RESEARCH ARTICLE

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Non Size Based Morphology Criteria for Assessment of Response in Patients with Liver Metastases of Gastrointestinal Origin Receiving Systemic Treatment

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Abstract

Background and Aim: Liver is the main site of metastases of gastrointestinal cancers, chemotherapy with or without targeted therapy is the standard treatment. Radiologic assessment of tumor response is usually done by the use of Response Evaluation Criteria in Solid Tumor (RECIST) criteria. RECIST depends on tumor size changes but it does not address morphologic changes as overall attenuation, enhancement and tumor liver interface changes which may shown early before tumor size changes. We aimed to evaluate use of contrast enhanced computed tomography (CECT) new morphologic criteria in assessment of response in patients with hepatic metastases of gastrointestinal origin. **Methods:** This study was carried out by cooperation between Clinical Oncology and Nuclear Medicine and Radiodiagnosis Departments, Faculty of Medicine, Menoufia University. During the period from April 2015 to December 2016 forty patients with stage IV gastrointestinal cancers with hepatic metastases were included, CECT was done before and after systemic treatment, response evaluation was done by RECIST 1.1 and morphology response criteriac. **Results:** By RECIST, partial response (PR) observed in 57.5%, stable disease (SD) 22.5% and progressive disease (PD) in 20% of patients compared to Optimal response 42.5%, incomplete response 35% and no response in 22.5% of patients by Morphologic response criteria. Regarding survival, patients with PR had median survival of 20 months (95% CI, 17.988 to 22.012months) versus 11 months (95% CI, 1.235 to 8.580 months) in SD or PD by RECIST, (P=.002). while by morphology response criteria the median overall survival of optimally responded patients 23 months (95% CI, 20.04 to 27.81months) versus 16 months (95% CI, 5.590 to 5.044 months) in patients with incomplete or no morphologic response (P=.001). **Conclusion:** Morphologic response criteria are accurate method for assessment of response of hepatic metastases and correlated well with patients' survival and better to be incorporated to treatment evaluation.

Keywords: Liver metastases- morphology response criteria

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Introduction

For solid tumors, assessment of treatment response is done by clinical, radiological, biochemical methods. The inclusion of median survival time into the assessment indices is crucial and used for determination of prognosis. Improvement of patients' survival and their clinical symptoms are considered the main proofs of the effectiveness of cancer therapy, using endpoints based on radiological responses are important to measure therapeutic effects (Meerten et al., 2010).

Gastrointestinal cancers tend to metastasize through portal circulation to liver. Imaging of hepatic metastases plays the main role in staging, monitoring treatment and follow up. They help to enumerate the number and sites of metastases, determine resectability and assess response to systemic therapy (Choi et al., 2006). Imaging is expected to be more objective and standardized than clinical results in evaluating the effects of chemotherapy (Suzuki et al., 2008).

The computed tomography (CT) appearance of liver metastases is variable. Metastases differ in their density, enhancement, it may be cystic, complex, calcified, or diffusely infiltrative. The CT appearance depends on tumor size, the presence of hemorrhage and necrosis, and the quality of the intravenous contrast (Suzuki et al., 2008; Valls et al., 2001).

Modified response criteria for solid tumor were initiated by primary liver cancer; hepatocellular carcinoma (HCC) with proposed changes to Response Evaluation Criteria in Solid Tumor (RECIST) criteria; for target lesions, not the total lesion size but only viable tumor should be measured; arterial phase enhanced lesion (Llovet et al., 2008).

The new response criteria of gastrointestinal stromal tumors (GIST) patients treated with imatinib- mesylate by

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Choi et al (a decrease in GIST size of ≥10% or a decrease in tumor density on CT of ≥15%) incorporating changes in tumor density on CT as more predictive of outcome than response according to RECIST; decrease in tumor volume is also not the best indicator to evaluate antitumor activity. Other solid tumor modified response criteria included MASS (Morphology, Attenuation, Size, And Structure) criteria for metastatic renal cell carcinoma patients undergoing systemic therapy (Smith et al., 2010; Shindoh et al., 2013).

After the introduction of these modified response criteria and the new targeted agents it has been reported that the RECIST criteria may underestimate the response to systemic treatment in liver metastases as it only address the changes in tumor size, resulting in studies questioning the adequacy of traditional size-based response criteria (Shindoh et al., 2013; Chun et al., 2009; Chung et al., 2012), we aimed to study the CT morphology criteria in comparison with RECIST 1.1 criteria and to assess if the morphology criteria correlated well with survival of patients with hepatic metastases of gastrointestinal origin.

