Original article

Gastrointestinal stromal tumor (GIST) with liver metastasis: role of CT in response evaluation before and after the first treatment of imatinib

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Objective The aim of this study was to evaluate the tumor response by computed tomography in patients receiving first treatment of imatinib therapy for liver metastases from gastrointestinal tumor (GIST).

Patients and method A total of 85 lesions in 27 patients, diagnosed as GIST with liver metastases between 2008 and 2013, were evaluated by abdominal CT images before and after initial imatinib treatment.

Results This study showed that after the first Imatinib treatment, decreased liver size, liver metastatic density, and non-contrast and contrast phases accounted for 16.21%, about19.35% and 41.02% of liver metastasis, respectively. One nodule (1.2%) showed a complete response, while 73 nodules (85.9%) of 85 showed a good response resulting from a significant decrease in tumor size and density. Seven nodules (8.2%) showed stable disease by means of a slight change in tumor size and density. Four nodules (4.7%) suggested a poor response, due to a significant increased in tumor size and density.

Conclusion A good response to liver metastases from GIST can be expected after the first treatment of Imatinib. However, evaluation of the tumor response must be performed with caution. The suggestion of this study is not to rely on the tumor size criteria alone. The tumor density, and careful evaluation of both non-enhanced computed tomography (NECT) and contrast enhanced computed tomography (CECT) have an impact on the determination of tumor response. **Chiang Mai Medical Journal 2014;53(3):135-142.**

Keywords: gastrointestinal stromal tumor (GIST) with liver metastasis, response evaluation, computed tomography, imatinib

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor in the gastrointestinal tract. GISTs manifest histologically in one of three patterns: predominantly spindle cells (most common), epithelioid cells or a mixture of both[1,2]. They are characterized as 95% posi-

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tive for immunoreactivity by the (CD117) KIT, and a tyrosine kinase growth factor receptor is distinguished from true leiomyoma or leiomyosarcomas. GISTs originate from the precursors of interstitial cells of the Cajal in the myenteric plexus. The most common sites for primary GISTs are the stomach (50%) and small bowel (25%), but they may occur anywhere in the GI tract and peritoneum[3]. Nearly half of the patients with GISTs present with metastasis, which occurs most often in the liver and peritoneum via hematogenous spreading and peritoneal seeding, respectively. CT findings of GIST metastatic lesions are similar to primary tumors that mostly show hyperattenuation, which enhances masses that can be heterogeneous, due to hemorrhage, necrosis or cystic degeneration[3].

Pharmacologic targeting of receptors with KIT/tyrosine kinase inhibitors has been utilized clinically in treating patients with metastatic GISTs. A tyrosine kinase inhibitor, known as imatinib (Glivec, Gleevec; Novatis Pharmaceuticals), was developed to inhibit tumor growth in GIST patients by competitive interaction at the adenosine triphosphate (ATP) binding site of the c-kit receptor.

For early diagnosis of GISTs, it is important for the effect of treatment and tumor progression to be monitored and evaluated, and computed tomography (CT) is the current modality of choice for these objectives. There have been few CT studies on the outcome of imatinib regarding liver metastasis morphology such as size and density of the liver nodule.

Results from previous studies of treatment with imatinib have shown that a decrease in the size of GISTS may take several months before satisfying the Response Evaluation Criteria in Solid Tumors (RECISTs). However, the authors observed that GISTs with liver metastasis, which respond after imatinib therapy, did not have the same image findings as other solid tumors. Recent studies have supported the fact that CT attenuation value has a role in evaluating the tumor response of liver metastasis, but no studies had evaluated initial treatment[4-10]. The purposes of this study was to assess the response to initial treatment of imatinib therapy on CT images by measuring both the tumor size and density of liver metastatic nodules.

Materials and methods

Patients

The institutional review board approved this study and informed consent was waived. A total of 90 patients, who were diagnosed pathologically as GIST between January 2008 and December 2013, were enrolled in this study. Fifty one patients were excluded, due to no evidence of liver metastasis. All of the patients had a CT performed at Siriraj Hospital, and only 27 had abdominal CT images in both pre contrast and portovenous phases. These patients were treated with 400 mg of imatinib daily.

