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Organ Atrophy Induced by Sorafenib and Sunitinib – Quantitative Computed Tomography (CT) Evaluation of the Pancreas, Thyroid Gland and Spleen

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Background:

To evaluate organ atrophy induced by sorafenib and sunitinib, we retrospectively reviewed the CT scans of renal cell carcinoma (RCC) patients receiving molecular targeted therapy (MTT) using sorafenib or sunitinib, and performed volumetric analysis of the pancreas, thyroid gland, and spleen.

Material/Methods:

Thirteen RCC patients receiving MTT were assigned as the evaluation cases (MTT group), while thirteen additional RCC patients not receiving MTT were retrieved as the Control group. We evaluated the baseline and follow-up CT studies. The volume of the three organs estimated by CT volumetry was compared between the baseline and follow-up CTs. The atrophic ratio of the organ volume in the follow-up CT to that in the baseline CT was calculated, and compared between the MTT and Control groups.

Results:

All measured organs in the MTT group showed statistically significant volume loss, while no significant change was observed in the Control group. Mean atrophic ratio in the MTT group was 0.74, 0.58, and 0.82 for the pancreas, thyroid and spleen, respectively. The differences in atrophic ratios between both groups were all statistically significant ($P < 0.05$).

Conclusions:

Single-agent sorafenib or sunitinib therapy induced statistically significant atrophy in the pancreas, thyroid, and spleen.

MeSH Keywords:

Atrophy • Pancreas • Spleen • Thyroid Gland

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Background

Tyrosine kinase inhibitors (TKIs), a newly developed molecular-targeted therapy (MTT), have significantly improved the prognosis of patients with various advanced malignancies [1-5]. Sunitinib (Sutent®; Pfizer Japan Inc., Tokyo, Japan) and sorafenib (Nexavar®; Bayer Yakuhin, Ltd., Osaka, Japan) are the mainstay of TKIs, and are currently considered the mainstream treatment for stage IV renal cell carcinoma (RCC) [1-5].

The novel therapeutic efficacy of TKIs is mainly achieved by targeting the intracellular kinase domains of the VEGF

receptor [1,4]. By suppressing the VEGF overexpression, TKIs are presumed to inhibit neovascularization of the tumour cells [1,4]. On the other hand, the anti-angiogenic activity of TKIs is considered to affect some non-tumour tissues and organs as well, leading to atrophic changes [6-10].

Thyroid gland atrophy is a well-known side effect, which is assumed to be accompanied by hypothyroidism [6-8]. Skeletal muscle atrophy has been reported as well [9]. Antoun et al. reported skeletal muscle loss in patients who had received sorafenib for 12 months [9]. Pancreatic atrophy is a newly demonstrated side effect [10]. Hescot et al. reported decreases in the volume of the pancreas on

volumetric CT in two patients who received sorafenib for more than 2 years [10]. They suggested that pancreatic atrophy might be a late toxic effect of long-term sorafenib use [10]. However, no consensus has been reached on its frequency and onset timing. It has also remained unclear whether pancreatic atrophy is caused by sunitinib treatment. Furthermore, to the best of our knowledge, there has been no research on whether TKIs induce volume reduction of organs other than those mentioned above.

To clarify the effect of TKIs on multi-organ atrophy, we retrospectively reviewed the CT scans of RCC patients who were treated with single-agent sunitinib or sorafenib therapy. We performed volumetric measurement of the thyroid gland, pancreas and spleen in each patient. The purpose of this study is to investigate if these organs show statistical significant atrophy within one year after the beginning of the treatment.

Material and Methods

This retrospective study was approved by our Institutional Review Board (H26-160). Written informed consent was waived by the Institutional Review Board due to the nature of the retrospective study. The patients' CT data was retrieved from the database of the medical image server.

Patient data

Among the patients pathologically diagnosed with RCC who underwent CT studies between April 2011 and March 2014, those treated with single-agent sunitinib or sorafenib therapy were retrieved. The inclusion criteria for the study were as follows: (i) the therapy had been continued for at least six months; (ii) a baseline CT scan was obtained within three months before starting the therapy; (iii) a follow-up CT was acquired six months to one year after beginning the therapy; and (iv) the range of both the baseline and the follow-up CT scans covers the pancreas, thyroid, and spleen. The following patients were excluded from the patient group: (i) patients who received other MTT (i.e. temsirolimus, everolimus, bevacizumab, and pazopanib) during the observation period; and (ii) patients having metastases of RCC to the pancreas, thyroid gland or spleen.

Thirteen patients made up the final group (MTT group). All patients underwent unilateral total nephrectomy. Ten patients received single-agent sunitinib therapy, and the remaining three were treated with single-agent sorafenib therapy. Sorafenib was orally administered at 400 mg twice daily or 400 mg once daily. Sunitinib was orally administered at 50 mg, 37.5 mg, or 25 mg daily for four weeks followed by two-week cessation repeatedly. The dose was modified based on related adverse events and individual tolerability. The therapy duration in each patient was defined as the number of days from when the TKI therapy started to when the follow-up CT was performed. The CT interval in each patient was defined as the number of days between the baseline and follow-up CT. The age of each patient at the baseline CT was regarded as the age of the patient in this study.

