IQR])	88.50 [70.75, 98.00]

Table 1. *Patient and imaging characteristics (n=120).*

Results

Sequential imaging analysis was available for 120 patients with both baseline and first evaluation [^{18}F]FDG PET/CT scans, and 77 patients at capecitabine discontinuation.

No patients showed hepatic steatosis at baseline. At first evaluation, hepatic steatosis was observed in 3/120 patients (2.5%). All 3 patients with steatosis underwent dose reduction due to other capecitabine toxicities (hand-foot syndrome in 2 patients, general condition deterioration requiring weight-based dose adjustment in 1 patient), resulting in resolution of CT steatosis in 2 patients.

Results

At final [^{18}F]FDG PET/CT, steatosis was present in 4/77 patients (5.2%) and resolved in 3 patients on follow-up imaging after changing treatment line. All patients who developed visible steatosis received capecitabine monotherapy. A representative case demonstrating reversibility is shown in **Figure 1**.

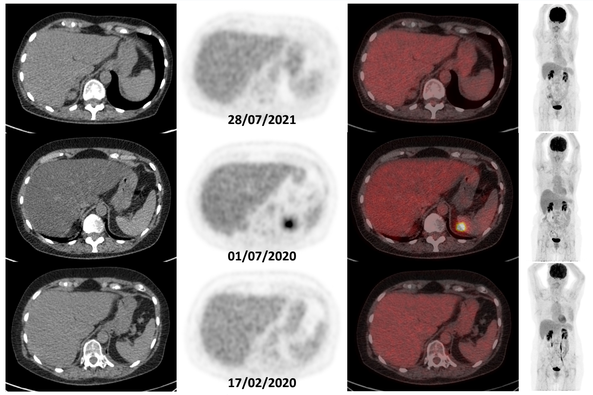


Figure 1. *71y woman, HR+/HER2-, normal DPD. Capecitabine monotherapy 3500 mg/day.* ***Bottom:*** *Baseline - normal liver density.* ***Middle:*** *First evaluation - hepatic steatosis detected. Subsequently developed grade I-II asthenia, weight loss and general condition deterioration requiring dose reduction to 3000 mg/day.* ***Top:*** *Final evaluation - complete steatosis resolution. CT images show decreased liver attenuation relative to spleen during steatosis with subsequent normalization.*

Results

Quantitative analysis revealed small magnitude hepatic changes during capecitabine treatment (**Figure 2**): mean HU liver decreased by -2.5 units (p=0.004) and SUVmean liver increased by +0.2 units (p<0.001). These quantitative changes occurred independently of baseline liver metastases presence (p=0.470 for HU, p=0.881 for SUVmean). Among clinico-biological variables, only baseline bilirubin showed significant correlation with HU changes (p=0.041), while other liver function tests, BMI, and DPD status showed no significant association.

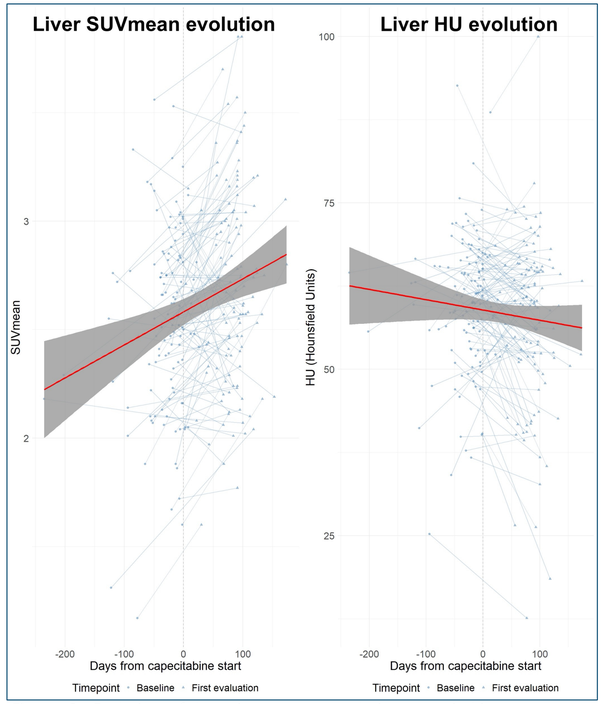


Figure 2. *Evolution of hepatic parameters during capecitabine treatment. Blue dots: individual patients; Red line: overall trend; Gray area: 95% CI. Changes occurred independently of baseline liver metastases presence.*

Conclusions

This study provides a first estimate of capecitabine-induced hepatic steatosis prevalence, and initial evidence supporting the feasibility of using follow-up [^{18}F]FDG PET/CT to assess its occurrence and reversibility after dose reduction or discontinuation. Further studies are needed to evaluate the potential impact of systematic steatosis evaluation on imaging follow-up, including shorter follow-up intervals and preemptive dose adjustments.

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Disclosures

The authors declare no conflicts of interest.

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