Imaging Techniques

All 27 patients were imaged with two 64 slice-CT scanners Lightspeed VCT; GEHealthcare or Dual-Source CT; Siemens. The study was performed in axial pre contrast and axial post contrast phases with a slice thickness of 1.25 and 5 mm, respectively. Intravenous contrast medium comprising 100 cc of non ionic contrast media with 20 cc of water fed intravenously at 2 cc/sec, and oral contrast, were obtained.

Imaging analysis and data collection

The demographic data, age and sex, as well as CT findings on features of liver metastasis were collected from patient record forms.

Eighty five liver nodules in 27 patients were assessed as pre and within four months from initial imatinib treatment. All studies were reviewed and collected by two observers in consensus, one radiologist with more than five years' experience in abdominal imaging and one senior radiology resident.

Data analysis

Demographic data such as size (centimeter, cm.) and attenuated coefficient (Hounsfield Unit, HU) of liver metastasis nodules were recorded by mean and standard deviation. Categorical data such as gender and primary site of tumor were

recorded by number and percentage. Comparison of liver metastatic nodule size pre and post treatment was found using the paired T-test. Correlation between tumor size differentiation and tumor density differentiation was found using Sperman rank correlation. Evaluation of treatment response was compared with the agreement of tumor size and each phase of tumor density by weight kappa.

Tumor size for each lesion was measured across the longest dimension of the cross section at the time of pre and post treatment.

CT attenuated coefficients measured each tumor by drawing a region of interest around the margin of the entire tumor. Non contrast and portovenous phases were used for tumor density measurement.

A previous study 7 claimed that the RECIST criteria underevaluated tumor response. Therefore, this study evaluated tumor response from both the tumor size and density, as inferred by the previous study[7].

Response evaluation was identified on the basis of CT findings as follows:

1. Complete response: Disappearance of lesion.
2. Good response: Decreased size of ≥10% or decreased tumor density (HU) ≥15%.
3. Stable disease: Does not meet the criteria for complete, good or poor response.
4. Poor response: Increased size of ≥10% and increased tumor density <15%.

Results

A total of 90 patients, who were diagnosed pathologically as GIST, were enrolled in this study. Only 39 patients had liver metastasis, and among those, 27 (10 male and 17 female) had abdominal CT images with pre and post contrast studies performed at both pre and post initial imatinib treatment. Their age ranged from 16 to 81 years, with a mean age of 57.04 years. Eighty five liver nodules were included in total, with an average tumor size ranging from 0.5 to 18.8 cm (mean 3.4 cm) and 0 to 15.6 cm (mean 2.8 cm) pre and within 1 to 4 months post imatinib treatment, respectively,.

In the non contrast study, the tumor density ranged from 22.1 to 45.32 HU (mean 33.71 HU) and 16.59 to 39.03 HU (mean 27.8 HU) before and after treatment, respectively. In the post contrast portovenous study, tumor density ranged from 38.64 to 91.84 HU (mean 65.2 HU) and 17.78 to 60.17 HU (mean 38.9 HU) before and after treatment, respectively. (Table 1)

On average, a tumor size decreases by a mean of 16.2% after initial treatment of imatinib. The tumor density (HU) decreases by a mean of 19.3% and 41.0% after treatment. This research shows a good relationship between the study of size and post contrast phase, which is more significant than that of size and non contrast phase (percentage difference in size = 0.304 and 0.033, respectively). (Table 2)

In terms of relationship between changes in tumor size and density of each individual liver nodule (Table 3), one nodule (1.2%) in this study disappeared, which meant a complete response. Seventy-three nodules (85.9%) of 85 showed good response resulting from tumor size and density decreasing by a mean of 15% and 39%, respectively (Figure 1,2). Seven nodules (8.2%) showed stable disease through a mean that decreased slightly in tumor size by about 0.5%, but

Table 1. Tumor size, tumor density on pre and post initial treatment (N=85)

	Size (cm)		Density (HU) in non contrast phase		Density (HU) in post contrast phase	
Data	Pre	Post	Pre	Post	Pre	Post
Mean	3.3976	2.8082	33.71	27.81	65.24	38.98
Range	0.05-18.8	0-15.6	22.1-45.32	16.59-39.03	38.64-91.84	17.78-60.17

cm: centrimetre, HU: hounsfield unit, pre: before treatment, post: after treatment

