JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2022, 52(10)1208–1214
https://doi.org/10.1093/jjco/hyac099
Advance Access Publication Date: 2 July 2022
Original Article

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Therapeutic role of deferred cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with nivolumab plus ipilimumab

Maki Yoshino[1], Hiroki Ishihara[1,*], Yuki Nemoto[2,3], Kazutaka Nakamura[2,4], Koichi Nishimura[1], Hidekazu Tachibana[5], Hironori Fukuda[2], Daisuke Toki[1], Kazuhiko Yoshida[2], Hirohito Kobayashi[1], Junpei Iizuka[2], Hiroaki Shimmura[4], Yasunobu Hashimoto[3], Kazunari Tanabe[2], Tsunenori Kondo[1] and Toshio Takagi[2]

[1]Department of Urology, Tokyo Women's Medical University Adachi Medical Center, Tokyo, Japan, [2]Department of Urology, Tokyo Women's Medical University, Tokyo, Japan, [3]Department of Urology, Saiseikai Kawaguchi General Hospital, Kawaguchi, Japan, [4]Department of Urology, Jyoban Hospital, Iwaki, Japan and [5]Department of Urology, Saiseikai Kurihashi Hospital, Saitama, Japan

*For reprints and all correspondence: Hiroki Ishihara, Department of Urology, Tokyo Women's Medical University Adachi Medical Center 4-33-1 Kouhoku, Adachi-ku, Tokyo 123-8558, Japan. E-mail: ishihara.hiroki@twmu.ac.jp

Received 29 March 2022; Editorial Decision 25 May 2022; Accepted 31 May 2022

Abstract

Objectives: To explore the therapeutic role of deferred cytoreductive nephrectomy in patients with metastatic renal cell carcinoma treated with nivolumab plus ipilimumab.

Patients and methods: Forty-one patients with synchronous metastatic renal cell carcinoma who received nivolumab plus ipilimumab as first-line systemic therapy at our affiliated institutions were retrospectively evaluated. We focused on the prognosis, including tumor responses in primary kidney and metastatic lesions in patients treated with deferred cytoreductive nephrectomy. In addition, the overall survival according to nephrectomy status (i.e. deferred cytoreductive nephrectomy vs. upfront cytoreductive nephrectomy vs. without cytoreductive nephrectomy) was compared.

Results: During a median follow-up period of 12.0 months, seven (30%) patients received deferred cytoreductive nephrectomy at a median time of 10.4 months after nivolumab plus ipilimumab initiation. All the patients showed tumor shrinkage in their primary kidney lesions, including six (86%) patients with ≥30% of shrinkage. Metastatic lesions were also shrunk by ≥30% in six (86%) patients, including two (29%) obtaining complete response. At the last time of follow-up, three (43%) patients were disease-free. The overall survival rate after nivolumab plus ipilimumab initiation tended to be higher in patients with deferred cytoreductive nephrectomy compared with those with upfront cytoreductive nephrectomy (1-year survival rate: 100% vs. 72.4%, $P = 0.0587$) and those without cytoreductive nephrectomy (vs. 58.2%, $P = 0.0613$).

Conclusions: The present retrospective data showed that deferred cytoreductive nephrectomy had the potential to exert a therapeutic effect in a subset of patients who obtained favorable tumor responses to nivolumab plus ipilimumab for a certain period. Prospective randomized clinical trials

are needed to confirm the prognostic impact of deferred cytoreductive nephrectomy after frontline immunotherapy in synchronous metastatic renal cell carcinoma.

Key words: immunotherapy, PD-1, CTLA-4, cytoreductive nephrectomy, systemic therapy

Introduction

Cytoreductive nephrectomy (CN) has played a central role in the treatment of metastatic renal cell carcinoma (mRCC) since previous clinical trials demonstrated its therapeutic effect in the cytokine therapy setting (1,2). However, two recent trials, namely, the CARMENA and SURTIME trials, rejected the superiority of upfront CN, at least in patients with poor performance status or poor-risk patients in the molecular-targeted therapy (mTT) era (3,4). Thus, current guidelines do not recommend upfront CN for patients requiring systemic therapy (5,6), and this approach is no longer a standard-of-care for mRCC.