Materials and Methods

This observational study included 40 patients who presented to department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Menoufia University during the period from April 2015 to December 2016, inclusion Criteria: patients with stage IV gastrointestinal cancers with hepatic metastases who were candidate for chemotherapy; with good performance status (World Health Organization; WHO) and adequate organ functions. Exclusion Criteria: Patients with short life expectancy (<6 months), Patients with liver metastasis smaller than 1 cm in diameter. An informed written consent was obtained from all participant approved by the Ethical Committee of Medical Research, Faculty of Medicine, Menoufia University.

All the patients were subjected to complete history taking, physical examination, complete blood picture, liver and kidney function tests, baseline CECT and serum tumor markers CEA and CA19.9. Staging was done according to AJCC the American Joint Committee on Cancer: the 7th edition (Edge et al., 2012). All patients received systemic treatment 3-6 chemotherapy cycles followed by repeated physical examination, CECT and tumor markers assessment. The response was then evaluated by both RECIST 1.1 and morphological response criteria (Therasse et al., 2000 Eisenhauer et al., 2009; Chun et al., 2009). After median follow up duration of 18 month, Survival was calculated from date of diagnosis to date of death, date of last contact or date of data collection.

Contrast enhanced computed tomography was done before and after chemotherapy; contrast enhanced CT of the studied patients was done using Multislice CT Scanner (Toshiba Alexion -16 detector rows). Serum creatinine was done and must be less than 1.5 mg/dl. Patients were fasting 6 hours before the study. The Upper gastrointestinal tract was opacifed before the examination by oral intake of 20 ml of 33% gastrographin added to one liter of tape water and in some patents a liter of tape water only was given , the patient drinks 200 ml six hours before the study , then another 200 ml 4 hours before the study , then another 200 ml 2 hours before the study, then another 200 ml 1 hour before the study .Then the patient complete the amount on table of CT machine. Non-Contrast enhanced images were taken to the liver , then triphasic study was done after injection of non-ionic contrast media (Iopromide-Ultravist 300) in a dose of 1-2ml per kilogram body weight with maximum dose of 150 ml. The triphasic study was done by bolus tracking technique with the arterial phase imaged when the attenuation at aorta is 110 HU, Then the portovenous phase starts 60 seconds after start of injection, finally the delayed phase obtained 7-10 minutes after start of injection.

Image analysis: Using the portovenous phase, the response of metastases to systemic treatment was evaluated by RECIST 1.1 Criteria (Therasse et al., 2000; Eisenhauer et al., 2009) and by non-size based morphology criteria classifying each metastasis to 1 of 3 groups:

-Morphology group 3: Thick poorly defined liver-tumor interface with heterogeneous attenuation of metastasis and may be peripheral enhancement.

-Morphology group 1: Thin sharply defined liver-tumor interface with homogenous low attenuation of metastasis and no peripheral enhancement.

-Morphology group 2: Metastases that could not be rated morphologically as 1 nor 3.

Response was defined as follow:

Optimal: if metastases change from group 2 or 3 to group 1.

In-complete: if metastases change from group 3 to group 2.

No response: if the group did not change or increased (Chun et al., 2009).

Statistical analysis

Data were statistically described as mean ± standard deviation (± SD), median and range, or frequencies and percentages. Comparison of numerical variables between the study groups was done using Chi-square (x^2) test. Survival analysis was done using Kaplan Maier curves calculating the median survival for each group with the log rank test and their 95%CI and the corresponding survival graphs. Overall survival was calculated from the date of diagnosis to date of death or the date of last contact. P values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Results

Forty patients were included in this study, the mean age was 57.55 ± 10.16, There were 25 males (62.5%) and 15 females (37.5%). About half of the included patients were of pancreatic origin (47.5%), Colorectal in (32.5%), Gastro-esophageal in (15%) and biliary in (5%). The most commonly used chemotherapy regimen was gemcitabine based chemotherapy in (45%) of patients then FOLFOX

in (17.5%), Capecitabine in (10%), FOLFIRI in (7.5%). While ECF (Epirubicin, Cisplatin and Fluorouracil), Fluorouracil/ leucovorin and Fluorouracil (5FU) only protocols represent the rest (20%) of the patients. The number of chemotherapy cycles range 3-6, four patients with colorectal cancers received targeted systemic treatment with 5FU based chemotherapy (two patients received bevacizumab, one patient received Cetuximab and another received Panitumumab). Hepatic focal lesions were multiple in (85%) and single in (15%) of patients. 17 patients (42.5%) had no extrahepatic disease and 23 patients (57.5%) had hepatic and extrahepatic disease, (Table 1).