Table 2. Percentage differentiation of size and density of pre and post initial treatment (n=85)

	Size (cm)	Density (HU) in non contrast phase (%)	Density (HU) in post contrast phase (%)
Mean	Decrease 13.58%	Decrease 12.18%	Decrease 34.88%
Median	Decrease 16.21%	Decrease 19.35%	Decrease 41.02%
SD	29.35	39.85	30.66

cm: centrimetre, HU: hounsfield unit, pre: before treatment, post: after treatment

Table 3. Relationship between change in tumor size and tumor density of each liver nodules on pre and post initial treatment (n=85)

	Change in size (%)	Change in density (HU) in post contrast phase (%)
Complete response (n=1, 1.2%)	Decrease 100%	Decrease 100%
Good response (n=73, 85.9%)	Decrease 15.2%	Decrease 39.46%
Stable (n=7, 8.2%)	Decrease 0.49%	Increase 3.88%
Poor response (n=4, 4.7%)	Increase 14.74%	Decrease 2.9%

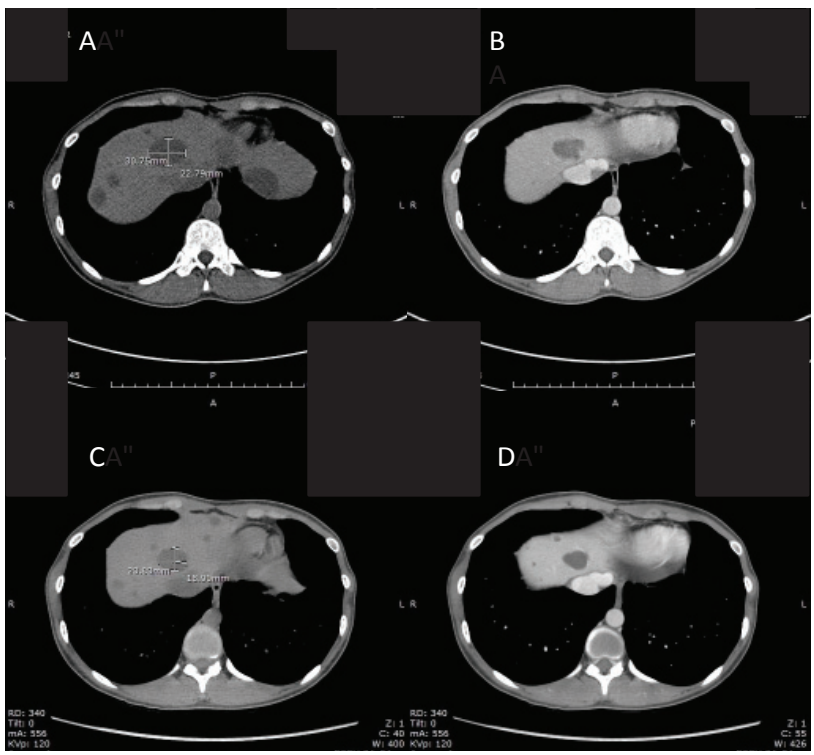

Figure 1. Good response in a 27-year-old female with liver metastases from small bowel GIST (a) Pre-treatment NECT, (b) Pre-treatment CECT, (c) Post-treatment NECT, (d) Post-treatment CECT.
Liver metastases showing decreased size and density after treatment, with one reduced from 3.1x2.3 cm (19,48 HU on NECT and CECT) to 2.4x1.9 cm (19,41 HU on NECT and CECT), thus finding decreased size of 23%, with unchanged density on NECT, and decreased density of 15% on CECT.

tumor density showed a slight increase by about 4% (Figure 3 and 4). Four nodules (4.7%) suggested a poor response due to increased tumor size by a mean of 15%, but tumor density decreased minimally by a mean of 3% (Table 3). Some nodules showed a good response, although they increased in tumor density by internal hemorrhage, and others showed a good response despite their size increasing through cystic change (Figure 5).