From the remaining RCC population who were examined by CT scans in the same period, additional patients who

did not receive any anti-cancer drugs including MTT were retrieved as the Control group. Patients with metastases in the thyroid gland, pancreas or spleen were excluded. The baseline CT studies were randomly selected from CT scans taken after the diagnosis of RCC had been confirmed. The follow-up CT studies were selected from CT scans taken at more than six months after the baseline CT studies were performed. The CT interval and the age of each patient were defined in the same way as in the MTT group. Thirteen patients who matched the cases in the MTT group for sex ratio, age and CT interval were assigned to the Control group. In that group, nine patients underwent unilateral total nephrectomy, three patients underwent unilateral partial nephrectomy, and one patient underwent bilateral partial nephrectomy.

CT technique

The CT examinations were performed using multi-row detector CT scanners with 256 or 64 detector rows (Brilliance iCT or Brilliance 64, Philips Medical Systems, Best, the Netherlands). The collimation width of each detector was 0.625 mm. In all patients, CT scans were performed in the supine position under inspiration breath-holding. The beam pitch was 0.5 to 0.6. The number of patients who underwent intravenous (IV) injection of iodinated contrast agents was nine out of thirteen in baseline CT studies of the MTT group, five out of thirteen in follow-up CT studies of the MTT group, seven out of thirteen in baseline CT studies of the Control group and six out of thirteen in follow-up CT studies of the Control group. Five patients in the MTT group and six patients in the Control group underwent IV contrast injection in both the baseline and follow-up CT studies.

Imaging analysis

The Centricity PACS RA1000 Radiology Workstation and AW Server 2.0 (GE Healthcare, Milwaukee, WI, USA) were used for imaging analysis. The volume of the pancreas, thyroid gland, and spleen in each CT scan was measured using the "Auto Contour" function installed in the AW Server 2.0. This function helps the interpreter to easily perform automated volumetric measurement by area summation [11,12].

All 5-mm-thick axial images of selected CT scans were anonymized and sent from the PACS workstation to the AW server for volume analysis. Initially, the region of interest (ROI) of each target organ was set by manually outlining the margins of the organ in all axial CT images in which the organ was depicted (Figure 1A). The ROI setting was based on the mutual agreement of two radiologists, having three and twenty years' experience in abdominal radiology respectively. Surrounding structures such as vessels and intestinal tract were carefully excluded from the ROI. The "Auto Contour" function automatically multiplied the ROI area by 5-mm slice thickness (Figure 1B), and estimated the organ volume by summing the products.

Statistical analysis

Statistical differences in age, sex ratio, and CT interval between the MTT and Control groups were compared using the Mann-Whitney U test (age and CT interval) or Pearson's

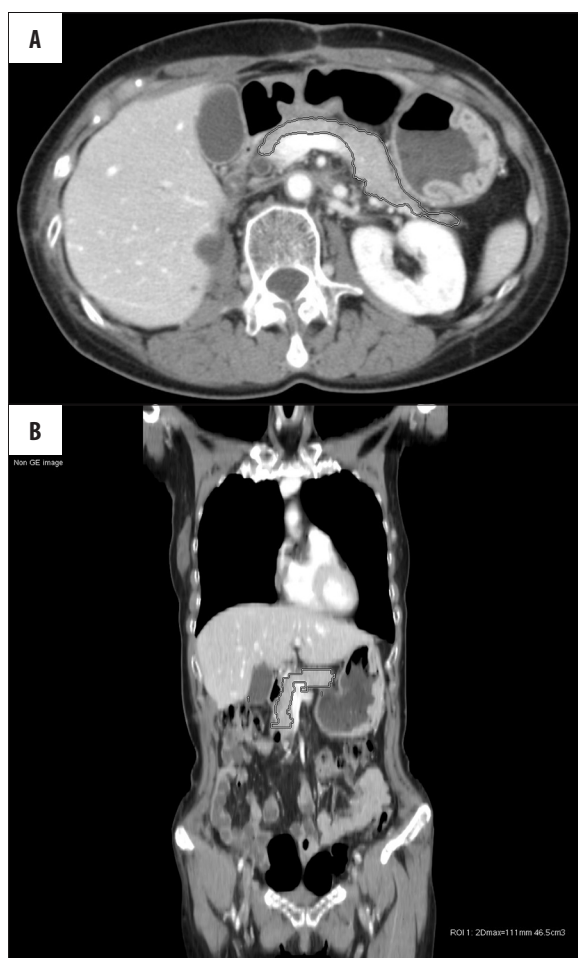


Figure 1. ROIs of each target organ (in this case, the pancreas) were set by manually outlining its margins in all CT images in which the organ was depicted (A). The “Auto Contour” function automatically multiplied the ROI area in each slice by the slice thickness, and estimated the organ volume by summing the products (B).

chi-squared test (sex ratio). Volume differences in the pancreas, thyroid gland, and spleen between the baseline and follow-up CT studies in both groups were statistically analysed using the Wilcoxon test. The atrophic ratio, defined as the ratio of the organ volume in the follow-up CT to that in the baseline CT, was compared between the MTT group and the Control group using the Mann-Whitney U test. All statistical analyses were performed using StatMate IV (ATMS Co., Ltd., Tokyo, Japan).