In recent years, systemic therapeutic strategies have dramatically changed after the implementation of immune checkpoint inhibitors (ICIs). Several randomized clinical trials have revealed the superior efficacy of ICI-based treatments over sunitinib as first-line systemic therapy in previously untreated mRCC (7–9). Currently, ICIs play a central role in systemic therapy of mRCC.

Although the implementation of ICIs contributes to improving patient outcomes, the prognosis in specific populations that did not undergo nephrectomy prior to initiation of ICIs remains unclear. The number of patients without prior nephrectomy is expected to increase, owing to evidence from the CARMENA and SURTIME trials. In addition, because ICI-based treatment exhibits a higher effect on tumor shrinkage (7–10), we are more likely to consider the indication of CN during therapy, namely deferred CN (dCN). However, the prognostic role of dCN in ICI-based treatments remains unclear.

Nivolumab plus ipilimumab combination therapy is one of the recommended regimens, as first-line therapy for mRCC patients with clear-cell histology categorized into the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) intermediate- or high-risk group (11). A recent post hoc analysis of the Checkmate 214 trial revealed a higher efficacy in terms of overall survival (OS) and objective response rate in the nivolumab plus ipilimumab arm than in the sunitinib arm in subpopulations without prior nephrectomy (12). In addition, ≥30% of tumor shrinkage in primary kidney lesions was observed in 35% of the patients treated with nivolumab plus ipilimumab. These data indicate that nivolumab plus ipilimumab has a feasible effect on outcomes in patients without prior nephrectomy, and more real-world data regarding the ratio of patients treated with dCN as well as their profile, including prognosis and tumor responses during the therapy, are needed.

In this context, we retrospectively investigated the prognostic impact of dCN in patients with synchronous mRCC treated with nivolumab plus ipilimumab as first-line therapy. We focused on the prognosis of patients with dCN, including tumor responses in primary kidney and metastatic lesions.

Materials and methods

Patients

Clinical and laboratory data were obtained from the electronic database and patient medical records. The study protocol was approved by the Institutional Ethics Review Board of Tokyo Women's Medical University (ID: 2020–0009). This study was performed in accordance with the principles outlined in the Declaration of Helsinki of 1964 and its later amendments. The requirement for informed consent was waived owing to the retrospective observational nature of the study.

Between September 2016 and July 2021, 47 patients with synchronous mRCC received nivolumab plus ipilimumab as first-line therapy at five affiliated institutions (Tokyo Women's Medical University Hospital, Tokyo Women's Medical University Adachi Medical Center, Saiseikai Kawaguchi General Hospital, Saiseikai Kurihashi Hospital and Tokiwakai Joban Hospital). Among them, we excluded six patients whose duration of post-treatment follow-up was short (i.e. <1 month) or whose clinical data were missing. The remaining 41 patients were evaluated, retrospectively. One patient that had been registered in the CheckMate 214 trial was also included.

The patients were divided into three groups, according to nephrectomy status: (i) patients who underwent nephrectomy after nivolumab plus ipilimumab initiation (i.e. deferred CN: dCN), (ii) patients who underwent nephrectomy prior to the initiation of therapy (i.e. upfront CN: uCN) and (iii) patients who did not undergo nephrectomy during therapy (nonCN).

There are currently no consensus indications for dCN in our institutions. In all dCN cases, physicians considered that frontline systemic therapy was the preferred treatment option, and then, after monitoring tumor responses, dCN was conducted. Thus, dCN was an unplanned surgery.