The studied group showed that the most frequent RECIST response was the partial response (PR) (57.5%) followed by stable disease (SD) (22.5%) then progressive disease (PD) (20%) and the most frequent morphological response was the optimal response (42.5%) followed by incomplete response (35%) then no response (22.5%) (Table 2).

This study showed that ≤ 3 cm pretreatment size of tumor (odds ratio, 1.8) was predictive factor for optimal morphologic response to systemic chemotherapy (Table 3). Morphologic response when correlated with

Table 1. Baseline Patient Characteristics

	No. (%) of Patients
Age	
Range	28 – 76 years
Mean	57.55 years ± SD 10.16
Sex	
Female	15 (37.5%)
Male	25 (62.5%)
Site of Primary Tumor	
Pancreas	19 (47.5%)
Colorectal	13 (32.5%)
Gastro esophageal	6 (15%)
Biliary	2 (5%)
Liver metastases	
Solitary	6 (15%)
Multiple	34 (85%)
Sites of metastases	
Liver only	17 (42.5%)
Liver and extra hepatic	23 (57.5%)
Tumor Size	
Range	1.5 – 15 cm
Mean (cm) before systemic treatment	4.225 ± 2.808 (SD)
Mean (cm) post systemic treatment	3.5 ± 2.506 (SD)
	P =0.004*
Chemotherapy type	
FOLFOX	7 (17.5%)
FOLFIRI	3 (7.5%)
Gemcitabine	18 (45%)
Capecitabine	4 (10%)
ECF	5 (12.5%)
fluorouracil -Ca leucovorin	2 (5%)
fluorouracil	1 (2.5%)

*, wilcoxon test 2.898

Table 2. RECIST and Morphologic Response of Patients

RECIST response	Frequency (n=40)	Percent (%)
Partial response (PR)	23	57.5
Stable disease (SD)	9	22.5
Progressive disease (PD)	8	20
Morphologic response		
Optimal response	17	42.5
Incomplete response	14	35
No response	9	22.5

RECIST response was independent, with no association between best morphologic response and RECIST response (P=0.281), (Figure 1).

Regarding survival, patients with PR (responders) had median survival of 20 months (95% CI, 17.988 to 22.012 months) compared to 11 months (95% CI, 1.235 to 8.580 months) in SD or PD (non-responders) by RECIST, Thus the survival time of patients who showed PD was

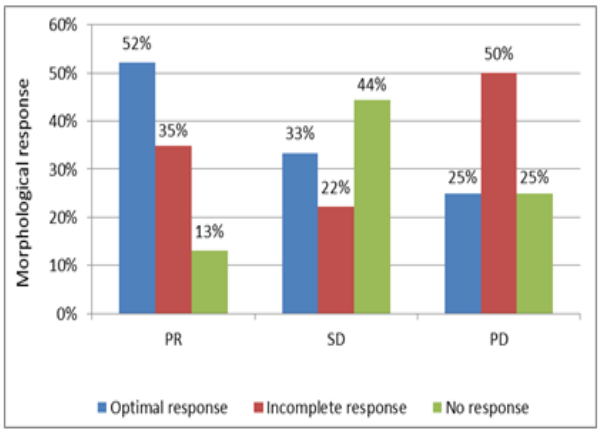

Figure 1. Correlation between Morphology Response and RECIST 1.1. Morphology response criteria when correlated with RECIST response criteria was independent, with no association between best morphologic response and RECIST response (P=0.281).

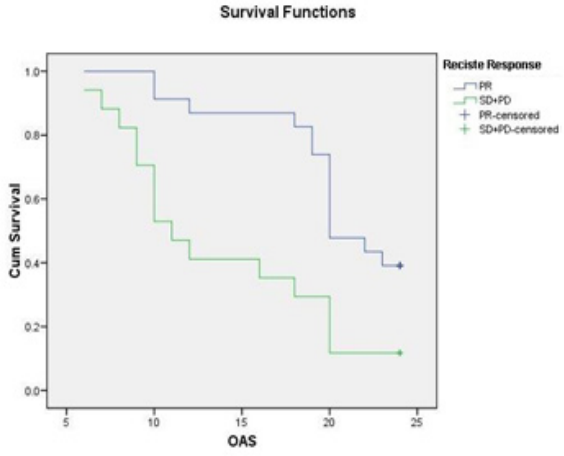

Figure 2. Kaplan Meier Curve for Overall Survival in Relation to RECIST Criteria. OAS; overall survival in months, Cum survival; cumulative survival, 1; 100% of cases. Patients with PR (responders) had better survival compared with SD and PD (non-responders) (P*=0.002).

