Case Report

Spatial and temporal responses of metastatic renal cell carcinoma lesions to sequential treatments over a 10-year period

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Abbreviations & Acronyms
CT = computed tomography
IFN = interferon
IL-2 = interleukin-2
IMDC = International Metastatic renal cell carcinoma Database Consortium
LN = lymph node
mRCC = metastatic renal cell carcinoma
MSKCC = Memorial Sloan Kettering Cancer Center
OS = overall survival
TKI = tyrosine kinase inhibitor

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Introduction: Survival among patients with metastatic renal cell carcinoma has been prolonged with advancements in treatment; however, its cure remains challenging. We describe three patients with metastatic renal cell carcinoma who showed long-term survival and discuss their response to sequential therapy.

Case presentation: Three patients underwent radical nephrectomy and subsequent treatment for metastatic renal cell carcinoma. They received cytokine therapy, target therapy, and an immuno-oncology drug. Metastatic growth patterns based on computed tomography scans were plotted using a line or bar graph to visualize the response to sequential therapy, and the numbers of International Metastatic renal cell carcinoma Database Consortium risk score were also calculated.

Conclusion: The metastatic lesions responded differently to the administered drugs, and the sum of the axis of measurable metastasis is valuable to get an overview of treatment. Furthermore, having the same or lower International Metastatic renal cell carcinoma Database Consortium risk score during sequential therapy, and long duration of each target therapy contributed to prolonged survival.

Key words: IMDC model, long-term survival, metastatic renal cell carcinoma, multiple metastasis, sequential therapy.

Keynote message

Some patients with mRCC have shown an excellent response to sequential therapy, as indicated by their long-term survival rates. In this paper, through line charts and bar charts, we demonstrate how metastatic lesion growth assessed by CT examination and changes in IMDC risk score during sequential therapy are useful for visualizing responses to various drug regimens and are valuable means to obtain an overview of treatment progress in patients with long survival periods.

Introduction

OS in patients with mRCC has improved as molecular targeted drugs are available and sequential therapy is recommended in guidelines.[1,2]

In this paper, we report three patients with mRCC who received sequential therapy for more than 10 years. The effectiveness of the drugs was evaluated by the rate of change from the baseline of the sum of the axis of measurable metastasis. The relationship between change in metastasis, sequential therapy, and IMDC risk score was discussed.

Case presentation

Three patients who underwent radical nephrectomy and developed mRCCs and underwent five or six sequential therapy regimens were included; CT was performed every 3–6 months. Patient characteristics and treatments are shown in Table 1. We examined each measurable metastatic lesion by CT and plotted the rate of the sum of the major axes of the metastatic

Table 1 Patients' characteristics

	Case 1	Case 2	Case 3
Gender	Male	Male	Female
Age (years)	50	73	78
Initial tumor	pT3bN0M1	pT1aN0M0	pT2N0M0
Pathology	Clear cell, G2	Clear cell, G2	Clear cell, G1
Metastasis	Lung, pleura, LN	Lung, LN	Pancreas, lung, skin, thyroid, LN
MSKCC risk	Intermediate	Favorable	Intermediate
treatment (months)			
1st line	IFN-alpha (6.3)	IFN-alpha (5.2)	IFN-alpha (12.0)
2nd line	IL-2 (9.8)	IL-2 (30.9)	IL-2 (7.0)
3rd line	Sorafenib (34.2)	Sorafenib (40.0)	Sorafenib (0.1)
4th line	Sunitinib (35.6)	Axitinib (33.4)	Sunitinib (61.0)
5th line	Axitinib (32.7)	Nivolumab (6.2)	Nivolumab (4.1)
6th line	Nivolumab (18.0)		Axitinib (6.2)

lesions and minor axes of the LNs metastasis using a line chart. Various responses of the metastatic lesions to each drug are shown using the stacked bar chart. IMDC risk score were assessed during every CT examination. This study was approved by the Review Board of Tokyo Women's Medical University (Approval number: 4882).

Case 1

The patient was a 50-year-old man diagnosed with right RCC and multiple lung metastases at 38 years of age. A line chart indicating the rate of change in the measurable metastatic lesions, change in IMDC risk score, and progress of sequential therapies are shown in Figure 1a. He underwent cytokine therapy followed by targeted therapy comprising sorafenib, a TKI, sunitinib, and axitinib. Some right lung metastatic lesions that were sensitive to sorafenib regressed significantly, but new lung lesions appeared during sunitinib therapy. These lesions were found to be sensitive to axitinib and therefore regressed in size when axitinib treatment was administered (Fig. 1b). A left lung S1 + S2 metastatic lesion responded to the three TKIs but never diminished (Fig. 1c). During axitinib administration, a left hilar LN metastatic lesion developed (Fig. 1d) and another left S1 + S2 lesion also demonstrated regrowth (Fig. 1c). Finally, nivolumab treatment commenced, and after only three administrations, the CT showed that the metastatic lesions had significantly diminished in size. The IMDC risk score was one or two during sequential therapy.

