

Case Report

# Deliberation on Deferred Cytoreductive Nephrectomy and Postoperative Treatment for Advanced Renal Cell Carcinoma: A Case Report

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## Keywords

Cabozantinib · Deferred cytoreductive nephrectomy · Immunotherapy · Renal cell carcinoma · The Morphology Attenuation Size and Structure criteria

## Abstract

In a rare case, free from systemic therapy, deferred cytoreductive nephrectomy was implemented in treating an advanced renal cell carcinoma with liver, lung, and splenic colon metastases. A 59-year-old man diagnosed with advanced renal cell carcinoma underwent deferred cytoreductive nephrectomy due to a partial response to systemic treatment after a period of 1 year. After the surgery, no additional treatment was implemented. Furthermore, after 10 months, the patient had no recurrence of renal cell carcinoma. Through a review of this case and deferred cases in the current literature, we could emphasize the importance of image evaluation and pathological findings as an indication for surgery and subsequent treatment options. However, there is room for debate with regards to the indications for deferred cytoreductive nephrectomy as well as a therapeutic strategy after the surgery. This report discusses the significance of deferred cytoreductive nephrectomy in terms of prognosis and quality-of-life improvement in advanced renal cancer.

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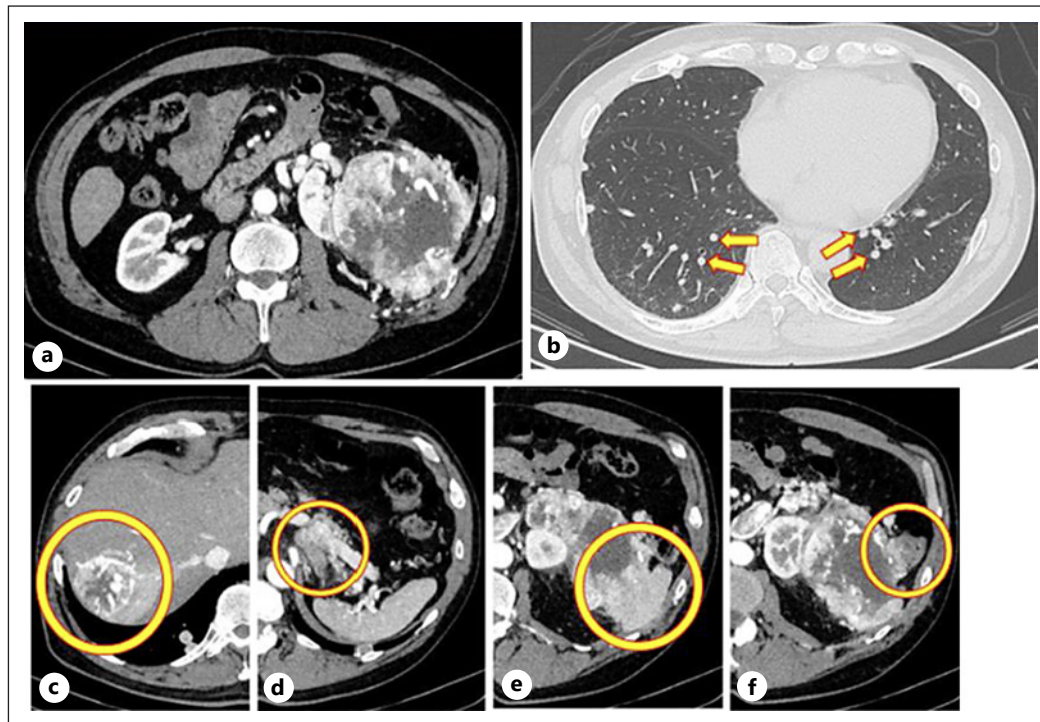
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## Introduction