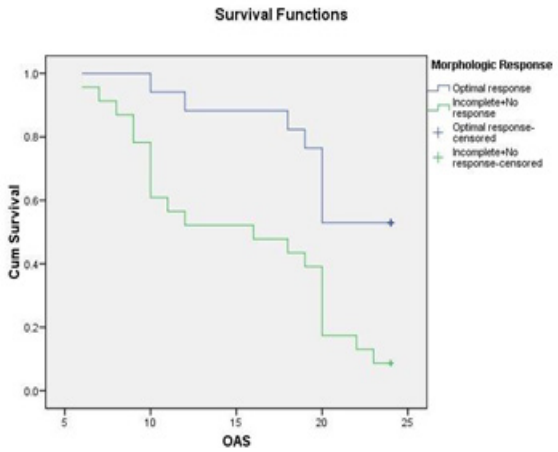

Figure 3. Kaplan Meier Curve for Overall Survival in Relation to Morphology Response Criteria. OAS; overall survival in months, Cum survival; cumulative survival, 1 ; 100% of cases. Patients with Optimal response (responders) patients had better survival than incomplete or no morphologic response (non-responders), (P*=0.001).

significantly shorter than those with SD or PD (P*=0.002). Also the median overall survival by morphology response criteria of optimally responded (responders) patients was 23 months (95% CI, 20.04 to 27.81months) compared to 16 months (95% CI, 5.590 to 5.044 months) in patients with incomplete or no morphologic response (non-responders), Thus the survival time of patients who showed optimal response was significantly longer than those incomplete or no morphologic response (P*=0.001) (Figure 2, 3).

Discussion

The management of metastatic gastrointestinal cancers has seen a changed in recent years leading to a significant increase in overall survival times for these patients to nearly 2 years from less than 6 months. This success can be attributed to the development of newer targeted and chemotherapeutic regimens, increased utilization of metastatectomies and hepatectomy in patients with oligometastases (Nishioka et al., 2015; Goldberg, 2005).

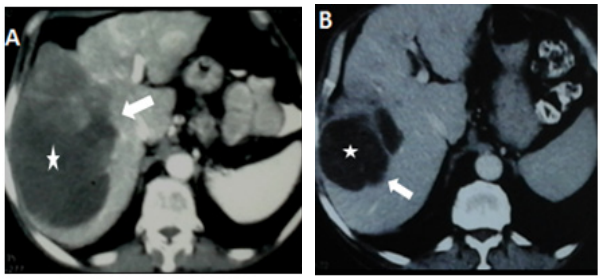

Figure 4. Case 1 A and B. Figure; CT of Liver metastasis pancreatic cancer; (A) Before treatment; partially defined liver-tumor interface (arrow) with heterogeneous attenuation (star), morphology group 2. (B) After treatment; thin well defined liver-tumor interface (arrow) with homogenous low attenuation (star), morphology group 1 (Optimal morphological response).

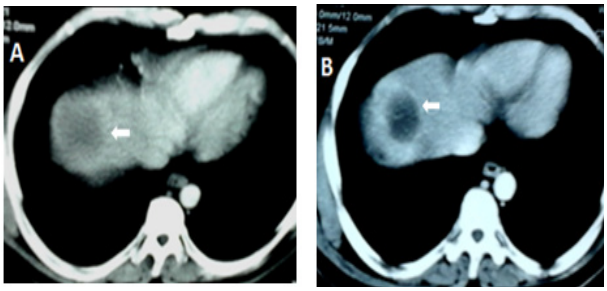

Figure 5. Case 2 A and B. Figure; CT of Liver metastasis pancreatic cancer; (A) Before treatment; Thick poorly defined liver-tumor interface with heterogeneous attenuation (arrow), morphology group 3. (B) After treatment; thin partially defined liver-tumor interface with homogenous low attenuation and some peripheral enhancement (arrow), morphology group 2 (Incomplete morphological response).

These advances in treatment should be combined with advances in imaging and interpretation of images and modification in response criteria to be more accurate and predictive. CT morphological changes may correlate better to early tumor response before the tumor size changes become apparent and could be used as an indicator of response which may be translated to better survival for those patients with optimal morphologic response (Chun et al., 2009).

Chun et al., (2009) described three patterns of liver metastases of colorectal origin in 50 patients based on the overall attenuation pattern, tumor-liver interface and presence/ absence of Peripheral rim of enhancement, changes in the criteria of the lesion define the type of response they found the significant association between the patterns of morphologic response and the pathologic response.

