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REVIEW ARTICLE

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Selection of Optimal Neoadjuvant Therapy Before Cytoreductive Nephrectomy and Its Biomarker in Renal Cell Carcinoma

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Cytoreductive nephrectomy (CN) has been a pivotal consideration in the treatment of metastatic renal cell carcinoma, with its role evolving significantly in the era of immuno-oncology (IO) therapies. This review examined the current evidence from randomized controlled trials and retrospective studies regarding the efficacy of upfront and deferred CN, particularly in the context of IO combination therapies. We explored patient stratification according to tumor burden and risk categories, emphasizing personalized treatment strategies that maximize therapeutic outcomes. For high-risk patients, early administration of IO therapies with strong antitumor effects is critical, whereas low-risk patients may benefit from upfront CN when combined with systemic therapies. Additionally, we discuss site-specific responses to IO therapies and highlight the importance of molecular profiles in guiding treatment choices. The development of biomarkers to dynamically monitor treatment efficacy will be essential in refining the role of CN and optimizing patient selection. This review underscores the need for further research to define the therapeutic potential of CN in the IO era.

Key Words: Renal cell carcinoma, Cytoreductive nephrectomy, Immune-oncology therapy, Neoadjuvant therapy

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INTRODUCTION

Cytoreductive nephrectomy (CN) has long been considered one of the treatment options for patients with metastatic renal cell carcinoma (mRCC) at initial presentation. CN can be categorized into 2 types based on the timing of surgery: upfront CN, which is performed before systemic therapy, and deferred CN, which is performed after systemic therapy.

Randomized controlled trials (RCTs) investigating CN included SWOG 8949 and EORTC 30947 from the cytokine era, and CARMENA and SURTIME from the targeted therapy era. These studies provide critical evidence regarding the survival benefits of CN. In the cytokine era, 2 RCTs demonstrated that CN contributed to improved survival outcomes [1,2]. In contrast, the CARMENA trial conducted in the targeted therapy era did not show a survival benefit for CN [3], although a *post hoc* analysis suggested the potential utility of deferred CN [4]. Based on these findings, current guidelines recommend considering CN for selected patients.

The approval of immuno-oncology (IO) combination

therapies as first-line treatment for advanced RCC has dramatically shifted the focus of systemic therapy from targeted therapies to IO therapies. This paradigm shift strongly suggests the need to re-evaluate the role and timing of CN. In particular, it is important to examine how combining the antitumor effects of IO therapy with CN impacts patient outcomes. This article reviews the current evidence regarding CN and provides perspectives on the selection of neoadjuvant systemic therapies and the appropriate indications for CN.

EVIDENCE OF CYTOREDUCTIVE NEPHRECTOMY IN THE IMMUNO-ONCOLOGY ERA

In the era of IO therapies, 2 RCTs, the NORDIC-SUN trial and the PROBE trial, are currently in progress. However, as the results of these trials have not yet been published, the utility of CN and the optimal neoadjuvant regimens in the IO era remain speculative, relying heavily on retrospective studies and subgroup analyses of RCTs evaluating IO combination therapies.

Data from 5 pivotal RCTs of IO combination therapies provide important insights into the treatment of mRCC [5-9]. Although only 20%–30% of patients in these trials had intact primary tumors, the results suggest that IO combination therapies offer substantial survival benefits compared with sunitinib. In terms of progression-free survival (PFS), IO combinations demonstrated significant reductions in the risk of progression (Checkmate 9ER: hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.43–0.92; JAVELIN Renal 101: HR, 0.75; 95% CI, 0.48–1.65; KEYNOTE-426: HR, 0.68; 95% CI, 0.45–1.03; CLEAR: HR, 0.38; 95% CI, 0.31–0.48). Similarly, in terms of overall survival (OS), 4 of the 5 trials, excluding JAVELIN Renal 101, showed a 30%–40% reduction in mortality risk (Checkmate 214: HR, 0.63; 95% CI, 0.42–0.94; Checkmate 9ER: HR, 0.79; 95% CI, 0.48–1.29; KEYNOTE-426: HR, 0.57; 95% CI, 0.36–0.89; CLEAR: HR, 0.52; 95% CI, 0.31–0.86). These findings underscore the superiority of IO combination therapies over targeted therapies and call for a reassessment of treatment strategies, including the role of CN in this new therapeutic landscape.