Protocol of nivolumab plus ipilimumab

In the induction phase, the nivolumab was intravenously administered at a dose of 3 mg/kg or as a 240 mg flat dose, and the ipilimumab was intravenously administered at a dose of 1 mg/kg. Each drug was administered every 3 weeks for four doses. In the maintenance phase, nivolumab alone was administered every 2 weeks at a dose of 3 mg/kg or as a 240 mg flat dose, or every 4 weeks at 480 mg flat dose. Dose modifications were not allowed, but the dosage interval could be modified in accordance with the patient's condition or the development of adverse events. Post-treatment radiographic examinations using plane or enhanced computed tomography of the chest, abdomen and pelvis were conducted at a regular 4–12-week intervals depending on the patient's condition. Magnetic resonance imaging or positron emission tomography-computed tomography was not routinely performed. Brain scans were not performed routinely. The nivolumab plus ipilimumab were administered until intolerable adverse events occurred or disease progression.

Statistical analysis

OS was calculated from the initiation of nivolumab plus ipilimumab therapy to death due to any cause. Patients lost to follow-up were censored at the time of the last contact. Survival data were collected until the end of October 2021. Survival was calculated using the Kaplan–Meier method and compared using the log-rank test. All

Table 1. Patient characteristics according to nephrectomy status

Variables	All ($n = 41$)	dCN ($n = 7$)	uCN ($n = 21$)	NonCN ($n = 13$)	*P* value
Sex					
Male (ref. female)	27 (65.9%)	6 (85.7%)	13 (61.9%)	8 (61.5%)	0.434
Age, years	64.0 (53.5–71.5)	56.0 (47.0–64.0)	64.0 (53.5–69.5)	70.0 (56.5–73.0)	0.131
Histopathology					
Clear-cell carcinoma	31 (75.6%)	5 (71.4%)	18 (85.7%)	8 (61.5%)	0.599
Non-clear-cell carcinoma	6 (14.6%)	1 (14.3%)	3 (14.3%)	2 (20.0%)	
Papillary renal cell carcinoma	3 (7.31%)	0 (0%)	2 (9.52%)	1 (7.7%)	
Others	3 (7.31%)	1 (14.3%)	1 (4.76%)	1 (7.7%)	
Unknown	4 (9.76%)	1 (14.3%)	0 (0%)	3 (23.1%)	
IMDC risk					
Intermediate	19 (46.3%)	1 (14.3%)	14 (66.7%)	4 (30.8%)	0.0286**
Poor	21 (51.2%)	5 (71.4%)	7 (33.3%)	9 (69.2%)	
Unknown	0	1 (14.3%)	0	0	
KPS					
<80 (ref. ≥80)	10 (24.4%)	2 (28.6%)	4 (19.0%)	4 (30.8%)	0.712
Serum CRP levels, mg/dL[a]	3.06 (0.37–11.6)	5.11 (2.73–12.8)	1.10 (0.16–2.47)	10.7 (4.5–13.5)	0.0028
Number of metastatic organ sites					
Multiple (ref. solitary)	28 (68.3%)	5 (71.4%)	13 (61.9%)	10 (76.9%)	0.641
Liver metastasis					
Presence (ref. absence)	5 (12.2%)	1 (14.3%)	3 (14.3%)	1 (7.70%)	0.824
Bone metastasis					
Presence (ref. absence)	8 (19.5%)	1 (14.3%)	7 (33.3%)	0 (0%)	0.0183
Time from diagnosis to systemic therapy initiation, days	22 (15–41)	15 (8–22)	40 (24–63)	16 (9.5–21)	0.001
Follow-up period, months[a]	12 (7–21)	19 (18–20)	12 (5–25)	11 (6–20)	0.258

dCN, deferred cytoreductive nephrectomy; uCN, upfront nephrectomy; NonCN, without nephrectomy; KPS, Karnofsky Performance Status; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium

[a]Median (interquartile range) **Analyzed with exclusion of one patient without IMDC risk data in dCN group

statistical analyses were performed using the JMP version 15 (SAS Institute Inc., Cary, NC, USA). Statistical significance was set at $P < 0.05$.