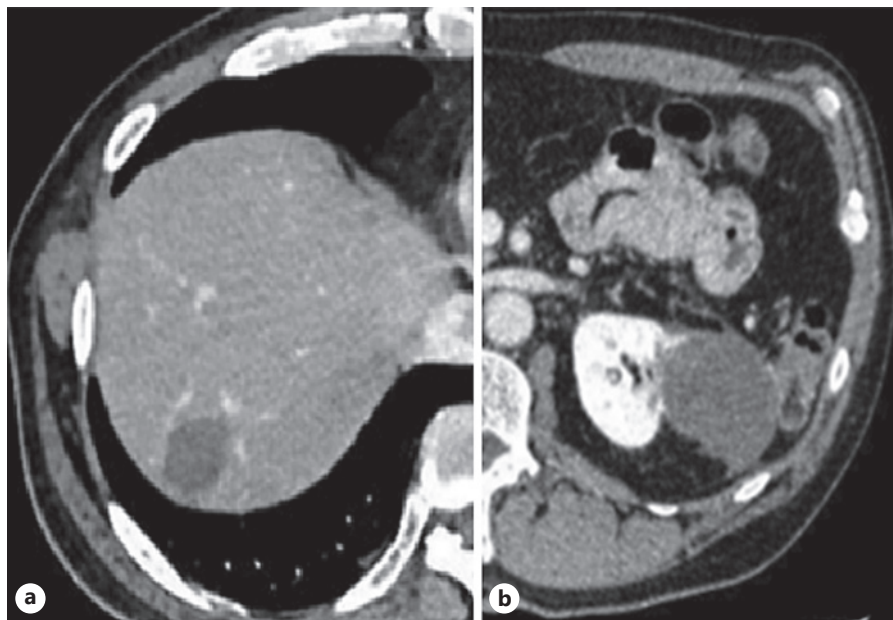
The indications of deferred cytoreductive nephrectomy (CN) in advanced renal cell carcinoma have not been clarified. Deferred CN can be used as an effective method in improving the prognosis of renal cell carcinoma [1]; however, its efficacy is not fully discussed [2]. Even though adverse events have been reported to immune checkpoint inhibitors and tyrosine kinase inhibitors [3, 4], postoperative systemic therapy is not discussed adequately. We observed a case in which deferred CN was successfully used to treat renal cell carcinoma. Throughout this case report, we will discuss the efficacy and indications of deferred CN.

## Case Presentation

The patient was a 59-year-old man, with no significant family or medical history. He was diagnosed with advanced renal cell carcinoma after examination by a physician and was thereafter introduced to our department. Contrast-enhanced computed tomography (CT) showed a left renal tumor, multiple lung metastases, a liver metastasis, and left adrenal metastasis. Furthermore, infiltration into the pancreas, spleen, and descending colon was also suspected (Fig. 1). We performed a percutaneous biopsy of the left renal tumor for pathological diagnosis as an unresectable renal cell carcinoma. Pathological findings revealed clear cell carcinoma with an acidophilic cytoplasm using hematoxylin-eosin-staining. The

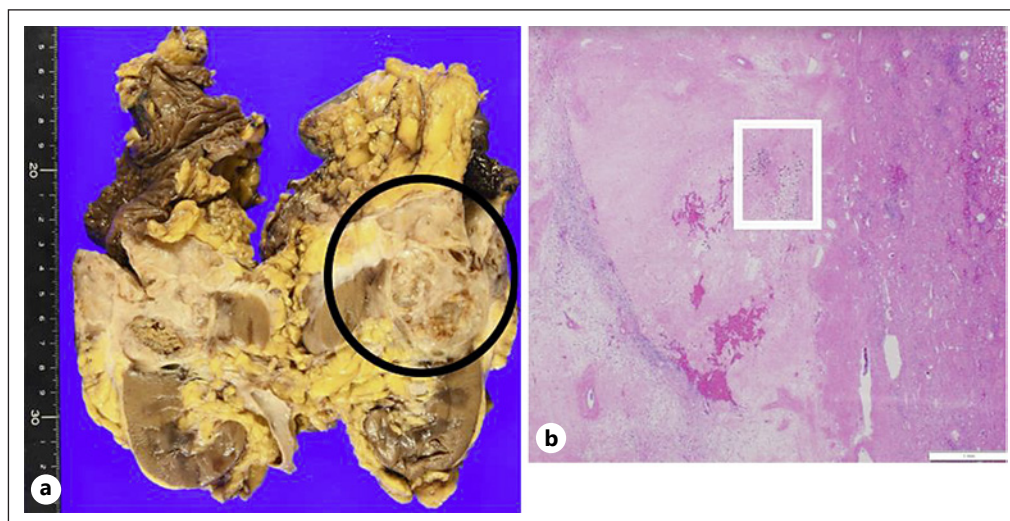


**Fig. 1.** Contrast-enhanced CT at the time of diagnosis. **a** Tumor with a major axis of 98 mm is found in the upper pole of the left kidney. **b** Bilateral lung metastases are indicated using arrows. **c** Liver metastasis is indicated using a circle. **d** Left adrenal metastasis is indicated using a circle. **e** Spleen infiltration of the primary lesion is indicated using a circle. **f** Descending colon infiltration of the primary lesion is indicated using a circle.