Results

The background of the patients in the MTT group and Control group is summarised in Table 1.

The MTT group consisted of thirteen patients, ranging from 12 to 89 years (mean 60.7 ± 18.1) and included ten males and three females. The therapy duration ranged from 180 to 363 days (mean 267.3 ± 66.3). The CT interval of the MTT group ranged from 196 to 396 days (mean 316.6 ± 77.2). On the other hand, the Control group consisted of thirteen patients ranging from 14 to 87 years (mean 60.1 ± 17.3) and included

ten males and three females. The CT interval of the Control group ranged from 182 to 376 days (mean 286.8 ± 73.8). Statistical analyses revealed no significant differences in age, sex ratio and CT interval between the two groups.

Pancreas

In the MTT group, the pancreatic volume ranged from 21.1 to 103.0 cm³ (mean 55.2 ± 26.5 cm³) in the baseline CT and from 14.6 to 93.6 cm³ (mean 39.3 ± 22.0 cm³) in the follow-up CT. In the Control group, the ranges were from 27.2 to 115.4 cm³ (mean 60.5 ± 21.7 cm³) in the baseline CT and from 25.0 to 119.1 cm³ (mean 61.1 ± 22.4 cm³) in the follow-up CT. Statistical analysis showed a significant difference in the pancreatic volume between the baseline and follow-up CT studies in the MTT group ($P < 0.01$), whereas no significant difference was found in the Control group (Figure 2).

The atrophic ratio of the pancreas was 0.74 ± 0.20 in the MTT group and 1.01 ± 0.04 in the Control group. A decrease of more than 10% in pancreatic volume was observed in eleven patients of the MTT group, whereas it was not demonstrated in any patients of the Control group. The difference in the atrophic ratio of the pancreas was statistically significant between the MTT group and the Control group ($P < 0.01$) (Figures 2, 3).

Thyroid gland

In the MTT group, the thyroid volume ranged from 4.4 to 37.9 cm³ (mean 14.5 ± 8.7 cm³) in the baseline CT and from 0.8 to 14.4 cm³ (mean 7.9 ± 4.2 cm³) in the follow-up CT. In the Control group, the ranges were from 6.0 to 21.5 cm³ (mean 11.1 ± 3.9 cm³) in the baseline CT and from 5.9 to 21.8 cm³ (mean 11.1 ± 4.0 cm³) in the follow-up CT. Statistical analysis showed a significant difference in the thyroid volume between the baseline and follow-up CT studies in the MTT group ($P < 0.01$), whereas no significant difference was found in the Control group (Figure 4).

The atrophic ratio of the thyroid gland was 0.58 ± 0.28 in the MTT group and 1.00 ± 0.04 in the Control group. In the MTT group, eleven out of thirteen patients showed a reduction in thyroid volume of more than 10%, while one patient showed thyroid enlargement of more than 10%. The difference in the atrophic ratio of the thyroid gland was statistically significant between the MTT group and the Control group ($P < 0.01$) (Figures 4, 5).

Spleen

In the MTT group, the splenic volume ranged from 53.7 to 229.4 cm³ (mean 124.2 ± 51.7 cm³) in the baseline CT and from 45.2 to 221.7 cm³ (mean 98.3 ± 49.2 cm³) in the follow-up CT. In the Control group, the ranges were from 63.0 to 345.4 cm³ (mean 143.8 ± 77.7 cm³) in the baseline CT and from 57.2 to 355.2 cm³ (mean 146.1 ± 76.2 cm³) in the follow-up CT. Statistical analysis showed a significant difference in the spleen volume between the baseline and follow-up CT studies in the MTT group ($P < 0.05$), whereas no significant difference was found in the Control group (Figure 6).

Table 1. Background of the patients in the MTT group and Control group.