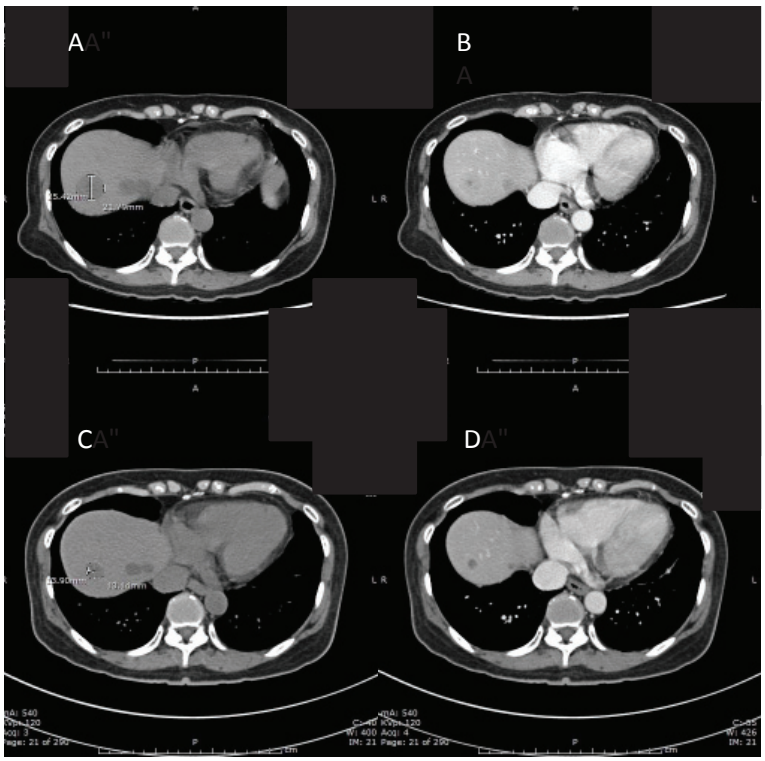

Figure 2. Good response in a 61-year-old female with liver metastases from mesenteric GIST; (a) Pre-treatment NECT, (b) Pre-treatment CECT, (c) Post-treatment NECT, (d) Post-treatment CECT. Liver metastases showing decreased size and density after treatment, with one reduced from 2.2x2.5 cm (31,114 HU on NECT and CECT) to 1.3x1.4 cm (18,29 HU on NECT and CECT), thus finding decreased size and density of 44% and 42%, respectively, on NECT and decreased density of 75% on CECT.