Results

Patient characteristics according to nephrectomy status

During the follow-up period with a median period of 12.0 months [interquartile range (IQR): 7.0–21.0 months], seven of the 41 (17%) patients received dCN. The dCN was performed at a median of 10.4 months after nivolumab plus ipilimumab initiation. Of the remaining 34 patients, 21 (51%) underwent nephrectomy prior to the nivolumab plus ipilimumab (i.e. uCN group) and 13 (32%) did not receive nephrectomy (i.e. nonCN group). When patient characteristics were compared according to nephrectomy status (i.e. dCN vs. uCN vs. nonCN groups), patients diagnosed with poor risk of IMDC or those with high serum C-reactive protein levels were significantly more frequent in the dCN and nonCN groups ($P = 0.0286$ and 0.0028, respectively) (Table 1). In contrast, bone metastasis was not frequent in the dCN and nonCN groups ($P = 0.0183$). Other factors, including sex, age, histopathology, Karnofsky performance status score, number of metastatic organ sites and status of liver metastasis did not differ among the groups (all, $P > 0.05$). The median time from the diagnosis of mRCC to nivolumab plus ipilimumab initiation was 15, 40 and 16 days, in the dCN, uCN and nonCN groups ($P = 0.001$), respectively; thus, the time between diagnosis and treatment initiation was significantly longer in the uCN group.

Prognosis and tumor response in patients with deferred CN

In all the patients receiving dCN, total tumor size was decreased in all targeted lesions [median: 51.5% (IQR: 43.8–58.6%)] (Fig. 1A). When separately analyzed between primary and metastatic lesions, tumors in primary lesions were shrunk in all patients [median: 38.7% (IQR: 32.5–43.3%)] (Fig. 1B), and six (86%) patients except for Patient E exhibited tumor shrinkage [median: 69.4% (IQR: 51.3–100%)] (Fig. 1C). A ≥ 30% of shrinkage in primary lesions was observed in six (86%) patients whose metastatic lesions were concurrently shrunk by ≥30%, including two (29%) patients with a complete response (Fig. 1B and C). An individual time-course change in tumor volume is shown in a spider plot (Fig. 2).

Figure 3 shows the individual clinical course during nivolumab plus ipilimumab combined with dCN by a swimmer plot. The median follow-up period after dCN was 10.0 months (IQR: 7.0–18.0 months). After the dCN, nivolumab monotherapy was restarted in six (86%) patients except for Patient F. At the last time of follow-up, a total of three (43%) patients were drug-free (Patient A, D and F) and three (43%) were disease-free (Patient A, C and F). One patient (Patient E), whose metastatic lesions were not responsive, had disease progression after dCN and was treated with cabozantinib as a second-line therapy.