Next, studies examining CN in the IO era are considered. Retrospective cohort studies have primarily focused on outcomes such as antitumor efficacy, OS, and surgical complications associated with both upfront and deferred CN [10-14] (Table 1). However, these studies have significant limitations, particularly selection bias, because patients

Table 1. Overview of studies reporting on upfront CN and deferred CN in IO the IO era

Study	Study design	Systemic therapy	No. of patients	Outcome
Yoshino et al. [10]	Retrospective cohort study	Nivo+Ipi	CN (n=28) Upfront CN (n=21) Deferred CN (n=7) Non-CN (n=13)	OS Tumor response
Navani et al. [11]	Retrospective cohort study	IO+IO IO+TKI	CN (n=193) Upfront CN (n=177) Deferred CN (n=26) Non-CN (n=719)	Imaging response OS
Gross et al. [12]	Retrospective cohort study	Nivo+Ipi Nivo (mono)	CN (n=232) Upfront CN (n=202) Deferred CN (n=32) Non-CN (n=135)	OS
Takemura et al. [13]	Retrospective cohort study	IO+IO IO+TKI	CN (n=206) Upfront CN (n=182) Deferred CN (n=24) Non-CN (n=179)	OS PFS ORR
Reese et al. [14]	Retrospective cohort study	IO+IO IO+TKI Nivo (mono)	Upfront CN (n=174) Deferred CN (n=46)	Surgical complication

CN, cytoreductive nephrectomy; IO, immune-oncology; Nivo, nivolumab; Ipi, ipilimumab; TKI, tyrosine kinase inhibitor; mono, monotherapy; OS, overall survival; PFS, progression-free survival; ORR, objective response rate.

undergoing CN often differ substantially in baseline characteristics from those who do not undergoing surgery. Furthermore, most studies have predominantly examined upfront CN, leaving limited evidence for deferred CN. A study by Takemura et al. [13] investigated the efficacy of upfront and deferred CN in patients receiving IO combination therapies using data from the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC). To address selection bias, the analysis included only patients who survived more than 12 months after initiating systemic therapy, thereby balancing patient backgrounds between the CN and non-CN groups. Kaplan-Meier analysis demonstrated a survival benefit for patients who underwent CN, and multivariate analysis identified CN as a significant factor for improved survival. However, as most CN cases in this study involved upfront CN, the findings cannot be directly applied to assess the utility of deferred CN.

Reports specifically focusing on deferred CN are scarce and mainly consist of single-center case series or retrospective cohort studies [15-18] (Table 2). Although these studies provide valuable insights into clinical outcomes, perioperative complications, and pathological findings, the overall evidence level remains low. The ongoing NORDIC-SUN and PROBE trials, both designed to evaluate the utility of deferred CN, are anticipated to provide more robust evidence to guide clinical practice. However, these 2 trials have different designs catering to distinct clinical scenarios.

The NORDIC-SUN trial enrolls patients with up to 3 IMDC risk factors and initially treats all patients with IO combination therapy for 12–16 weeks. Patients who have no disease progression and resectable primary tumors at this point are randomized to either deferred CN or continued IO maintenance alone. Patients who are not surgically resectable after the initial 12–16 weeks receive an additional 12 weeks of IO combination therapy. If they become resectable after this additional treatment, they are then randomized to either deferred CN or IO maintenance alone. In contrast, the PROBE trial randomizes patients with partial response or stable disease after 10–18 weeks of IO combination therapy to either deferred CN or continued IO therapy, without an additional treatment phase for initially unresectable patients.

Although these 2 prospective studies share the common goal of evaluating deferred CN, they differ in their approach to patient selection and treatment strategies. The results of these studies are expected to clarify the role of deferred CN and provide guidance on the appropriate timing for CN in different clinical contexts.

