Korean Urologic Oncology Society Guidelines:
Does Angioembolization Improve the Quality of Life for Renal Cell Carcinoma Patients With Intractable Symptoms Who Are Unfit for Surgery?

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Purpose: There is a lack of guidelines for using angioembolization to manage renal cell carcinoma (RCC) patients with intractable symptoms. Therefore, the Korean Urologic Oncology Society (KUOS) developed a set of recommendations for angioembolization for RCC patients with intractable symptoms who are unfit for surgery.

Materials and Methods: A rigorous systematic review was performed and GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology was used to rate the certainty of the evidence for the patient outcomes and to develop the evidence into recommendations. The steering group, guidelines development group, systematic review team, and external review group consisted of KUOS members involved in the guideline development process.

Results: The guidelines address the benefits, harms, patients' values and preferences, costs, and resources related to angioembolization by using a single clinical question: Does angioembolization improve the quality of life for RCC patients with intractable symptoms who are unfit for surgery?

Conclusions: The guideline development panel suggests angioembolization for RCC patients with intractable symptoms compared with supportive therapies, including systemic treatment (very low certainty of evidence, weak recommendation).

Key Words: Renal cell carcinoma, Therapeutic embolization, GRADE approach, Guideline
INTRODUCTION

Renal cell carcinoma (RCC) represents 3%–5% of adult malignancies worldwide and is the 6th most frequently diagnosed cancer in males and the 10th most diagnosed cancer in females [1]. Although most cases are small tumors at diagnosis, approximately 25% of RCC patients had metastases at diagnosis [2, 3]. Although radical and partial nephrectomy is still the gold standard treatment method for localized RCC, radiofrequency ablation, cryoablation, and angioembolization are treatment options for inoperable patients [4-6]. Angioembolization as a treatment for RCC was first tried in 1973 [7]. However, none of these therapies has resulted in a complete response.

RCC usually has no symptoms when it is a small renal mass. However, symptoms appear when the mass grows and presses on the adjacent organs. The most common symptoms are gross hematuria, flank pain, and palpable abdominal mass. These symptoms are more severe as the cancer stage progresses.

Palliative nephrectomy is palliative for patients with intractable pain or hemorrhage and severe tumor necrosis syndrome, but it has no clear benefit in improving the quality of life [8, 9]. Since RCC has a low sensitivity to radiation, the radiation treatment effect is poor [10]. Given that the blood vessels supplying the RCC are almost exclusively supplied by the renal artery, angioembolization to block the renal arterial blood flow is considered an effective treatment for intractable symptoms in RCC patients. The European Association of Urology (EAU) guidelines suggest that angioembolization can control symptoms, including visible hematuria and flank pain [11]. However, the American Urological Association guidelines [12], the European Society for Medical Oncology guidelines [13], and the National Comprehensive Cancer Network guidelines do not mention the role of angioembolization in this setting [14]. Therefore, the Korean Society of Urological Oncology (KUOS) has developed recommendations for angioembolization to improve the quality of life of RCC patients with intractable symptoms unsuitable for surgery. To support these recommendations, the guideline development group conducted a systematic review of the effectiveness of angioembolization in inoperable RCC patients. Based on this systematic review, KUOS has developed recommendations based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) [15-17].

MATERIALS AND METHODS

1. Structure of the Guideline Teams

The steering group, the guideline development group, the systematic review team, the external review group consisting of KUOS members, and the Korean Renal Cancer Study group were involved in developing of these guidelines (Supplementary Table 1).

The steering group provided administrative support for developing, determining the scope and key questions, and organizing the guidelines. The development group and the systematic review team supervised the publication of the guidelines and oversaw the dissemination of the guidelines. The systematic review team drafted the protocols for the systematic review, completed the comprehensive literature search and eligibility review, extracted the data, conducted the meta-analyses, assessed the risk of bias, and produced the summary of finding tables with GRADE certainty of evidence (CoE). The guideline development group, which included experts in health research methodology and urology from the medical society, interpreted the evidence with explicit consideration of patient values and preferences, resources, and other practical issues. Then, they formulated recommendations according to the GRADE methodology. The external review group, which consisted of 4 clinical experts, provided suggestions for improving and clarifying the recommended guidelines.

2. Target Audience for the Recommendations

The target subjects for these guidance statements were RCC patients with intractable symptoms who were unfit for surgery. Children were excluded from this study. The users of these guidelines include clinical physicians, such as urologists and medical oncologists, and RCC patients. These guidelines were developed based on the best available evidence to support on-site clinical decision-making between patients and their physicians. The guidelines must be flexible.
regarding the age, comorbidities, and social conditions of the individual patient and the clinical expertise of the physician.