**Fig. 2.** Contrast-enhanced CT just before deferred cytoreductive nephrectomy. **a** Compared with Figure 1a–f, the left renal tumor has shrunk and infiltration of the spleen and descending colon has reduced after systemic treatment. **b** Reduction and disappearance of liver metastasis after systemic treatment is indicated using a circle.

patient was diagnosed with cT4N0M1 renal cell carcinoma using the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) guidelines and was classified as intermediate risk. In the scoring system of the Registry for Metastatic Renal Cell Carcinoma (REMARCC), the patient was scored by the number of metastases, lung metastases, and liver metastasis [5]. We started a nivolumab and ipilimumab combination regimen as the first-line therapy due to the patient still being relatively young [2]. Additionally, this regimen has a good expected prognosis in the long run as well as the highest complete response rate. After four courses of first-line therapy, CT showed reduction of the primary lesion and liver lesion. The effect of poor contrast enhancement in the liver lesion had suggested the effect of treatment. CT also indicated the disappearance of the lung lesions, left adrenal lesion, and reduced infiltration to the pancreas, spleen, and descending colon. However, grade 1 immune checkpoint-related interstitial pneumonia, destructive thyroiditis, and hypopituitarism appeared after four courses of the first-line therapy. Pneumonia and thyroiditis improved with conservative treatment, while hypopituitarism improved with temporary steroid replacement therapy. Thereafter, monotherapy using nivolumab was implemented as the first-line treatment strategy; however, it was discontinued due to immune-related adverse events, specifically a repeated case of pneumonia. Due to the above observations, the treatment strategy was amended and cabozantinib was used as the second-line therapy. After initiating cabozantinib (60 mg/day), symptoms such as fatigue, hoarseness, and hand-foot syndrome appeared. The dose of cabozantinib was then reduced to 40 mg/day; however, the adverse reaction to the drug remained throughout the course of the second-line therapy. The reduced appearance of the liver lesions (Fig. 2a) and primary lesion (Fig. 2b) was maintained for almost 1 year after the start of the first-line therapy strategy. We established that the patient exhibited a partial response to the systemic treatment strategy. Even though the adverse reaction was minor, the patient had a strong desire to be free from the negative effects caused by cabozantinib. Due to a partial response to the



**Fig. 3.** Findings of excised specimens. **a** Macroscopic findings: total splenectomy and partial colon resection were performed. The white lesion measuring 7 × 6 cm in the upper pole of the kidney in the circled area is where the tumor disappeared after the systemic treatment. **b** Microscopic findings: viable tumor cells were found only in a very small area of 2 mm–3 mm indicated by the square; however, the other tumor cells were replaced with fibrous tissue.

systemic treatment, deferred CN was performed 53 weeks after the start of treatment in order to achieve a complete response. The primary lesion adhered strongly to the pancreas, spleen, and descending colon. The pancreas could be detached from the primary lesion; however, the adhesion to the spleen and the colon was so severe that a total splenectomy and a partial colectomy were required to remove the primary lesion. The total operation time was 6 h and 17 min, and the amount of blood lost intraoperatively was 567 mL. The resected specimen macroscopically showed a white lesion of 7 cm × 6 cm in the upper pole of the kidney (Fig. 3a). Pathological findings revealed viable renal cell carcinoma existing only in a very small area of 2 mm–3 mm, which indicated that most of the tumor had disappeared with the subsequent appearance of fibrosis due to the systemic treatment (Fig. 3b). Although pancreatic fistula appeared on day seven after the surgery, the patient was discharged on day 31 in generally good condition. He was observed following the surgery, with no implementation of further systemic treatment, due to the positive pathological findings. At 6 months post-surgery, local recurrence, progression in metastatic lesions, and development of new metastatic lesions were not observed.

### Discussion and Conclusion

Deferred CN refers to the use of surgical means to remove renal cell carcinoma lesions selectively in patients who show a favorable response to upfront systemic therapy [6]. In the field of respiratory surgery, primary lesion resection following the use of immuno-oncology (I-O) drugs for metastatic lung cancer has been performed with a good prognosis [7]. The National Comprehensive Cancer Network (NCCN) guidelines published in 2021 state that primary lesion resection may be considered for metastatic renal cell carcinoma if the patient is in relatively good condition (ECOG PS <2) [8]. The European Association of Urology guidelines also state that preoperative use of I-O drugs for metastatic renal cell carcinoma may lead to the improvement of progression-free survival (PFS) and overall survival (OS) compared to

therapy involving the use of sunitinib [9]. Indications of deferred CN are unclear due to fewer reports relating to cytoreductive nephrectomy after the use of I-O drugs.