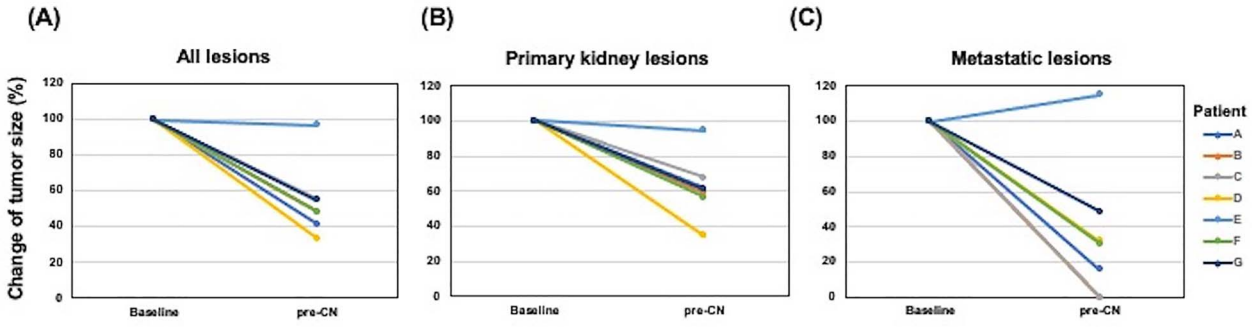

Figure 1. Change of tumor volumes between baseline and timing of deferred cytoreductive nephrectomy (A) All targeted lesions; (B) primary kidney lesions; (C) metastatic lesions. CN, cytoreductive nephrectomy.

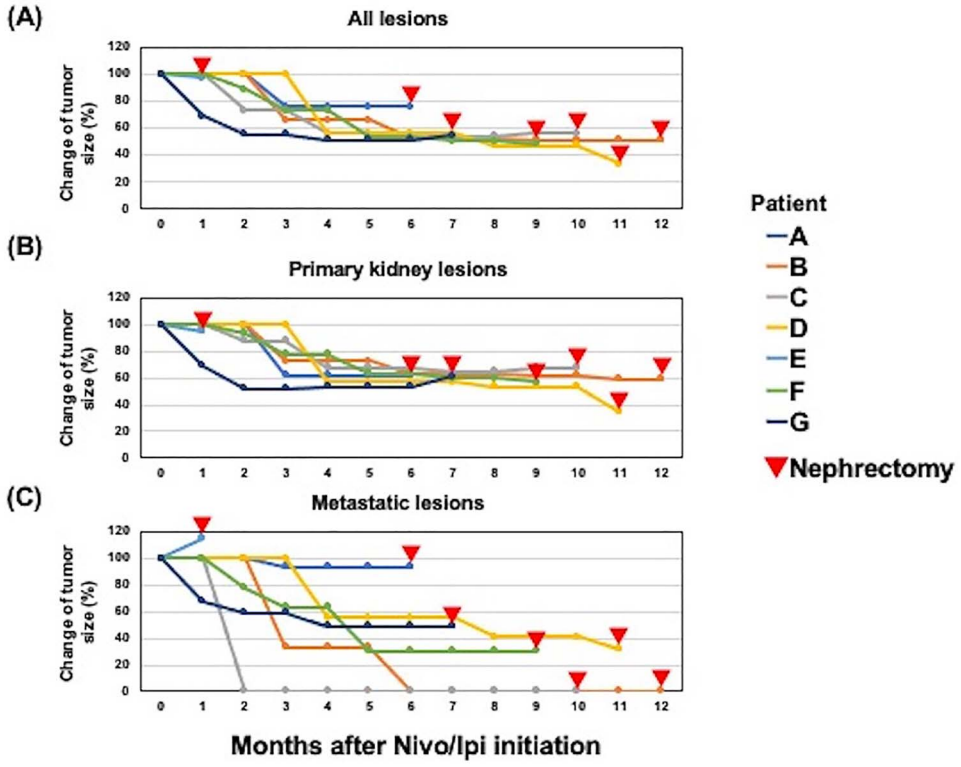

Figure 2. Spider plot showing change of tumor volumes in patients with deferred cytoreductive nephrectomy. (A) All targeted lesions; (B) primary kidney lesions; (C) metastatic lesions.

To compare tumor responses between the dCN and nonCN groups, we additionally evaluated the best overall response in the nonCN group. The decrease of total tumor size was likely to be higher in the dCN compared with the nonCN group [median: 51.5% (IQR: 43.8–58.6%) vs. 2.5% (IQR: −37.1 to 54.4%), $P = 0.15$]. In primary lesions, the decrease of tumor size was significantly higher in the dCN compared with the nCN group [38.7% (IQR: 32.5–43.3%) vs. −2.1% (IQR: −60.4 to 67.4%), $P = 0.04$]. In contrast, the decrease of size in metastatic lesions was likely to be higher in the dCN compared with the nCN group [69.4% (IQR: 51.3–100%) vs. −22% (IQR: −60 to 67.4%), $P = 0.11$].