In this study we tried to use these morphology response criteria in forty patients with liver metastases of gastrointestinal origin treated with chemotherapy and to explore its relation with baseline tumor size; if lesion is smaller its morphologic changes will be shown earlier and also we tried to correlate morphology criteria with standard RECIST criteria and with patients' survival.

In this study, the mean age of the studied patients was 57.55 ± 10.1, (62.5) % men and (37.5%) women this

Table 3. Baseline Tumor Size (before chemotherapy) and Morphologic Response Criteria

	Morphological Response			
Tumor Size	Optimal response	Incomplete + No Response	Total	Odds Ratio
Tumor Size ≤ 3	9	10	19	1.8
	(47%)	(53%)	(100%)	
Tumor Size > 3	7	14	21	
	(33%)	(67%)	(100%)	
Total	16	24	40	

agreed with the result of Nishioka et al., (2015). where the median age of their studied group was 61.5 years and where men represents (57%) and women represented (43%).

In this study, the commonest primary cancer was the pancreas (47.5%) then colorectal cancer (32.5%). Similar results were reported by Halldórsdóttir et al, (2006); in which about two thirds of patients diagnosed with liver metastases of unknown origin were discovered to have primary pancreatic and colorectal cancers.

In this study, most of cases had multiple hepatic metastases (85%) and only (15%) had solitary liver metastases. These results were comparable to other studies; Chun et al., (2009) reported that the percentage of multiple liver metastases was 95%while the solitary was 5%. Also, Dietrich et al., (2006) stated that most liver metastases were multiple while in only 10% of cases metastasis was solitary.

In this study PR observed in (57.5%), SD in (22.5%) and PD in (20%) of patients by RECIST, compared to Optimal response in (42.5%), incomplete response in (35%) and no response in (22.5%) of patients by Morphologic response criteria.

Correlation between morphologic response criteria with RECIST was independent; with no association between best morphologic response and RECIST response (P=0.281); morphologic changes independent of change in tumor size this can be explained by the idea that a tumor displayed good morphologic response but did not decrease sufficiently in size to qualify for PR by RECIST or because a tumor decreases in size qualifying as a PR by RECIST but did not undergo morphologic changes. Similarly Shindoh et al., (2013) reported statistically insignificant (P =0.06) correlation between the morphologic response and RECIST.

In this study, pretreatment size of a tumor ≤ 3 cm (odds ratio, 1.8) was a predictive factor for optimal morphologic response to systemic chemotherapy. This is in agreement with Shindoh et al., (2013) who stated that, use of bevacizumab (odds ratio, 6.7) and pretreatment size of a tumor ≤ 3 cm (odds ratio, 2.1) were predictive factors for optimal morphologic response to systemic chemotherapy.

The survival time of the patients who showed PR (responders) by RECIST in our study was significantly longer than those with SD or PD (non responders). The median overall survival was 20 months compared to 11 months with SD and PD (P=.002). This agrees with Nishioka et al., who stated that when the study cohort was stratified according to RECIST response, patients with a PR or SD had a better overall survival rate than those with PD (Nishioka et al., 2015).

Chun et al., (2009) found different results as response by RECIST was not associated with an improvement in survival; median overall survival was 28 months in patients with PR and 22 months in those with SD and PD (P=.45).

This disagreement may be attributed to difference in patients group our study included patients with liver metastases from pancreatic (47.5%), colorectal (32%) and other gastrointestinal cancer, while Chun et al. studied patients with colorectal cancer only. Second, our study showed higher percent of solitary liver metastases (15%) versus (5%) reported by Chun et al., (2009) which could be more responsive and with better survival.

This study showed that morphologic response criteria more correlated with overall survival; the survival time of the patients who showed optimal response (responders) was significantly longer than those with incomplete or no response (non responders) with median overall survival of 23 months compared to 16 months with incomplete or no morphologic response (P=.001). Similarly, Chun et al., (2009) stated that patients with optimal morphologic response had significantly better overall survival than patients with incomplete or no response, with median overall survival of 31 months and 19 months, respectively (P=.009).

This agrees with Nishioka et al., (2015) who concluded that, when stratified according to the CT morphology of colorectal liver metastases after chemotherapy, optimal response had better long-term outcomes in terms of both overall survival and recurrence- free survival than suboptimal response.

In conclusion, these morphological criteria are useful, non-invasive markers of tumor response in patients with gastrointestinal liver metastases receiving systemic treatment and need to be incorporated to treatment evaluation. The occurrence of discordance between morphologic and RECIST based responses indicates that both evaluation methods need to be implemented.

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