Gross et al. [1] reported results expressing the survival outcomes for CN compared to non-CN as well as deferred CN compared to immediate CN in a retrospective study. The median OS was 56.3 months in the CN group as opposed to 19.1 months in the non-CN group, indicating a significant prolongation of OS when CN was implemented ( $p < 0.0001$ ). Furthermore, the median OS in the deferred CN group was found to be 72.0 months as opposed to 53.5 months in the immediate CN group, indicating a slight tendency of prolonged OS in the deferred CN group; however, the results were not significantly different.

If there were some suggestions for deferred CN, it would be easier to select operative cases. Smith et al. [10] classified the PFS of metastatic renal cell carcinoma by using the Morphology, Attenuation, Size, and Structure (MASS) criteria. We consider the MASS criteria a useful suggestion for deferred CN. The MASS criteria are based on changes in tumor size and morphology. According to the MASS criteria, the response to treatment is positive if any one of the following is true: central necrosis of 50% or more of metastatic lesions, change of CT value of 40 HU or more in contrast-enhanced CT, and size reduction of 20% or more. Therefore, it can be deduced that a positive treatment response corresponds to an improved PFS (median PFS is 500 days or more). Using these criteria, we could expect an improvement in prognosis with deferred CN due to the positive response to treatment, which we observed throughout this case.

Additionally, we also investigated the best treatment strategy using systemic therapy after deferred CN. We reviewed 6 cases of deferred CN without postoperative treatment for metastatic renal cell carcinoma, including the present case [11–14]. All patients responded well to preoperative treatment according to the MASS criteria. The pathological findings for all six cases were indicative of negative margins, extensive fibrosis, and less than 20% of residual tumor (Table 1). Not all of the cases were observed for recurrence following 6 months after surgery, whereby no further treatment was implemented.

It is useful to select cases of deferred CN based on the MASS criteria and to determine the postoperative treatment based on the pathological evaluation of the specimen. We have indicated the importance of the MASS criteria and pathology findings following deferred CN for the improvement of prognosis as well as the reduction of adverse events caused by systemic treatment.

We believe that randomized controlled trials are currently unsuitable for indications of deferred CN and whether to continue systemic therapy after surgery. This is because good prognosis can be achieved in cases who undergo deferred CN at the appropriate time by carefully evaluating the efficacy of each systemic therapy. In some cases, including our case, if the primary lesion and metastases were well controlled and a new metastatic lesion was not observed with systemic therapy for a certain period, deferred CN could be selected considering surgical invasiveness.

When deferred CN was performed, the patient could obtain a drug holiday with well quality of life depending on the MASS criteria with evaluation of the specimen.

In conclusion, our study has indicated that the MASS criteria and operative specimen findings are useful in determining the indication of deferred CN as well as postoperative treatment.

## Statement of Ethics

The study protocol was reviewed and approved by the Ethics Committee of Tohoku University Hospital (approval number: 26151). Written informed consent was obtained from the patient for the publication of this case report and accompanying images.

**Table 1.** Review of case reports without postoperative treatment after deferred CN for metastatic renal cell carcinoma

Case	Authors	Reported year	Age	Sex	Metastases	Perioperative treatment	Resect margin	Extensive fibrosis	Residual tumor	PFS
1	Ikarashi et al. [11]	2018	68	Female	Lung and liver	sunitinib→Nivo	Negative	Exist	None	3 months
2	Okada et al. [12]	2020	47	Male	Lungs	Nivo+Ipi→Nivo	Negative	Exist	None	6 months
3	Okuno et al. [13]	2020	67	Male	Lungs	Nivo+Ipi	Negative	Unknown	About 10%	Unknown
4	Okuno et al.	2020	47	Male	Brain and lungs	pazopanib→Nivo+Ipi	Negative	Unknown	About 10–20%	6 months
5	Shirotake et al. [14]	2019	52	Male	Brain and lungs	TKI→Nivo	Negative	Exist	None	3 months
6	Our case	2020	59	Male	Lungs, liver, and adrenal glands	Nivo+Ipi→Nivo	Negative	Exist	None	6 months

Nivo, nivolumab; Ipi, ipilimumab; TKI, tyrosine kinase inhibitor; PFS, progression free survival.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Takuya Nakagawa and Yoshihide Kawasaki contributed to the writing of the manuscript. Satoko Sato provided a histological illustration. Hiromichi Katayama, Yohei Satake, Shuichi Shimada, Takuma Sato, Naoki Kawamorita, Shinichi Yamashita, Koji Mitsuzuka, and Akihiro Ito served as the attending physicians for the presented patient. Atsushi Kohyama, Masaharu Ishida, Hideo Ohtsuka, and Michiaki Unno assisted in that patient's surgery. All the authors agree to be accountable for all aspects of this work.