Surgical and pathological outcomes of deferred CN

The surgical outcomes of dCN are summarized in Table 2. Robot-associated partial nephrectomy was conducted in two patients, whereas open and laparoscopic radical nephrectomy was performed in three and two patients, respectively. Regarding the pathological findings in the resected kidney, no viable cells were observed in two cases. The median surgery time was 191 min (IQR: 179–203 min), and the median blood loss volume was 50 ml (IQR: 50–1290 ml). Three (43%) patients required blood transfusion (Clavien-Dindo grade 2), whereas the remaining four (57%) did not experience any complications. The median length of hospital stay after the surgery was 6 days (IQR: 4–8 days).

When comparing operative findings between the dCN and uCN groups, the operating time was significantly shorter in the dCN group [median: 191 (IQR: 179–203) vs. 250 (IQR: 200–356) min, $P = 0.03$]. In contrast, the amount of blood loss and transfusion rate were comparable between the two groups [1163 (237–1750 ml) vs. 50 (50–1290 ml), $P = 0.17$], (42% vs. 75%, $P = 0.12$).

Table 2. Clinical characteristics and perioperative outcomes in patients undergoing deferred cytoreductive nephrectomy

Pt.	Age, years-old	Sex	Clinical stage	The number of IMDC risk at diagnosis	Time to surgery (month)	Procedure	Operating time (min)	Blood loss (ml)	Complications	Pathological diagnosis	Length of stay (day)	Follow-up period after operation(month)	Current treatment	Current outcome
A	56	M	cT3aN0M1	5	4	RAPN	199	50	None	With viable cells	4	19	None	CR
B	47	M	cT3bN0M1	5	10	ORN	239	1290	CD grade 2 (transfusion)	With viable cells	7	10	Nivolumab	SD
C	57	M	cT4N1M1	N/A	11	LRN	200	50	None	With viable cells	4	12	Nivolumab	CR
D	41	M	cT1aN0M1	1	12	RAPN	203	50	None	No viable cells	4	9	None	SD
E	51	M	cT2bN0M1	3	1	ORN	171	2055	CD2 (transfusion)	With viable cells	8	18	Cabozantinib	PD (On cabozantinib)
F	64	F	cT3aN1M1	5	11	LRN	189	20	None	No viable cells	6	7	None	CR
G	76	M	cT3aN2M1	3	8	ORN	199	315	CD2 (transfusion)	With viable cells	8	5	Nivolumab	SD

Pt, patient; RAPN, robot-assisted partial nephrectomy; OPR, open radical nephrectomy; LRN, laparoscopic radical nephrectomy; CR, complete response; PR, partial response; SD, stable disease; CN, cytoreductive nephrectomy; CD, Clavien–Dindo

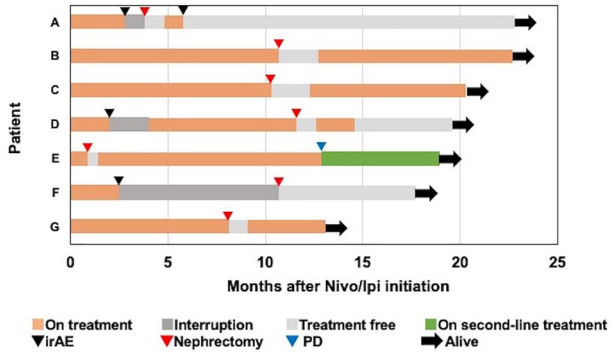

Figure 3. Swimmer plot showing clinical course of patients with deferred cytoreductive nephrectomy. Nivo, nivolumab; Ipi, ipilimumab; irAE, immune-related adverse event; PD, progressive disease.