Case 2

The patient was a 73-year-old man who underwent radical nephrectomy at 55 years of age. He developed multiple lung metastasis, 74 months after the surgery. The rate of metastatic lesions and sequential therapies are shown in Figure 2a, and stacked bar charts of sum of the measurable lung metastasis and LNs are shown in Figure 2b,c. He was administered cytokine therapy followed by sorafenib, and he then developed hoarseness due to mediastinum LN metastasis. Axitinib therapy was commenced, after the regrowth of metastatic lesions; further, nivolumab was administered and the metastatic lesions regressed rapidly. The patient was diagnosed with fulminant type I diabetes mellitus after nivolumab had been administered 14 times. Although treatment was stopped, regrowth of metastatic lesions has not been observed for >1 year. IMDC risk score were zero or one during sequential therapy.

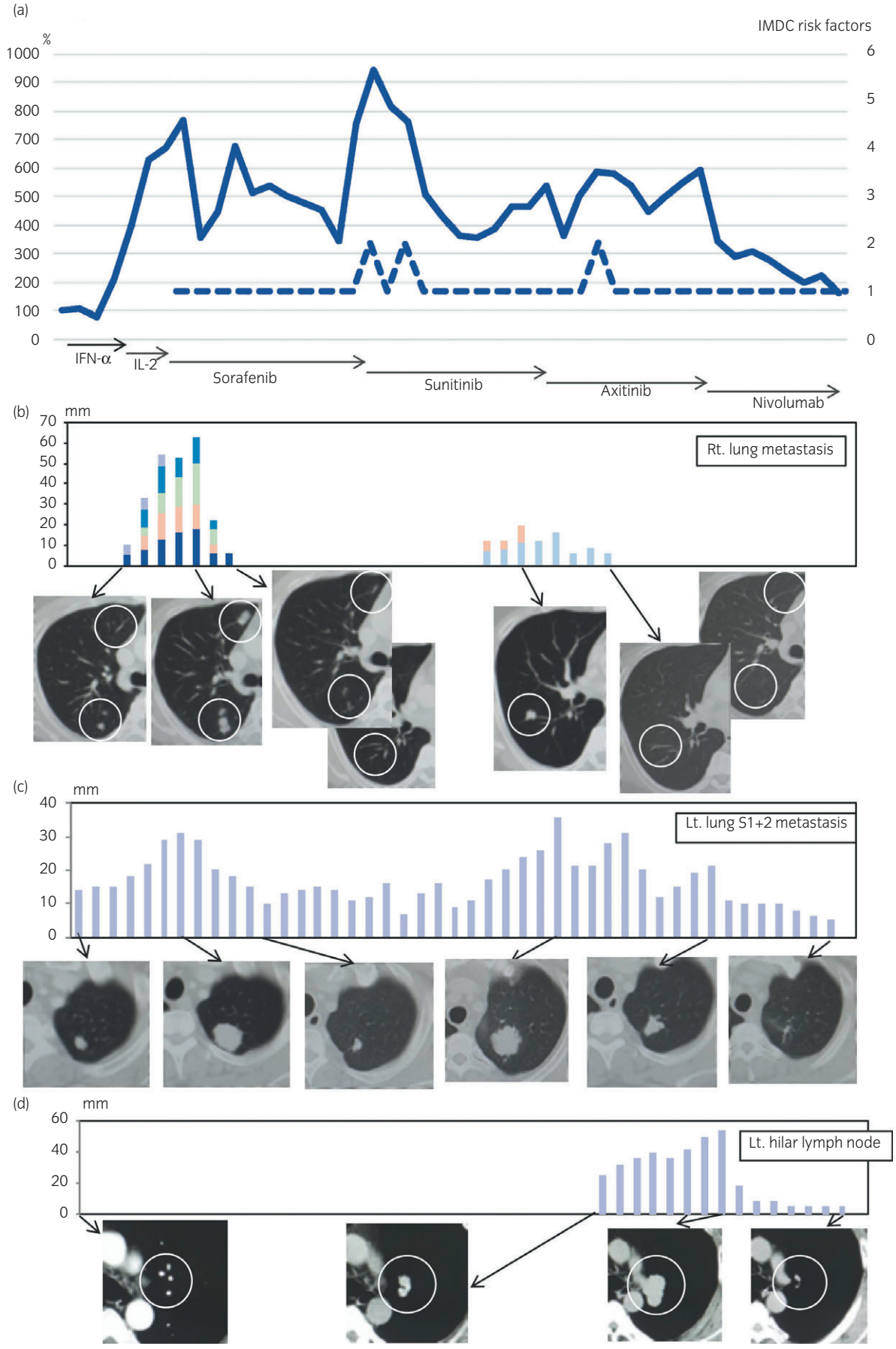
Case 3

The patient was a 75-year-old woman who underwent radical nephrectomy at 58 years of age. Approximately 5 years after the surgery, she underwent a duodenum-preserving total pancreatectomy due to mRCC. The rate of metastatic lesions and sequential therapies was shown in Figure 3a. She underwent cytokine therapy followed by sunitinib therapy, which resulted in a decrease in the size of the lung and LN metastatic lesions. Eventually, LN and thyroid metastatic lesions slowly increased in size, and sunitinib was administered. Following this, nivolumab therapy was commenced, but metastatic lesions in the thyroid and right paratracheal LN grew larger; thus, nivolumab was discontinued and axitinib therapy was administered. Approximately 2 months later, the CT showed that the metastatic lesions had decreased in size (Fig. 3b–d).