No	Sex	Age (years)	Drug	Therapy duration (days)	CT interval (days)	Volume baseline(cm ³) – Volume follow-up (cm ³) – Atrophic ratio								
						Pancreas			Thyroid			Spleen		
MTT group														
1	M	69	Sorafenib	325	394	53.6	45.9	0.86	8.7	8.5	0.98	62.5	65.1	1.04
2	M	74	Sorafenib	363	375	21.1	14.6	0.69	12.2	9.9	0.81	123.2	75.1	0.61
3	M	89	Sorafenib	193	233	21.1	20.7	0.98	11..7	7.3	0.62	129.2	132.1	1.02
4	M	52	Sunitinib	180	247	103.0	93.6	0.91	8.4	9.9	1.18	58.5	77.9	1.33
5	M	54	Sunitinib	189	196	77.3	23.1	0.30	11.3	5.8	0.51	76.5	51.4	0.67
6	M	56	Sunitinib	267	308	38.9	34.2	0.88	19.8	14.4	0.73	138.0	106.1	0.77
7	M	62	Sunitinib	341	396	72.9	62.5	0.86	16.0	4.5	0.28	96.9	48.2	0.50
8	M	71	Sunitinib	275	322	46.4	37.7	0.81	25.9	13.8	0.53	229.4	221.7	0.97
9	M	72	Sunitinib	210	217	90.6	62.5	0.69	15.6	7.5	0.48	140.3	164.6	1.18
10	M	72	Sunitinib	189	265	22.5	19.6	0.87	37.9	13.1	0.35	163.8	103.1	0.63
11	F	12	Sunitinib	272	299	41.3	30.2	0.73	6.5	0.8	0.12	194.2	116.3	0.60
12	F	43	Sunitinib	311	359	83.2	47.6	0.57	10.1	4.6	0.46	53.7	45.2	0.84
13	F	63	Sunitinib	360	377	46.7	18.9	0.40	4.4	2.0	0.45	138.8	70.8	0.48
Control group														
1	M	41			182	115.4	119.1	1.03	21.5	21.8	1.01	99.7	109.8	1.10
2	M	50			234	59.4	57.6	0.97	6.0	5.9	0.97	115.3	106.2	0.92
3	M	57			187	55.7	56.6	1.02	9.2	9.2	1.02	167.6	161.4	0.96
4	M	58			284	86.0	84.5	0.98	11.0	10.6	0.96	63.0	57.2	0.91
5	M	63			365	73.5	75.0	1.02	13.9	14.5	1.02	286.3	265.3	0.93
6	M	71			357	53.1	54.6	1.03	9.2	9.3	1.03	129.5	144.5	1.12
7	M	71			369	55.4	57.6	1.04	12.6	12.5	1.04	95.6	96.9	1.01
8	M	71			376	27.2	25.0	0.92	6.7	6.6	0.92	115.2	125.3	1.09
9	M	73			282	63.5	66.3	1.04	10.3	9.1	1.04	97.6	97.8	1.00
10	M	87			364	49.0	50.6	1.03	7.1	7.4	1.03	117.4	121.5	1.03
11	F	14			219	32.8	34.0	1.04	11.4	11.5	1.04	106.2	118.7	1.12
12	F	62			321	48.9	48.2	0.99	11.8	12.5	0.99	345.4	355.2	1.03
13	F	63			189	66.2	64.7	0.98	13.4	13.3	0.98	130.2	139.4	1.07

The atrophic ratio of the spleen was 0.82 ± 0.26 in the MTT group and 1.02 ± 0.07 in the Control group. Reduction rate in splenic volume of more than 10% was observed in eight out of thirteen patients in the MTT group, while two patients showed splenic enlargement of more than 10%. The difference in the atrophic ratio of the spleen was statistically significant between the MTT group and the Control group ($P < 0.05$) (Figures 6, 7).

Discussion

The pancreas, thyroid gland and spleen of the patients in the MTT group showed statistically significant volume loss

after TKI induction, while no significant volume change was observed in any of the three organs of the patients in the Control group. In the comparison of atrophic ratios between the MTT and Control groups, a statistically significant difference was demonstrated in all the organs of interest.

Previous study reported that prolonged sorafenib administration for more than 2 years induced pancreatic atrophy [9]. In our study, the mean therapy duration was 267.3 days, and the most prominent pancreatic volume reduction (atrophic ratio=0.30) was observed in a patient who received sunitinib for 189 days. Our result demonstrated

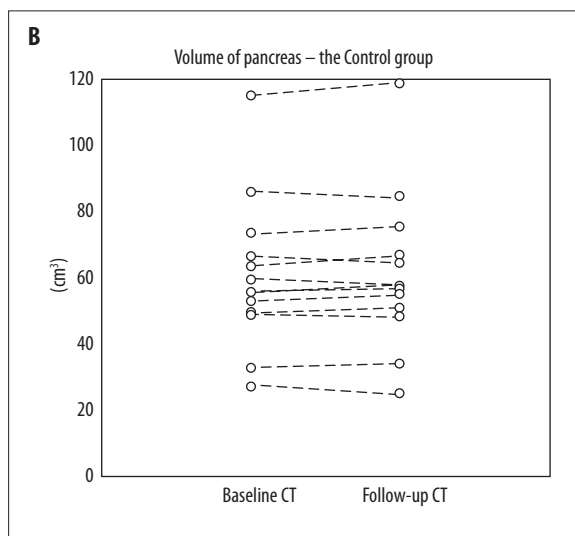
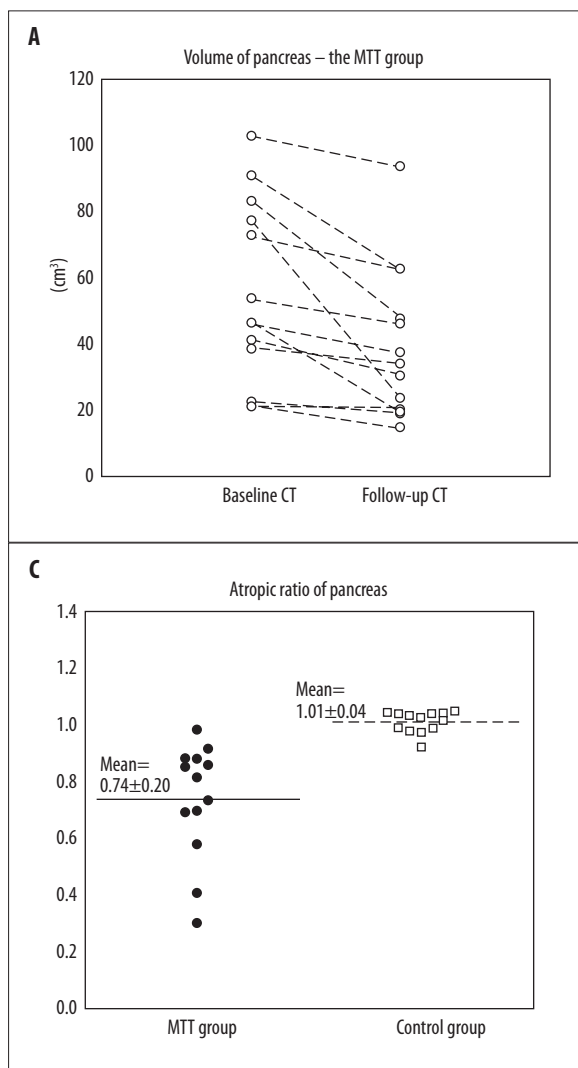