3. Population/Patient/Problem, Intervention, Comparison, Outcome Questions, and Study Eligibility Criteria

These guidelines address a single clinical question regarding the benefit and harm related to angioembolization by the following question: Does angioembolization improve the quality of life for RCC patients with intractable symptoms who are unfit for surgery? The panel of the guideline development group found that the quality of life measured by validated questionnaires before and after angioembolization was critical for developing the recommendations. The panel of the guideline development group considered patient value and preference, cost, and resources when making a direction of recommendation.

4. Systematic Review Method

A systematic review was conducted based on an a priori method (protocol was not published but was submitted to the national cancer guideline development group) to influence the recommendations. In consultation with an expert librarian (MHK), a systematic review team searched the major literature databases (MEDLINE, Embase, Cochrane Library, Scopus, and Web of Science) and regional databases (KoreaMed and KMBASE) with no restrictions to the publication language or publication status up until October 6, 2021, to identify all relevant studies on the benefits and harms regarding RCC patients with intractable symptoms who underwent angioembolization. The team also searched for clinical trial registries (United States National Institutes of Health Ongoing Trials Register ClinicalTrials, World Health Organization International Clinical Trials Registry Platform) (Supplementary Table 2). Randomized controlled trials and nonrandomized studies were sought, but only nonrandomized studies were included because there were no randomized studies on this subject. The initial review outcome was quality of life (measured using validated questionnaires); however, there were no studies that investigated the quality of life. Therefore, the review outcome was changed to overall survival and symptom improvement (critical outcomes). Three review authors (JHJ, JYK, and HMG) participating on the systematic review team independently examined the full-text reports, identified the relevant studies, and assessed the eligibility of the studies for inclusion using a reference management software (EndNote) and an online systematic review production toolkit (Covidence). Three review authors (JHJ, JYK, and HMG) extracted the data using a dedicated data abstraction form and assessed the risk of bias using the RoBANS (Risk of Bias Assessment tool for Non-randomized Studies) [18]. Statistical analyses were performed using a random-effects model and Review Manager (RevMan 5, Cochrane Collaboration, Oxford, UK). Heterogeneity was identified through a visual inspection of the forest plots to assess the amount of overlap of the confidence intervals and the I² statistic, which quantified the inconsistencies across the studies [19]. Funnel plots were used to assess the publication bias (small study effect) if 10 or more studies were included. The CoE was assessed according to GRADE [17, 20]. Any disagreements regarding any step of the systematic review were resolved through discussions and consensuses.

5. Moving From the Evidence to the Recommendations

The steering group invited potential panel members without perceived conflicts of interest. If important competing issues were identified, the potential panelist was not invited to the guideline development group. Before the initial guidelines panel meeting, the methodologist and guideline panel shared the draft questions, received the results of the systematic review, and incorporated feedback. At the initial meeting, the guideline panel discussed the scope of the project and agreed on the research questions. At 3 subsequent meetings, the panel developed the recommendations for the guidelines according to the GRADE methodology based on the systematic review in terms of benefit, harm, patient value and preference, cost, and resources [16, 21].

6. How to Interpret the Recommendations?

Recommendations for the guidelines were made according to the GRADE methodology. The GRADE method classifies
each recommendation as strong or weak [15, 16]. A strong recommendation is usually supported by a moderate to high CoE. A strong recommendation indicates that the desirable effects of following the recommendation clearly outweighed the undesirable effects (or vice versa); therefore, the course of action would apply to all or almost all the patients [15, 16].

A weak recommendation is usually supported by a low CoE, a very low CoE, or a close balance between the desirable and undesirable effects. A weak recommendation indicates that the desirable effects of following the recommendation probably outweigh the undesirable effects; therefore, the course of action would apply to most patients but not all patients [15, 16]. Weak recommendations always warrant shared decision-making regarding the choice of treatment for individual patients while considering their values and preferences. Therefore, we used the phrase “we suggest” for the weak recommendations rather than “we recommend” or “clinicians should” [15, 16].

We used the best available evidence and presented it in a transparent and systematic manner. We have provided a summary of the supporting evidence for each recommendation. When there was no evidence, we indicated and considered a very low CoE according to the GRADE methodology [15, 16, 20].

7. Updates to Guidelines

To keep the guidelines current with the best available evidence, the guidelines development group decided to update the guidelines every 5 years.