Discussion

Before January 2008, only cytokine therapies were available for mRCC in Japan. The median OS time was 21.4 months among 1463 Japanese patients with mRCC during the cytokine era.[3]

Fig. 1 (a) The response of the metastatic lesions measured by CT examination and progress of sequence therapy of patient 1. The measurable major axis of metastatic lesions and the minor axis of LN metastasis were measured by CT examination at each time point. Each size measurement of the metastatic lesion was summed, and the rate of change from the baseline and numbers of IMDC risk score were assessed at each CT examination and were plotted on the line graph. Lung metastatic lesions were separated by laterality. The drugs used in the sequence therapies are indicated below the chart by time series. (b) The major axis of each right lung metastatic lesion was summed and plotted on the stacked bar chart. The CT examination showed that some of the metastatic lung lesions showed growth during cytokine therapy and regression during sorafenib therapy. However, during the second round of therapy with the TKI sunitinib, new lung metastatic lesions appeared and then regressed entirely with axitinib administration. (c) The major axis of left S1 + S2 lung metastasis was plotted on the stacked bar chart. The CT examination showed that the left S1 + S2 lung metastasis temporarily responded to the three TKIs and almost diminished with the administration of nivolumab. (d) The minor axis of left hilar LN metastasis was plotted on the stacked bar chart. The LN metastatic lesions appeared after two TKIs and were also resistant to the third TKI, axitinib. However, these lesions rapidly shrunk with the administration of nivolumab.