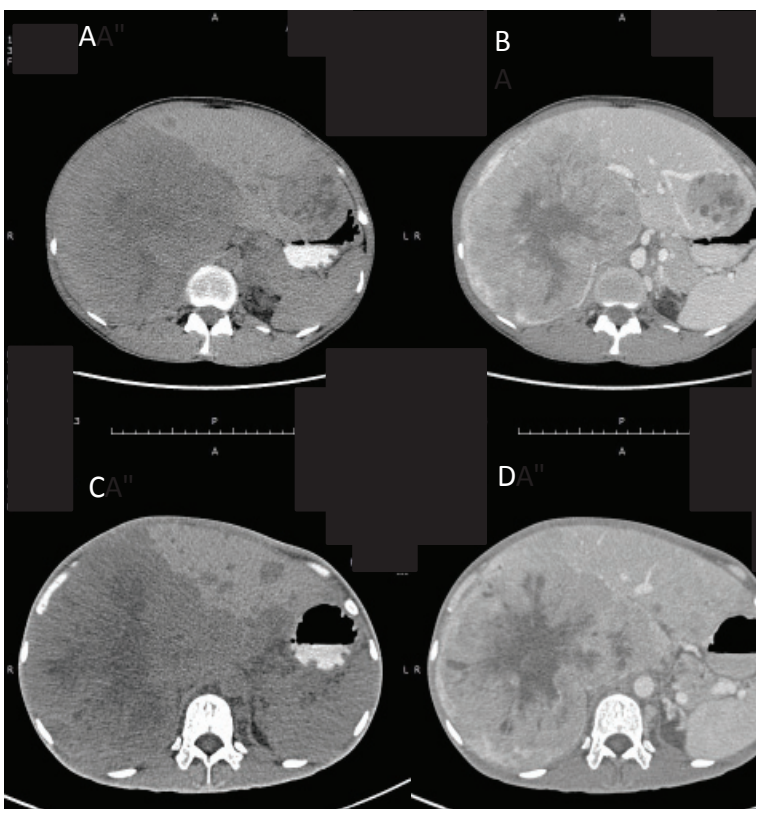

Figure 3. Stable disease in a 33-year-old female with liver metastases from gastric GIST; (a) Pre-treatment NECT, (b) Pre-treatment CECT, (c) Post-treatment NECT, (d) Post-treatment CECT.
Follow up CT showing that liver mass size had increased slightly from 11.1x15.6 cm (33,51 HU) to 15.4x16.1 cm(39, 76 HU) on both NECT and CECT after nearly 3 months of treatment, due to soft tissue component with cystic change and area of hemorrhage, thus finding increased size and density of 3% and 18%, respectively, on NECT, and increased density of 49% on CECT.

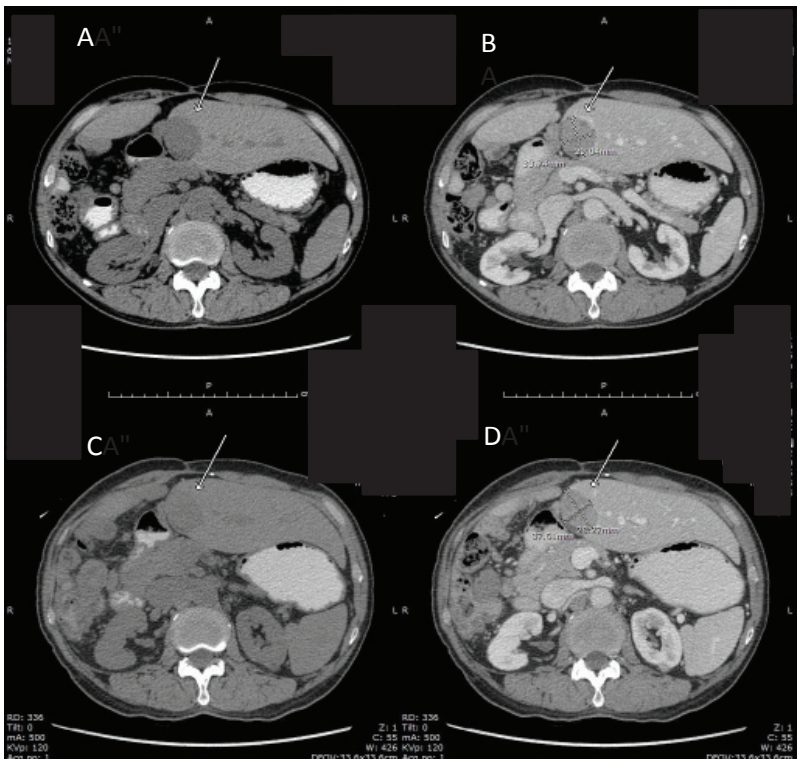

Figure 4. Stable disease in a 65-year-old male with mesenteric GIST; (a) Pre-treatment NECT (b) Pre-treatment CECT (c) Post-treatment NECT (d) Post-treatment CECT. Follow up CT showing an insignificant change of liver mass size and HU from 3.4x2.9 cm (40,81 HU) to 3.7x2.8 cm (42,83 HU) on NECT and CECT nearly 4 months after treatment, thus finding increased size and density of 9% and 5%, respectively, on NECT, and increased density of 2% on CECT.