However, in clinical practice, we experience cases where patients who initially show a favorable treatment response demonstrate progression during the course of treatment. The designs of the aforementioned prospective studies may not provide clear answers for such clinical scenarios. RCC is characterized by intra- and intertumor heterogeneity, and it has been molecularly elucidated that certain clones within the primary tumor progress at metastatic sites [19]. Considering this molecular mechanism, if the treatment effect reflects a reduction in clones responding well to systemic therapy, subsequent progression can be attributed to the proliferation

Table 2. Summary of studies reporting on deferred CN in IO the IO era

Study	Study design	Systemic therapy	No. of patients	Outcome
Shirotake et al. [15]	Case series	Nivo+Ipi	Deferred CN (n=10)	PFS OS ORR
Fransen van de Putte et al. [16]	Retrospective cohort study	Nivo+Ipi	Deferred CN (n=23) Non-CN (n=97)	Pathological response PFS CSS
Shapiro et al. [17]	Retrospective cohort study	IO+IO IO+TKI	Deferred CN (n=75)	Surgical complication
Panian et al. [18]	Retrospective cohort study	IO+IO IO+TKI Nivo mono TKI mono	Deferred CN (n=52)	Pathological outcome

CN, cytoreductive nephrectomy; IO, immune-oncology; Nivo, nivolumab; Ipi, ipilimumab; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; CSS, cancer-specific survival; TKI, tyrosine kinase inhibitor; mono, monotherapy.

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of resistant clones. Therefore, the indication for CN in such patients should be carefully determined. Additionally, a scenario can be envisioned where disease progression occurs due to a decrease in the dose intensity of systemic therapy because of poor patient tolerability. In these patients, systemic therapy is interrupted for a certain period during the perioperative period; thus, the risk of disease progression during the treatment interruption becomes a concern. In these cases, the indication for CN should also be carefully evaluated. On the other hand, performing CN has the advantage of directly assessing the histological treatment effect within the primary tumor. This evaluation may provide additional information to determine whether the current treatment is effective or not. It is necessary to carefully weigh these clinical significances and treatment-related risks and benefits to determine the optimal treatment strategy according to each patient's situation.

SELECTION OF OPTIMAL NEOADJUVANT IMMUNO-ONCOLOGY THERAPY

The introduction of IO combination therapies with high antitumor efficacy has raised new clinical challenges. A key question is whether CN should be performed in patients with metastatic RCC after achieving shrinkage of metastatic lesions. The choice of initial systemic therapy plays a critical role in this decision-making process, because it determines the ability to achieve effective tumor control.

Although multiple risk models have been developed to predict the benefit of CN in mRCC during the cytokine and targeted therapy eras [20,21], it is difficult to directly apply these models in clinical practice [22]. However, based on the accumulation of research to date, a consensus has been reached regarding the characteristics of high-risk and low-risk patients for CN. High-risk patients include those with IMDC poor risk or poor performance status (PS), large tumor burden in metastatic sites, multiple organ metastases, and tumors with sarcomatoid differentiation [3,23,24]. These patients have a high perioperative risk for CN, and it has been pointed out that the prognostic improvement effect of surgery is unclear due to the rapid progression of the disease. On the other hand, low-risk patients include those with low-volume metastases, good PS, and patients in whom surgical complete remission is expected. RCTs on CN in the TKI era only included patients requiring systemic therapy with sunitinib [3,25], and thus could not clearly demonstrate the significance of CN in patients with low-volume metastases. However, prospective studies have shown the possibility of long-term prognosis in such patients without the need for systemic therapy [26,27]. Furthermore, a *post hoc* analysis of the CARMENA trial showed that patients with only lung metastases had better OS in the upfront CN group compared to the non-CN group (44 months vs. 31.5 months; HR, 1.24; 95% CI, 0.62–2.47). Based on these findings, we believe that the prognostic improvement effect of upfront CN is likely to be maintained in the IO era, especially in low-risk patients.