Figure 2. (A, B) Change in pancreatic volume from the baseline CT to the follow-up CT. The pancreatic volume decreases in all patients of the MTT group (A). On the other hand, no significant volume change is found in the patients of the Control group (B). (C) Atrophic ratio of the pancreas. The differences in the atrophic ratio of the pancreas between the MTT and Control groups are statistically significant ($P < 0.01$).

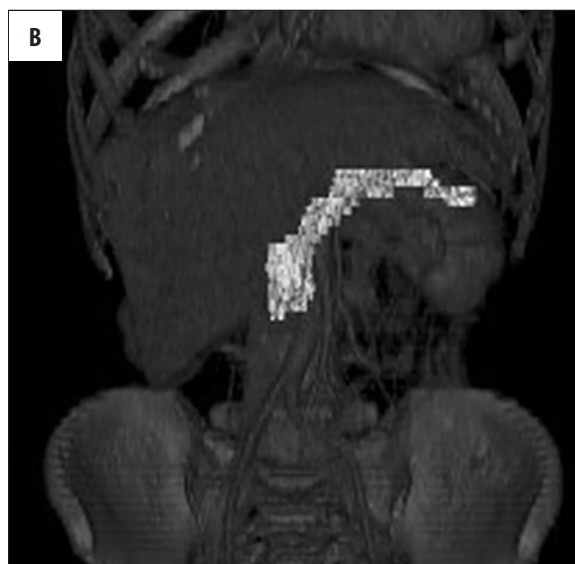
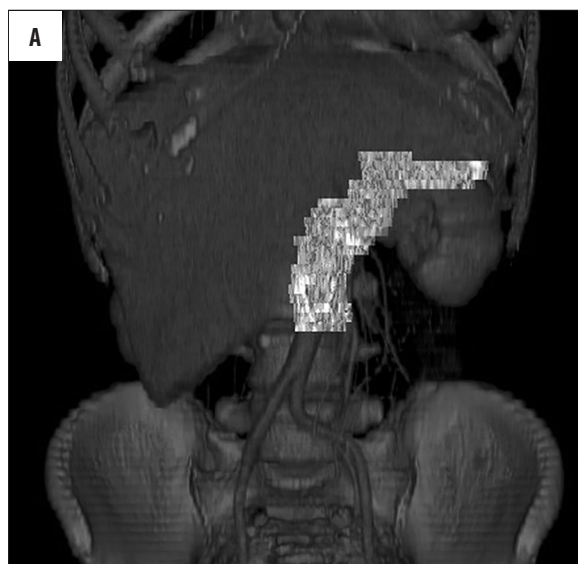


Figure 3. Baseline (A) and follow-up (B) reconstructed images under CT-volumetry of a 54-year-old male receiving single-agent sunitinib therapy for 189 days, whose atrophic ratio of the pancreas was 0.30. Pancreas atrophy is clearly observed in Figure (B) in comparison with Figure (A).