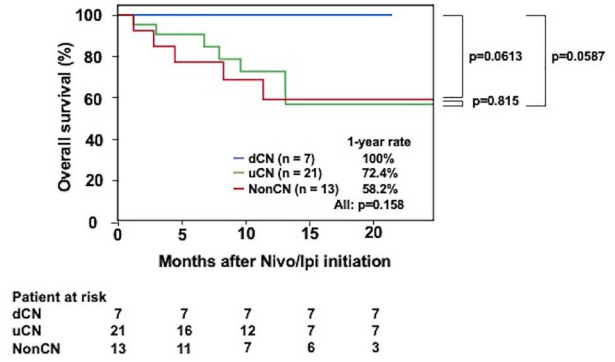

Figure 4. Overall survival according to nephrectomy status. dCN, deferred cytoreductive nephrectomy; uCN, upfront cytoreductive nephrectomy; NonCN, without cytoreductive nephrectomy; Nivo, nivolumab; Ipi, ipilimumab.

OS according to nephrectomy status

Finally, we evaluated the association between the nephrectomy status and OS in patients with synchronous mRCC. During the follow-up period, 13 (32%) patients died. Patients in the dCN group had the highest OS rate compared with those in the uCN and nonCN groups (1-year rate: 100% vs. 72.4% vs. 58.2%, $P = 0.158$) (Fig. 4). Specifically, the OS rate tended to be higher in the dCN group compared with that in the uCN group ($P = 0.0587$) and in the nonCN group ($P = 0.0613$). There was no difference in the OS rate between the uCN and nonCN groups ($P = 0.815$).

The rates of complete response during the therapy among the three groups were 43% ($n = 3/7$), 14% (3/21) and 0% (0/13), for the dCN, uCN and nonCN groups, respectively; thus, the rate of complete response was significantly higher in the dCN group ($P = 0.01$).

Discussion

This retrospective study, using data from multiple institutions, showed that a subset of patients with simultaneous tumor shrinkage in primary and metastatic lesions received dCN during frontline nivolumab plus ipilimumab treatment for synchronous mRCC. These patients exhibited a favorable prognosis compared with those with upfront and without nephrectomies. In addition, some patients were drug-free or disease-free for at least a certain period. These findings suggest that in patients without prior nephrectomy for synchronous mRCC, a feasible tumor response could be expected in not only the primary lesions but also the metastatic lesions, and dCN potentially contributed to improved outcomes.

Since the CARMENA and SURTIME trials rejected evidence regarding the therapeutic effect of uCN (3,4), the role of this approach is strongly limited in the current treatment strategy for mRCC. The post hoc analysis of the CheckMate 214 trial showed that 35% of patients without prior nephrectomy obtained ≥30% of tumor shrinkage in primary lesions (12). In addition, several real-world studies, including ours, reported that 33–53% of patients without prior nephrectomy presented ≥30% of reduction in primary lesions, whose metastatic lesions were concurrently shrunken (13–15). In this study, a ≥ 30% shrinkage in primary lesions was observed in 86% of the patients with dCN, together with simultaneous shrinkage of ≥30% in metastatic lesions, in line with those previous findings (13–15).

The significant effect of frontline nivolumab plus ipilimumab therapy on tumor shrinkage in primary lesions gives rise to dCN. In the previous mTT era, the therapeutic effect of dCN was indicated. The SURTIME trial reported that OS tended to be higher in patients with dCN following sunitinib than in those with uCN, although the difference was not statistically significant (4). Furthermore, data from the CARMENA trial revealed a significantly longer OS in patients receiving dCN than in those receiving sunitinib alone (16). Real-world data from the IMDC also showed that sunitinib followed by dCN was significantly associated with improved OS compared with sunitinib alone and uCN, followed by sunitinib (17). These data suggest that dCN may have therapeutic effects in the mTT era. However, in the current era of ICI-based treatment, such data are still limited. A recent study indicated that ICIs combined with nephrectomy, including upfront and deferred ones, were significantly associated with longer OS compared with ICIs alone (18). In this context, the present data suggest that dCN following nivolumab plus ipilimumab treatment was likely to be associated with prolonged OS. In addition, nephrectomy may prevent symptoms, such as hematuria or pain, which decreases patient's quality of life. Furthermore, dCN may contribute to drug-free or disease-free intervals, as shown in our data. Collectively, dCN after frontline systemic therapy has the potential to improve outcomes in the current era of ICI-based treatment.