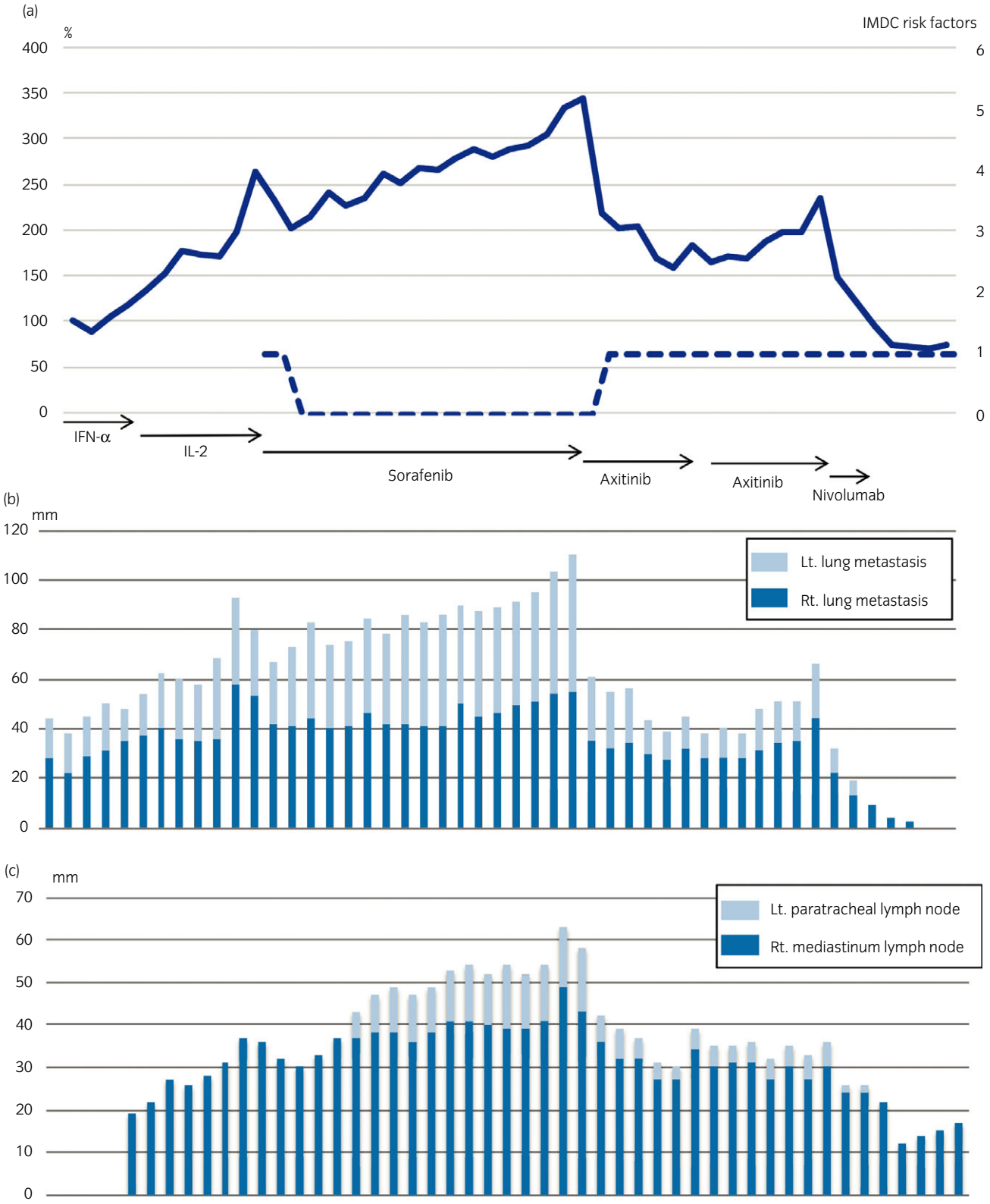


Fig. 2 (a) The response of the metastatic lesions measured by CT examination and progress of sequence therapy of patient 2. Each size measurement of the metastatic lesion was summed, and rate of change from the baseline and IMDC risk score were assessed at each CT examination and were plotted on the line graph. (b) The major axis of each right and left lung metastatic lesion was summed and plotted on the stacked bar chart. (c) The minor axis of each right and left lung metastatic lesion was summed and plotted on the stacked bar chart.