### Data Availability Statement

All data generated or analyzed during this study are included in this article. Data supporting the findings of this study are available from the corresponding author; Yoshihide Kawasaki, upon some request.

### References

- Gross E, Li M, Yin M, Orcutt D, Hussey D, Trott E, et al. MP14-08 A multicenter assessment of survival in patients with metastatic renal cell carcinoma (mRCC) who received immune checkpoint inhibitor therapy (ICI) with or without cytoreductive nephrectomy (CN). *J Urol*. 2021 Sep;206(Suppl 3):e255.
- Rizzo A, Mollica V, Santoni M, Ricci AD, Rosellini M, Marchetti A, et al. Impact of clinicopathological features on survival in patients treated with first-line immune checkpoint inhibitors plus tyrosine kinase inhibitors for renal cell carcinoma: a meta-analysis of randomized clinical trials. *Eur Urol Focus*. 2022;8(2):514–21.
- Rizzo A, Mollica V, Santoni M, Massari F. Risk of selected gastrointestinal toxicities in metastatic renal cell carcinoma patients treated with immuno-TKI combinations: a meta-analysis. *Expert Rev Gastroenterol Hepatol*. 2021 Oct;15(10):1225–32.
- Mollica V, Santoni M, Matrana MR, Basso U, De Giorgi U, Rizzo A, et al. Concomitant proton pump inhibitors and outcome of patients treated with nivolumab alone or plus ipilimumab for advanced renal cell carcinoma. *Target Oncol*. 2022 Jan;17(1):61–8.
- Okita K, Hatakeyama S, Naito S, Numakura K, Kato R, Koguchi T, et al. External validation of the REMARCC model for the selection of cytoreductive nephrectomy in patients with primary metastatic renal cell carcinoma: a multicenter retrospective study. *Urol Oncol*. 2021 Dec;39(12):836.e11–7.

- 6 Bhindi B, Graham J, Wells JC, Bakouny Z, Donskov F, Fraccon A, et al. Deferred cytoreductive nephrectomy in patients with newly diagnosed metastatic renal cell carcinoma. *Eur Urol*. 2020 Oct;78(4):615–23.
- 7 El Husseini K, Piton N, De Marchi M, Grégoire A, Vion R, Blavier P, et al. Lung cancer surgery after treatment with anti-PD1/PD-L1 immunotherapy for non-small-cell lung cancer: a case-cohort study. *Cancers*. 2021 Sep 30;13(19):4915.
- 8 Motzer RJ, Jonasch E, Agarwal N, Alva A, Baine M, Beckermann K, et al. Kidney cancer, version 3.2022, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2022 Jan;20(1):71–90.
- 9 Ljungberg B, Albiges L, Abu-Ghanem Y, Bedke J, Capitanio U, Dabestani S, et al. European Association of Urology guidelines on renal cell carcinoma: the 2022 update. *Eur Urol*. 2022;82(4):399–410.
- 10 Smith AD, Shah SN, Rini BI, Lieber ML, Remer EM. Morphology, Attenuation, Size, and Structure (MASS) criteria: assessing response and predicting clinical outcome in metastatic renal cell carcinoma on antiangiogenic targeted therapy. *AJR Am J Roentgenol*. 2010 Jun;194(6):1470–8.
- 11 Ikarashi D, Kato Y, Katagiri H, Takahara T, Uesugi N, Shiomi E, et al. Case of complete response to neoadjuvant therapy using nivolumab in a patient with metastatic renal cell carcinoma. *Int J Urol*. 2018 Jun;25(6):630–2.
- 12 Okada T, Hamamoto S, Etani T, Naiki T, Sue Y, Banno R, et al. Complete response of renal cell carcinoma with an inferior vena cava tumor thrombus and lung metastases after treatment with nivolumab plus ipilimumab. *Int Cancer Conf J*. 2020 Apr;9(2):88–91.
- 13 Okuno Y, Tanaka R, Mikami K, Takeuchi T. Renal cancer tissue after nivolumab/ipilimumab combination therapy for metastatic renal cell carcinoma. *Hinyokika Kiyo*. 2020 Jan;66(1):13–7.
- 14 Shirotake S, Kaneko G, Nagata K, Oyama M, Nishimoto K. Histological complete response with nivolumab for renal cell carcinoma with multiple metastases: a case report. *Mol Clin Oncol*. 2019 Feb;10(2):244–8.