Based on these findings, this review categorizes patients who were unlikely to benefit from CN before the IO era as high-risk and those who were known to benefit from CN before the IO era as low-risk (Fig. 1). This classification is based on existing evidence, but it should be noted that it includes a certain degree of subjectivity. On the other hand, when deciding on the indication for CN, it is necessary to develop an individualized treatment strategy considering the biological characteristics of the tumor and the patient's general condition, and it is important to envision the actual patient profile. High-risk patients (Fig. 1A) have bulky primary tumors and multiple large metastatic lesions involving multiple organs. In contrast, low-risk patients have a limited number of metastases and a lower tumor burden. Treatment priorities differ significantly between the 2 groups, as shown in Fig. 1B. For high-risk patients, achieving rapid and strong antitumor effects is critical for preventing functional decline and short-term mortality. Conversely, low-risk patients with slow-growing tumors may benefit from a balanced approach considering both efficacy and safety. Low-risk patients may include those who can achieve surgical complete remission with CN and metastasectomy, offering the potential for long-term survival benefits [28]. Additionally, a *post hoc* analysis of the CARMENA trial showed that patients with lung metastases only had better OS outcomes in the upfront CN group compared with the non-CN group (upfront CN vs. non-CN: 44 months vs. 31.5 months; HR, 1.24; 95% CI, 0.62–2.47) [4]. This suggests that CN, particularly upfront CN, may play a crucial role in improving the survival of low-risk patients.

For high-risk patients, therapeutic priority lies in rapidly

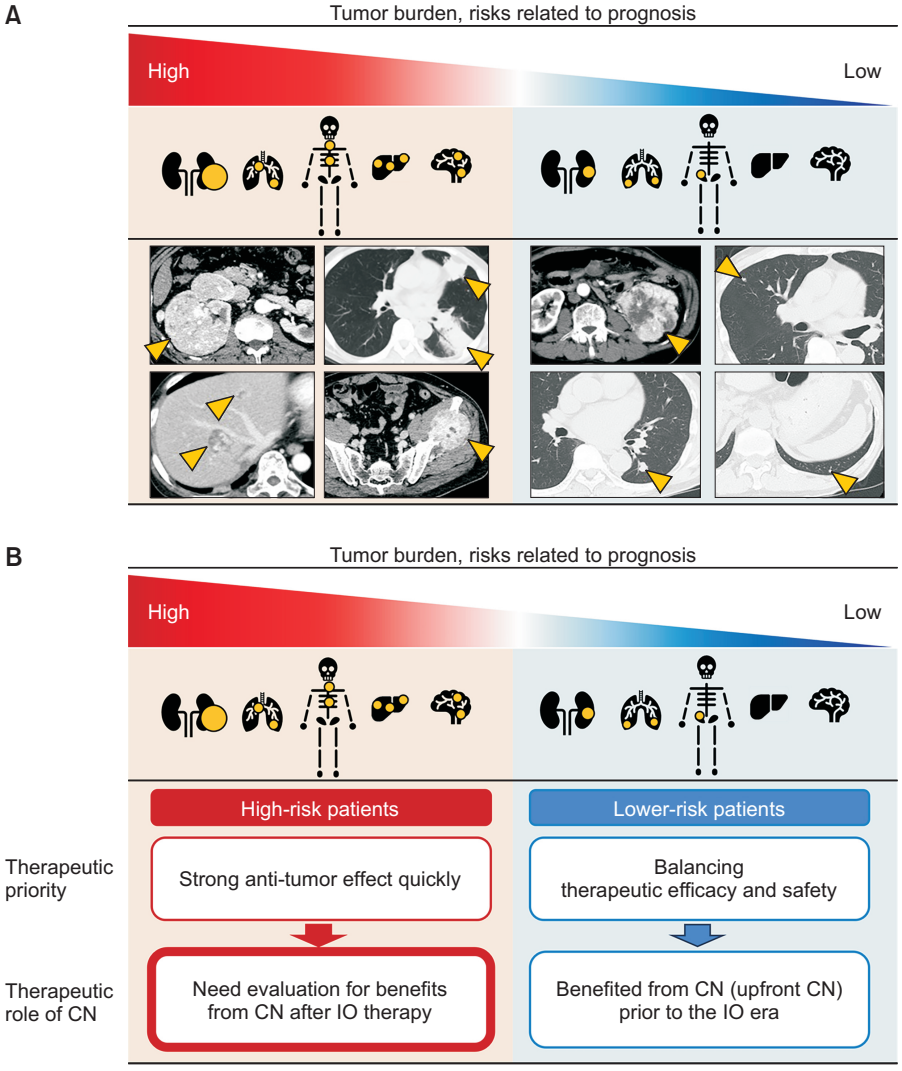

Fig. 1. (A) Conceptual framework: tumor burden and prognosis in risk groups. (B) Therapeutic priorities and the role of CN across risk groups. CN, cytoreductive nephrectomy; IO, immune-oncology.