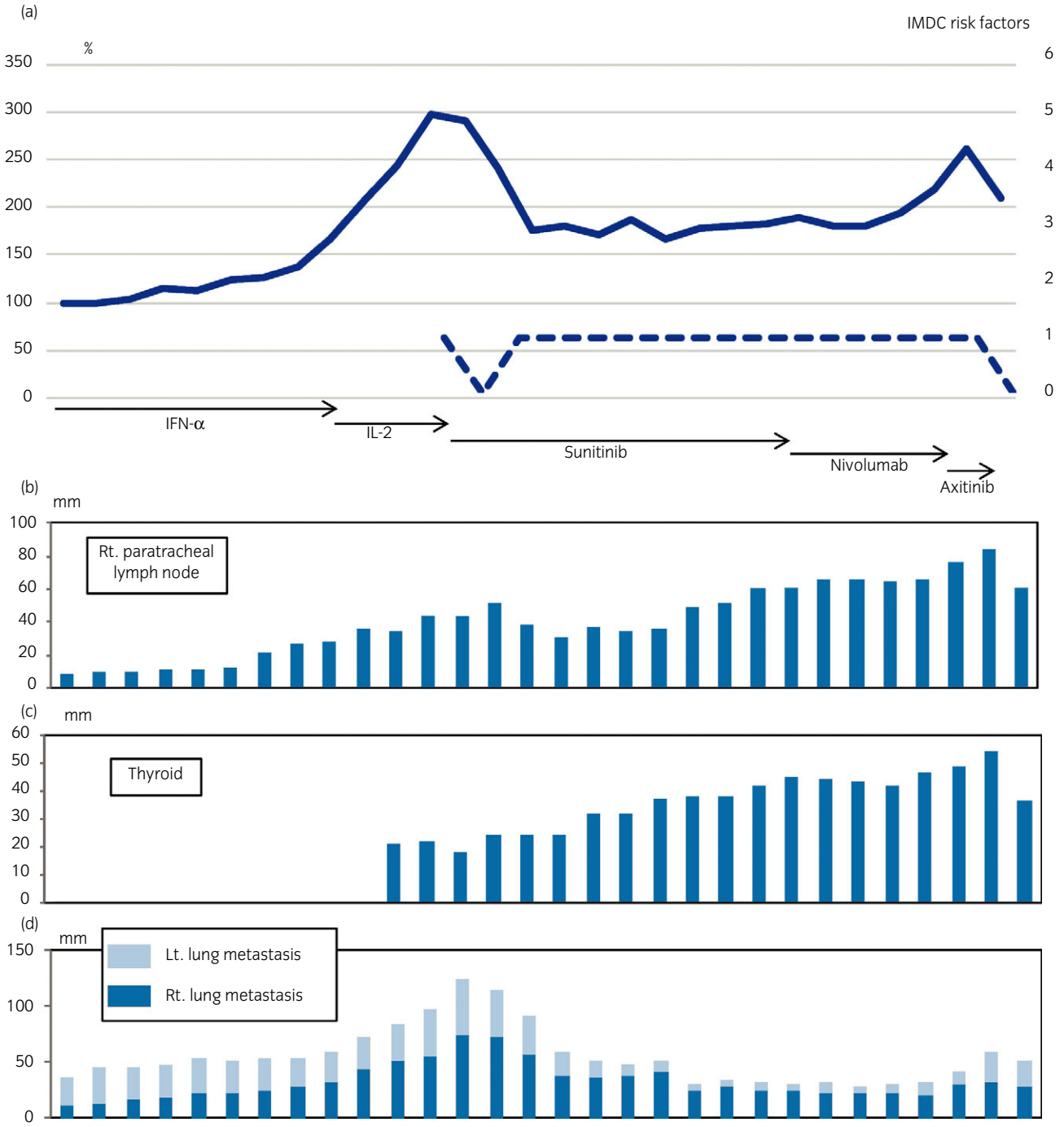


Fig. 3 (a) The response of the metastasis measured by CT examination and progress of sequence therapy of patient 3. Each size measurement of the metastatic lesion was summed and rate of change from the baseline and numbers of IMDC risk score were assessed at each CT examination and were plotted on the line graph. (b) The minor axis of right paratracheal LN measured by CT examination was plotted by bar chart. (c) The major axis of thyroid metastasis measured by CT examination was plotted by bar chart. (d) The major axis of each lung metastasis in the right and left lung measured by CT examination was summed and plotted by stacked bar chart.

The OS has clearly improved now that molecular targeted drugs are available. The median OS was 26.4 and 22.9 months for first-line TKIs (sunitinib and pazopanib, respectively)[4,5] and that for a second-line TKI was 15.2 months for axitinib after sunitinib.[6] The median OS was 25.0 months for second-line nivolumab and the survival benefit of nivolumab was not affected by prior administration of TKIs.[7]

Detailed examination of metastatic growth patterns revealed that the response to each drug varied (Figs 1b–d, 2b,c, and 3b–d). Next-generation sequencing studies would help clarify the mechanisms of different responses. The different response to each drug may depend on different mutation variants of each metastatic lesion. Sankin *et al.* reported on the intratumoral genetic heterogeneity of RCC[8] and Becerra *et al.* reported on mutation discordance within

matched primary and mRCC tumor pairs.[9] Their study indicates that mutation discordance can occur within different lesions of mRCC.

It is difficult to evaluate the response of bone metastasis by CT and to measure metastatic lesions exhibiting central necrosis. We presented three cases in this paper; none had bone metastasis or metastatic lesions with central necrosis. Although our study has these limitations, we believe that change in the rate of the sum of the axis of measurable metastasis is valuable to obtain an overview of treatment progress in patients with long survival. The three patients had different IMDC risk score, but we think that having the same or lower IMDC risk score during sequential therapy, and long duration of each target therapy contributed to prolonged survival. We reported that patients who achieve a long-term response after first-line TKI therapy could have a favorable prognosis with second-line molecular targeted therapy.[10] We think that those patients reported in this paper could have a long-term administration of each TKI therapy and could have a favorable prognosis. Two out of three patients showed that nivolumab therapy was effective in inhibiting the metastases. Administration of TKIs for longer periods does not necessarily indicate good response to nivolumab therapy.

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Conflict of interest

The authors declare no conflict of interest.

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