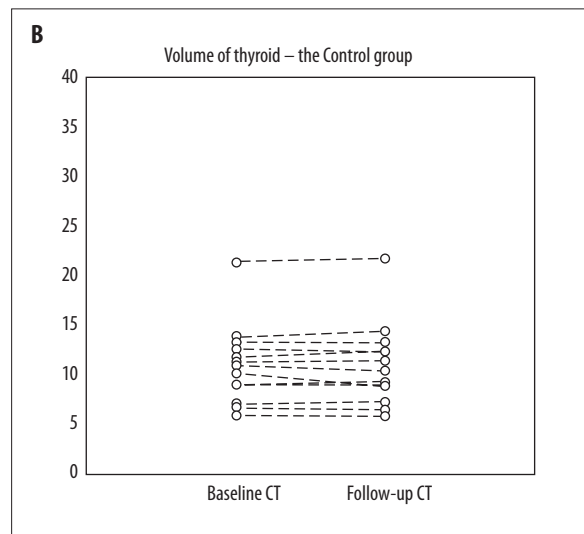
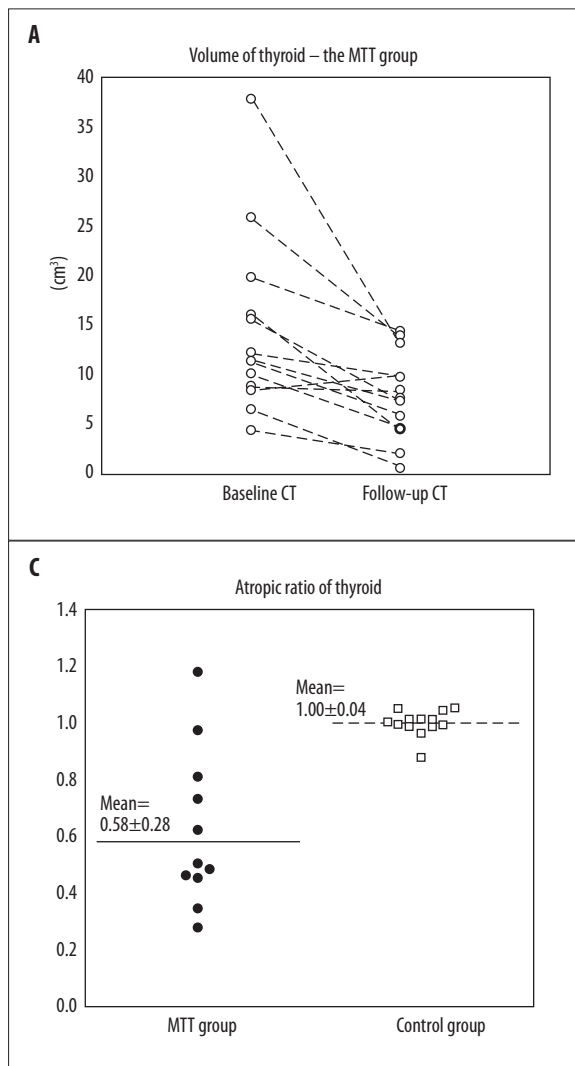


Figure 4. (A, B) Change in thyroid volume from the baseline CT to the follow-up CT. Statistically significant reduction in thyroid volume is found in patients of the MTT group (A). No significant volume change is found in the patients of the Control group (B). (C) Atrophic ratio of the thyroid gland. The differences in the atrophic ratio of the thyroid gland between the MTT and Control groups are statistically significant ($P < 0.01$).

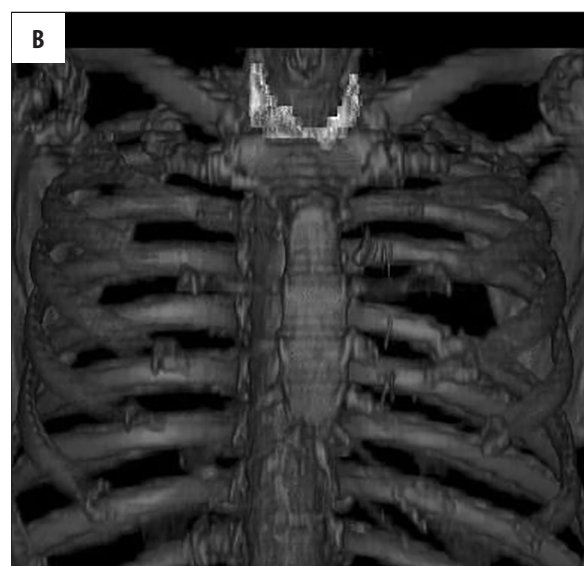
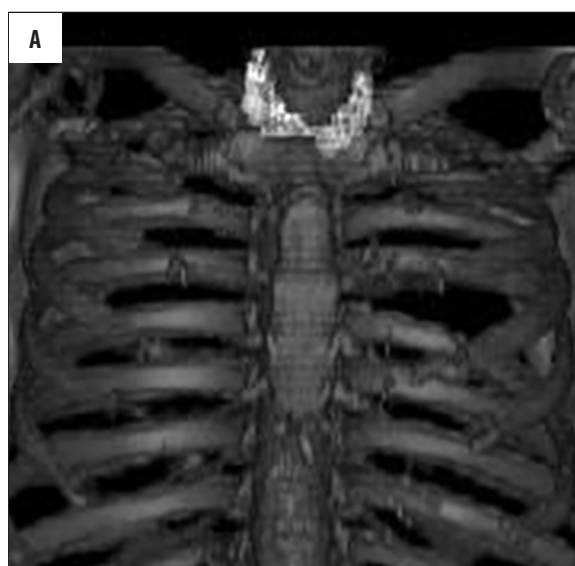


Figure 5. Baseline (A) and follow-up (B) reconstructed images under CT-volumetry of a 71-year-old male receiving single-dose sunitinib therapy for 275 days, whose atrophic ratio of the thyroid gland was 0.53. The thyroid gland seems smaller in Figure (B) than in Figure (A).