Several studies have indicated the feasibility of surgery after ICI-based treatment (19). Indeed, the present data also demonstrated the shorter surgical time in the dCN group compared with the uCN group. This finding may be attributed to decreased surgical invasiveness as a result of tumor down-sizing in response to ICI-based treatment. In addition, our data showed that initiation of nivolumab plus ipilimumab treatment was delayed in the uCN group, potentially resulting in the relatively poor outcomes observed in that group.

The appropriate timing of dCN is another issue. For example, in the SURTIME trial, dCN was conducted at 16 weeks after the initiation of upfront sunitinib (4). Moreover, real-world data from IMDC database showed that dCN following sunitinib was conducted at a median 7.8 months from the diagnosis (17). In the ICI setting, a recent study showed survival data of patients receiving dCN and the median time from diagnosis to dCN was 123 days after ICI initiation (18). In this study, dCN was conducted ~10 months after nivolumab plus ipilimumab initiation. Notably, Patient E, who underwent dCN 1 month after treatment initiation without exhibiting sufficient response, presented remaining viable cells in the resected kidney tissues, and their disease progressed soon thereafter (Table 2).

In this specific case, a longer duration of monitoring might have been required. Collectively, these data suggested that dCN does not appear to have a negative impact on prognosis once patients obtain sufficient disease control for a certain period (i.e. at least 3–6 months) after initiation of upfront ICI-based treatment.

Most of the patients receiving dCN in this study were poor-risk with increased CRP levels at the time of nivolumab plus ipilimumab treatment initiation and were considered to have a poor prognosis (20). Thus, at least for this high-risk patient population, frontline systemic therapy is preferred, and dCN can be considered as one treatment option once the tumor's response to treatment is confirmed.

This study had several limitations. First, the retrospective nature of our analysis, using a small sample size, inevitably induced selection bias, which may have affected our findings. Moreover, as previously mentioned, our institutions have no consensus criteria for dCN yet. In all patients reported here, dCN was unplanned and frontline systemic therapy with nivolumab plus ipilimumab was preferred at the time of mRCC diagnosis; subsequently, dCN was conducted because the patients' primary and metastatic lesions presented sufficient response. Thus, a strong selection bias was inevitably introduced, and patients treated with dCN might inherently have indolent disease, resulting in a more favorable outcome. Indeed, tumor responses were more favorable in the dCN group compared with the nonCN group, and the rate of complete response was also higher in the dCN group compared with the other two groups. Second, the relatively short follow-up period made it difficult to interpret the OS findings.

Conclusions

The present data from multiple institutions showed that dCN following frontline nivolumab plus ipilimumab therapy was associated with improved OS in patients with synchronous mRCC. Thus, dCN may be an effective treatment option for a subset of patients who exhibit favorable responses for a certain period in primary lesions with simultaneous shrinkage of metastatic lesions, although careful patient selection is required. Further prospective randomized trials are required to confirm our findings.

Approval of the research protocol by an Institutional Reviewer Board

This study was approved by the institutional review board for Tokyo Women's Medical University (ID: 2020–0009).

Conflicts of interest

Toshio Takagi received honoraria from Bristol-Myers Squibb and Ono Pharmaceutical. Tsunenori Kondo received honoraria from Pfizer, Novartis, Bristol-Myers Squibb and Ono Pharmaceutical.

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