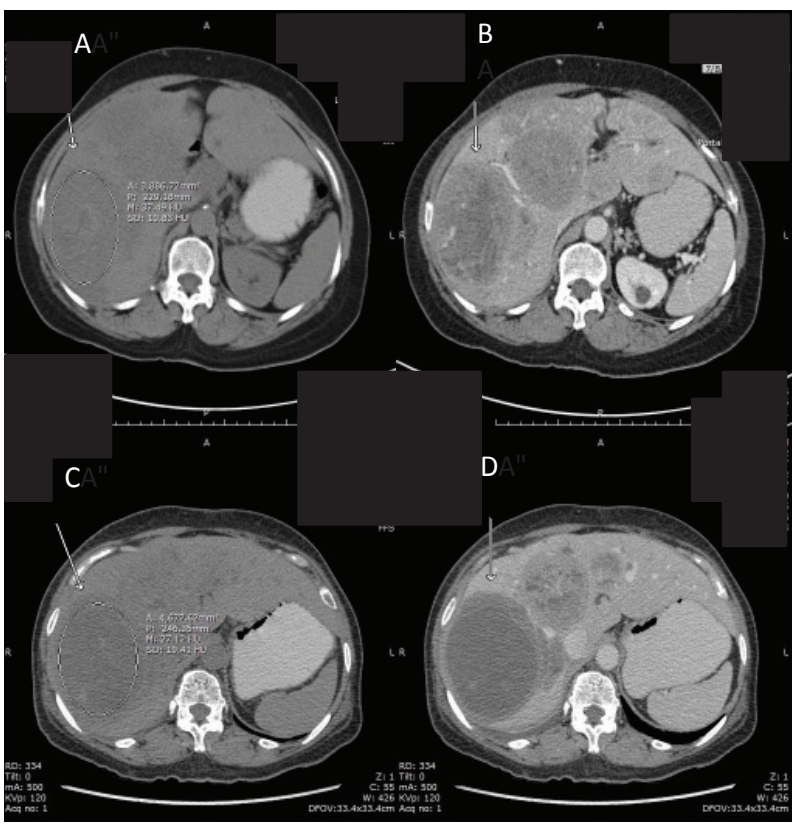

Figure 5. Good response in a 63-year-old female with liver metastases from small bowel GIST; (a) Pre-treatment NECT, (b) Pre-treatment CECT, (c) Post-treatment NECT, (d) Post-treatment CECT.
Follow up CT showing that liver mass had decreased HU on NECT and CECT, but slightly increased size from 10.6x8.5 cm (37,45 HU) to 11.1x8.7 cm (27,29 HU) 4 months after treatment, thus finding decreased size and density of 5% and 27%, respectively, on NECT, and decreased density of 36% on CECT.

Discussion

Gastrointestinal stromal tumor (GIST) is considered the most common mesenchymal tumor of the gastrointestinal tract. There has been a recent shift of practice strategy toward RESIST solid tumor response criteria, which are based on only tumor size.

However, recent investigations have suggested that by using RECIST, size measurements of liver metastasis alone substantially underestimate metastatic GIST response to targeted therapy. This study showed that not only tumor size, but also tumor density are important prognostic factors that determine tumor response after initial treatment of Imatinib.

Metastatic liver lesions, which were defined as having good response in this study by showing progression in size, but decreased density in both NECT and CECT, may be explained by cystic transformation.

In the meantime, lesions that are considered as having good response, but increased density on NECT could have internal hemorrhage. Therefore, both NECT and CECT play a major role in determining enhancement of a viable tumor that could be mistaken for an internal hemorrhage. NECT is very necessary for evaluating a tumor hemorrhage.

Therefore, objective measurements of changes should be carried out for both tumor size and attenuation in the study of both NECT and CECT after initiating first imatinib therapy for GIST, with the accuracy of therapeuric response assessment of liver metastasis being shown to improve markedly.

This study also showed a good response to liver metastastes, despite it being only from the initial treatment of imatinib. This information may be essential for clinicians, as they can expect a good result from the first initiation of imatinib therapy.

Not all liver nodules showed decreased density in the first treatment of Imatinib. This may be explained by several factors such as delayed tumor response, differentiation and aggressiveness. Thus, further treatment and a longer follow up period may be needed.

Furthermore, for liver nodules that consist of hemorrhagic, and cystic and solid parts, adjustment to the region of interest (ROI) and measurement of tumor density within the solid part, or enhancement of the portion for better accuracy, are recommended by this study.

The limitations of this study include the small sample size and short period of follow up after only the initial treatment of imatinib. The duration of follow up varied from 1 to 4 months from the initial treatment, which may affect the degree of tumor response.

Conclusion

A good response to liver metastases from GIST can be expected after the initial treatment of Imatinib. However, evaluation of the tumor response must be performed with caution. The suggestion of this study is not to rely on only the tumor size criteria. Tumor density and careful evaluation of both NECT and CECT have an impact on the determination of tumor response.