Table 3. Efficacy of IO combination therapy in IMDC intermediate/poor-risk patients

Trial	Rate of intermediate/poor risk in IDG (%)	OS, HR (95% CI) Intermediate/poor	PFS, HR (95% CI) Intermediate/poor
Checkmate 214 [29]	79.0/21.0	0.68 (0.58–0.81)	0.73 (0.61–0.87)
KEYNOTE-426 [8]	55.1/13.0	0.63 (0.50–0.81)	0.69 (0.56–0.84)
JAVELIN Renal 101 [30]	66.7/12.2	0.83 (0.62–1.20)/0.57 (0.36–0.90)	0.76 (0.60–0.95)/0.51 (0.34–0.77)
Checkmate 9ER [31]	58.2/18.9	0.58 (0.45–0.76)/0.36 (0.23–0.56)	0.74 (0.50–1.08)/0.45 (0.27–0.76)
CLEAR [32]	59.2/9.0	0.72 (0.50–1.05)/0.30 (0.14–0.64)	0.39 (0.29–0.52)/0.28 (0.13–0.60)

IO, immune-oncology; IMDC, International Metastatic Renal Cell Carcinoma Database Consortium; IDG, investigational drug group; OS, overall survival; HR, hazard ratio; CI, confidence interval; PFS, progression-free survival.

achieving cancer control to mitigate the risk of functional decline or cancer-related death in the short term. This condition necessitates the early administration of therapies with strong antitumor effects. The IMDC intermediate- and poor-risk groups have demonstrated significant improvements in OS and PFS with IO combination therapies [8,29-32] (Table 3). These findings highlight the importance of selecting a systemic therapy regimen capable of achieving adequate tumor control for both primary tumors and metastatic lesions.

Regarding the antitumor effects on primary tumors, IO combination therapies have shown superior efficacy compared to sunitinib. In the Checkmate 214 trial, the proportion of patients achieving 30% or greater tumor shrinkage was 35% in the nivolumab plus ipilimumab (Nivo+Ipi) group,

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compared to 20% in the sunitinib group [33]. Similarly, the CLEAR trial demonstrated a tumor shrinkage rate of 71% with pembrolizumab plus lenvatinib (Pem+Len), compared to 26% with sunitinib [32].

For metastatic lesions, IO combination therapies have demonstrated variable effects depending on the site of metastasis [31,32,34] (Table 4). For lung and liver metastases, IO combination therapies have shown significant improvements in both OS and PFS compared to sunitinib. However, for bone metastases, the efficacy of IO combination therapies differs among regimens. While Nivo plus cabozantinib (Nivo+Cabo) and Pem+Len have demonstrated over 50% reductions in the risk of progression, Nivo+Ipi has shown limited efficacy in improving PFS for bone metastases. Moreover, Gulati et al. [35] revealed differences in molecular subtypes between primary tumors and metastatic sites using RNA sequencing. This study showed that angiogenesis-related genes were predominantly expressed in bone metastases. These findings underscore the importance of tailoring IO combination therapies according to the molecular characteristics of metastatic lesions and their locations.

Table 4. Efficacy of IO combination therapies by metastatic site

Variable	Lung	Liver	Bone
OS			
Nivo+Ipi [34]	0.70 (0.59–0.83)	0.73 (0.54–1.00)	0.81 (0.61–1.11)
Nivo+Cabo [31]	0.73 (0.58–0.92)	0.62 (0.41–0.95)	0.57 (0.38–0.84)
Pem+Len [32]	-	0.52 (0.27–0.99)	0.50 (0.30–0.83)
PFS			
Nivo+Ipi [34]	0.77 (0.64–0.93)	0.85 (0.61–1.18)	1.07 (0.76–1.51)
Nivo+Cabo [31]	0.56 (0.46–0.69)	0.54 (0.36–0.81)	0.45 (0.30–0.66)
Pem+Len [32]	-	0.43 (0.25–0.75)	0.33 (0.21–0.54)

Values are presented as hazard ratio (95% confidence interval).
IO, immune-oncology; OS, overall survival; PFS, progression-free survival; Nivo, nivolumab; Ipi, ipilimumab; Cabo, cabozantinib; Pem, pembrolizumab; Len, lenvatinib.