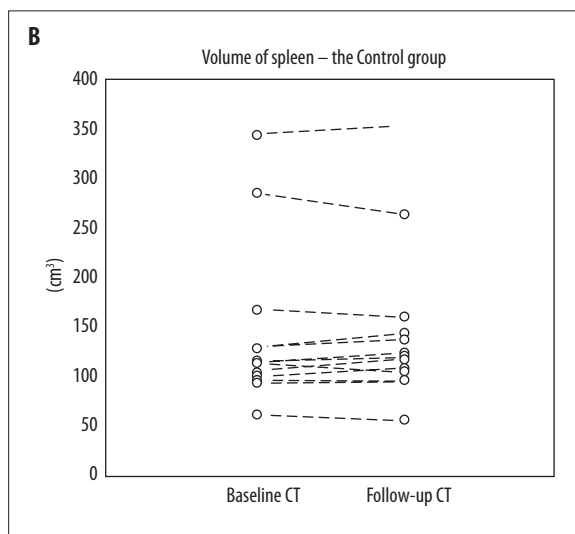
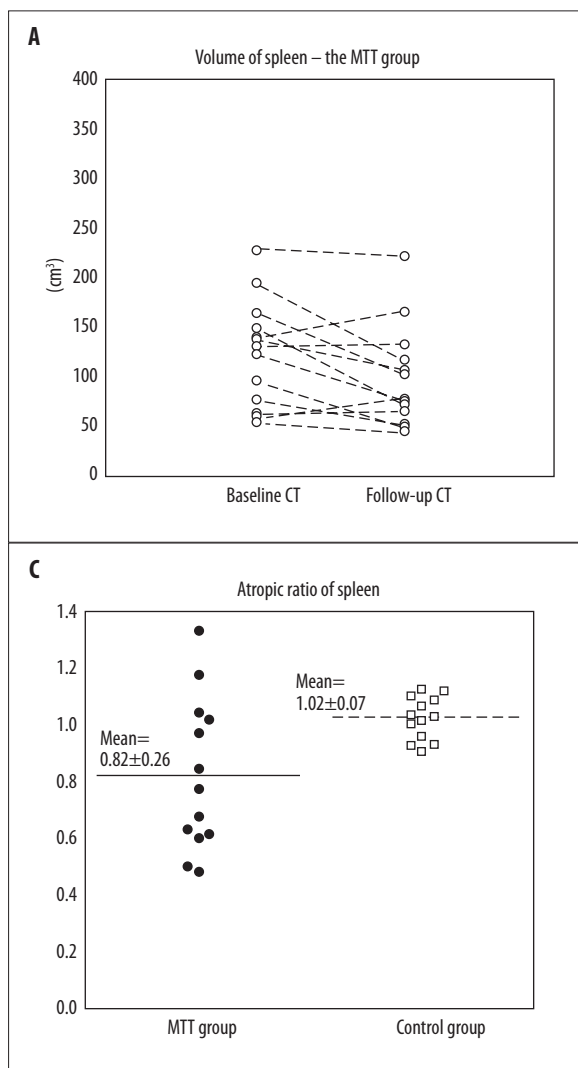


Figure 6. (A, B) Change in splenic volume from baseline CT to follow-up CT. Statistically significant reduction in splenic volume is found in patients of the MTT group (A). No significant volume change is found in the patients of the Control group (B). (C) Atrophic ratio of the spleen. The differences in the atrophic ratio of the spleen between the MTT and Control groups are statistically significant ($P < 0.05$).

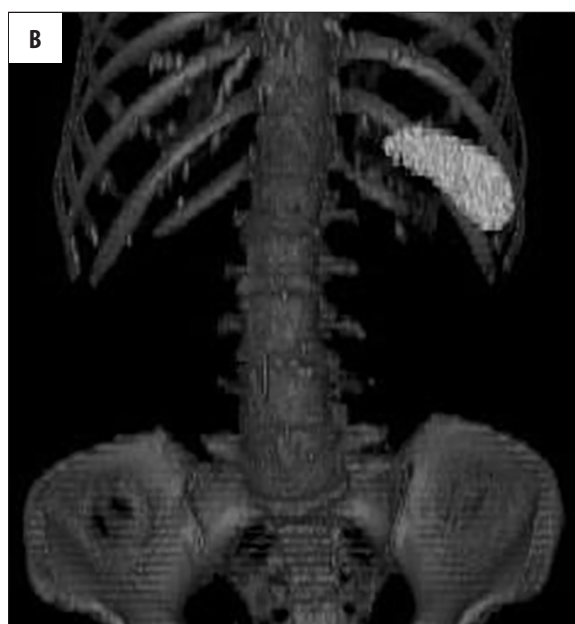
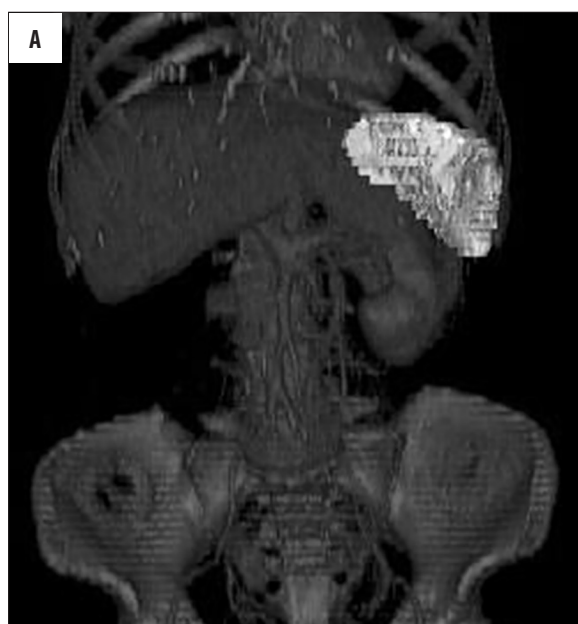