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บทบาทของเอกซเรย์คอมพิวเตอร์ในการประเมินการตอบสนองต่อโรคมะเร็งของเนื้อเยื่อในระบบทางเดินอาหาร (gastrointestinal stromal tumor) ที่มีการกระจายไปที่ตับ ก่อนและหลังการรักษาด้วยยาอิมมาตินิบ

มาศอุมา เตชเจริญพานิช, พ.บ., และ สิทธิพงศ์ ศรีสัจจากุล, พ.บ.
คณะแพทยศาสตร์ ศิริราชพยาบาล มหาวิทยาลัยมหิดล

วัตถุประสงค์ คณะผู้นิพนธ์มีสมมติฐานว่าทั้งขนาดและค่าความเข้มของก้อนมะเร็งที่กระจายไปที่ตับผู้ป่วยโรคมะเร็งเนื้อเยื่อในระบบทางเดินอาหารที่มีการกระจายไปที่ตับมีส่วนเกี่ยวข้องในการประเมินการตอบสนองต่อการรักษาด้วยยาอิมมาตินิบ การศึกษานี้ทำเพื่อประเมินการตอบสนองหลังการรักษาด้วยยาอิมมาตินิบครั้งแรก

วัสดุและวิธีการ ก้อนมะเร็งที่กระจายไปที่ตับทั้งหมด 85 ก้อน ในผู้ป่วย 27 รายที่ได้รับการวินิจฉัยว่าเป็นโรคมะเร็งเนื้อเยื่อในระบบทางเดินอาหารที่มีการกระจายไปที่ตับตั้งแต่ปี ค.ศ. 2008-2013 ได้ทำการศึกษาย้อนหลังโดยการประเมินขนาดและค่าความเข้มของก้อนมะเร็งที่กระจายไปที่ตับด้วยเอกซเรย์คอมพิวเตอร์ก่อนและหลังการรักษาด้วยยาอิมมาตินิบ

ผลการศึกษา หลังรักษาด้วยยาอิมมาตินิบ ค่าเฉลี่ยของขนาดลดลงร้อยละ 16.21 และค่าความเข้มข้มของก้อน ลดลงร้อยละ 19.35 และร้อยละ 41.02 ในภาพก่อนและหลังฉีดสารทึบรังสีตามลำดับ จากทั้งหมด 85 ก้อน พบว่า 1 ก้อน (ร้อยละ 1.20) ยุบหายไป 73 ก้อน (ร้อยละ 85.90) ตอบสนองที่ดีต่อการรักษาด้วยยาเนื่องจากขนาดและความเข้มของก้อนมะเร็งมีค่าลดลงอย่างมีนัยสำคัญ 7 ก้อน (ร้อยละ 8.20) ไม่พบการเปลี่ยนแปลงอย่างมีนัยสำคัญต่อการรักษา เนื่องจากขนาดและความเข้มของก้อนมะเร็งมีค่าเปลี่ยนแปลงเล็กน้อย และ 4 ก้อน (ร้อยละ 4.7) พบการตอบสนองที่ไม่ดีต่อการรักษา เนื่องจากขนาดและความเข้มของก้อนมะเร็งมีค่าเพิ่มขึ้นอย่างมีนัยสำคัญ

สรุป การตอบสนองที่ดีต่อยาของก้อนมะเร็งจากเนื้อเยื่อทางเดินอาหารที่กระจายไปตับสามารถคาดการณ์ได้ตั้งแต่หลังการรักษาด้วยยาอิมมาตินิบครั้งแรก แต่อย่างไรก็ตาม การประเมินผลการตอบสนองต่อการรักษาควรจะกระทำด้วยความระมัดระวัง จากผลการศึกษาครั้งนี้การประเมินโดยดูผลของการเปลี่ยนแปลงของก้อนมะเร็งเพียงอย่างเดียวอาจไม่เพียงพอต่อการประเมินผลการตอบสนองต่อยา การใช้การเปลี่ยนแปลงของความเข้มของก้อนมะเร็ง ร่วมกับการประเมินโดยใช้ภาพก่อนและหลังฉีดสารทึบรังสีด้วยความรอบคอบ มีส่วนสำคัญอย่างมากสำหรับการการประเมินการตอบสนองต่อการรักษาด้วยยาอิมมาตินิบ **เชียงใหม่เวชสาร 2557;53(3):135-142.**

คำสำคัญ: โรคมะเร็งของเนื้อเยื่อในระบบทางเดินอาหารที่มีการกระจายไปที่ตับ ยาอิมมาตินิบ