Based on these data, selection of IO combination therapy tailored to the metastatic organ sites at diagnosis is considered crucial in devising an effective treatment strategy (Fig. 2). For example, Pem+Len may be an appropriate treatment option for cases involving large primary tumor volume or the presence of inferior vena cava thrombus. In contrast, for lung metastases requiring rapid response, Nivo+Ipi may be a viable option, whereas Pem+Len or Nivo+Cabo may be more suitable for bone metastases. This highlights the need for personalized treatment strategies that consider the molecular profiles and characteristics of metastatic organ sites.

It is important to consider the differences in the efficacy of IO combination therapy based on the histological subtypes of RCC. For example, sarcomatoid differentiation is known as a highly aggressive histological subtype, but the high efficacy of Nivo+Ipi has been demonstrated [36]. However, it has not been currently shown that CN improves prognosis in sarcomatoid RCC [37]. While sarcomatoid RCC has high immunogenicity, it is also thought to have properties that create an environment that suppresses antitumor immunity [38]. Therefore, it is necessary to consider the effectiveness of IO therapy and the effect of CN separately. The evidence for the efficacy of IO combination therapies in non-clear cell subtypes is also limited compared to the clear cell subtype. The KEYNOTE-B61 trial has shown high antitumor efficacy of Pem+Len [39]. Treatment outcomes with Nivo+Cabo and Cabo monotherapy have also been reported [40,41]. However, non-clear cell subtypes include multiple histological types such as papillary RCC, chromophobe RCC, and translocation RCC, each with different molecular subtypes

Factor		IO+IO	IO+TKI
Primary tumor	High volume		Pem+Len
	IVC thrombus		
Metastatic sites	Multiple organ		Pem+Len/Nivo+Cabo
	High risk to vital functions		
	Metastatic site: lung	Nivo+Ipi	Any
	Metastatic site: bone		Pem+Len/Nivo+Cabo
	Metastatic site: liver		
Histology	Sarcomatoid/rhabdoid	Nivo+Ipi	Pem+Len/Nivo+Cabo
Host	Low tolerance		Ave+Axi

Fig. 2. Strategic insights: personal opinion on neoadjuvant regimen selection. IVC, inferior vena cava; IO, immune-oncology; TKI, tyrosine kinase inhibitor; Nivo, nivolumab; Ipi, ipilimumab; Pem, pembrolizumab; Len, lenvatinib; Cabo, cabozantinib; Ave, avelumab; Axi, Axitinib.

and immune profiles [42]. This heterogeneity necessitates caution when extrapolating clinical trial results to individual patients. The role of CN in non-clear cell RCC remains unclear, as prospective trials evaluating CN in the TKI era did not include non-clear cell subtypes [3,25]. Moreover, while a recent study assessed the efficacy of upfront CN in the IO era, it was a retrospective study with inherent limitation [43], making the current level of evidence insufficient. The NORDIC-SUN trial is designed to include all histological subtypes, and it is expected that new findings on the usefulness of deferred CN for non-clear cell subtypes will be obtained from the results of this trial. We hope that future prospective studies will clarify the optimal treatment strategies for each histological subtype.

Additionally, another significant challenge lies in establishing biomarkers capable of dynamically monitoring the therapeutic effects of IO therapy and determining the optimal timing for treatment in individual patients. Such advancements would enable more precise identification of patients who could benefit from CN, ultimately enhancing the accuracy and effectiveness of treatment.

CONCLUSIONS

At present, it is difficult to draw definitive conclusions regarding the utility of CN or its indications. However, personalized strategies based on patient risk groups and treatment outcomes are important for treatment optimization.

Future progress in ongoing RCTs and the development of biomarkers to dynamically monitor treatment effects are expected to enable more precise patient selection and enhance the efficacy of CN as a therapeutic option.

NOTES

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