Figure 7. Baseline (A) and follow-up (B) reconstructed images under CT-volumetry of a 63-year-old female receiving single-agent sunitinib therapy for 360 days, whose atrophic ratio of the spleen was 0.48. Splenic atrophy is observed in Figure (B) in comparison with Figure (A).

that pancreatic atrophy can be induced by sunitinib as well as sorafenib, and it might be classified into earlier manifestations of TKI administration rather than previously expected. Further investigation is necessary to assess the correlation between volume reduction of pancreas and abnormal exocrine or endocrine pancreatic function.

Thyroid dysfunction is also a well-known side effect of TKI administration [1,5–8]. Previous reports have revealed that TKIs can cause volume reduction in the thyroid gland as well as hypothyroidism [5–8]. Van Doom et al. demonstrated two cases of thyroid gland atrophy in patients with hepatocellular carcinoma receiving sorafenib for 72 and 76 weeks, respectively [6]. Shinohara et al. showed that the median reduction rate of thyroid gland was 30% at the last evaluation during sunitinib treatment (median six cycles, range 1–23 cycles) [8]. In our study, eleven out of thirteen patients who received TKI therapy showed thyroid volume decrease of more than 10%, and the mean atrophic ratio of the thyroid gland was 0.58 in the MTT group. The present study confirmed that single-agent sunitinib or sorafenib therapy can induce statistically significant thyroid volume reduction in patients who receive the drugs for more than six months.

To our knowledge, there is no previous clinical study investigating splenic volume change in patients under TKI treatment. In the present study, the difference of the splenic atrophic ratio between the MTT and Control groups was statistically significant. Our result suggests that single-agent sunitinib or sorafenib therapy might induce splenic atrophy within one year after the beginning of the treatment. However, the mean atrophic ratio of the spleen in the MTT group was 0.82, which was higher than that of the pancreas and thyroid gland. This is because two patients in the MTT group showed splenic enlargement of more than 10%, although splenic volume reduction of more than 10% was observed in eight out of thirteen patients. Shem et al. reported pathological organ toxicity following oral administration of sunitinib in rats and monkeys [13]. In their non-clinical study, lymphoid atrophy including splenic atrophy was evident in the rats and monkeys, while increased splenic hematopoiesis occurred in the rats [13]. In our study, it is presumed that the anti-angiogenic activity of TKIs might cause splenic atrophy in some patients, whereas the drugs might also induce splenic hematopoietic enhancement, resulting in splenic enlargement in others. Further investigation is necessary to assess the correlation of the hematopoietic function and spleen volume reduction, with the adjustment for other confounders such as anemia, liver dysfunction, hypovolemia and weight loss.

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Further analysis for targeted effect of TKIs on other organs remains an issue. As it is previously reported that TKIs can cause renal dysfunction, renal volume change after TKI administration should be investigated [15]. In our case, since all of the patients in the MTT group had undergone unilateral total nephrectomy, it is presumed that the compensatory enlargement of the remaining kidney would influence the results, making the evaluation for kidney volume reduction difficult. Liver dysfunction is also reported as a side effect of TKI administration [14]. However, the evaluation of liver toxicity should include morphological deformity as well as total size change. In our case, as the effects of TKI therapy were assessed by volumetric technique alone, morphological analysis was not possible. For these reasons, we eliminated the kidney and liver from the list of analysed organs in this study.

Our retrospective study has several limitations. First, some CT scans were taken without IV contrast enhancement due to renal dysfunction. As a consequence, we could not evaluate the change in blood perfusion of the organs of interest after TKI administration. Second, patients receiving sorafenib therapy and patients receiving sunitinib therapy are assigned to the same MTT group, making it impossible to compare the difference in atrophic effects between sunitinib and sorafenib.

Conclusions

In our study, single-agent sorafenib or sunitinib therapy induced statistically significant atrophic changes in the pancreas, thyroid gland and spleen within one year after the beginning of the treatment. Our result suggests that evaluating the organ volume changes in patients receiving TKIs may be of importance for radiologists to assess their clinical side effects. Further evaluation will be necessary to investigate the correlation between the degree of organ volume reduction and the frequency of clinical manifestations.

Conflict of interest

The authors have no conflict of interest.

Acknowledgement

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