RESULTS

1. Recommendation for Angioembolization

We developed one recommendation for angioembolization for RCC patients with intractable symptoms who are unfit for surgery. However, the recommendation is weak based on a very low CoE and a small important magnitude of effect. Table 1 presents the recommendation with the CoE.

2. Evidence Summary

Regarding the effects of angioembolization, we found 4 nonrandomized studies involving 351 RCC patients older than 18 years of age with intractable symptoms (Table 2) [22-25]. The flow of the literature throughout the systematic review process is shown in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart (Fig. 1). Twenty-eight studies did not meet the inclusion criteria or were irrelevant to the guideline question (Supplementary Table 3). All the studies were conducted in an inpatient urology clinic setting.

The mean ages of the patients in the included studies ranged from 58 to 66 years. One study compared angioembolization to no systemic treatment [22], and the remaining 3 studies compared angioembolization with systemic therapy (chemotherapy, immunotherapy using interferon-α or interleukin-2, or tyrosine kinase inhibitor) to systemic therapy [23-25]. All the studies investigated overall survival to estimate the effect of angioembolization compared with the conservative or systemic therapies. Symptom improvement was evaluated in 2 studies [23, 24]. One study specified funding sources and reported no conflicts of interest [25].

Supplementary Fig. 1 shows the risk of bias in the included studies. The following comparison was made, and the results were interpreted according to the GRADE narrative statement using a minimally contextualized approach [26, 27].

3. Angioembolization Compared to Supportive Care for Advanced RCC (Supplementary Table 4)

1) Overall survival

Angioembolization may increase overall survival, but the evidence was very uncertain (hazard ratio, 0.62; 95%
confidence interval (CI), 0.56–1.06; I² = 94%; 4 studies; 289 participants; very low CoE), corresponding to 84 more overall survivors for every 1000 patients (range, 6 fewer to 253 more overall survivors for every 1,000 patients) [22-25].

2) Symptom improvement
Angioembolization may increase symptom improvement, but the evidence was very uncertain (risk ratio, 31.71; 95% CI, 2.05–489.96; I² = 0%; 2 studies; 79 participants; very low CoE), and the absolute difference could not be calculated since there were no events in the control group [23, 24].

4. Balance Between Desirable and Undesirable Effects
None of the studies reported a difference in the major adverse event rates. The included studies reported that the adverse events of angioembolization, such as fever, back pain, and myalgia, were usually seen in daily practice [23, 24]. These symptoms usually disappeared after appropriate medication [23]. Although angioembolization may have small effects on overall survival and symptom improvement, we could not extrapolate if this could improve a patient’s quality of life, which was the original outcome of this guideline.

5. Values and Preferences
We found no studies on patient values and preferences regarding interventions involving the patient. Since angioembolization for RCC is covered by the national health insurance system, the cost ranges from approximately 110 to 200 United States dollars (150,000 to 250,000 Korean won). We also found no studies on the resources (e.g., cost) regarding interventions involving the patient.

6. Costs and Resources
None of the studies reported a difference in the major adverse event rates. The included studies reported that the adverse events of angioembolization, such as fever, back pain, and myalgia, were usually seen in daily practice [23]. These symptoms usually disappeared after appropriate medication [23]. Although angioembolization may have small effects on overall survival and symptom improvement, we could not extrapolate if this could improve a patient’s quality of life, which was the original outcome of this guideline.

Table 2. Baseline characteristics of the included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcome</th>
<th>Follow-up</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bakke et al.</td>
<td>Inpatient/ Norway</td>
<td>44 Metastatic renal cell carcinoma</td>
<td>Renal artery embolization (n=18)</td>
<td>No treatment (n=18)</td>
<td>Overall survival</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>1985</td>
<td>64±6.3 (overall)</td>
<td></td>
<td>Nephrectomy (n=8)</td>
<td></td>
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</tr>
<tr>
<td>Kim et al.</td>
<td>Inpatient/ Korea</td>
<td>42 Poor performance or advanced-stage renal cell carcinoma</td>
<td>Renal artery embolization with interferon-α/interleukin-2/5-fluouracil (5-FU) or radiation (n=28)</td>
<td>No treatment (n=4)</td>
<td>Overall survival, symptom improvement</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>2003</td>
<td></td>
<td>65.5±6.75/63.2±6.25</td>
<td></td>
<td>Interferon/Interleukin-2/5-FU or radiation only (n=10)</td>
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<td></td>
<td></td>
<td>27.15</td>
<td></td>
<td>Nephrectomy with interferon therapy or tyrosine kinase inhibitor (n=54)</td>
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<tr>
<td>Kim et al.</td>
<td>Inpatient and outpatient/</td>
<td>211 Synchronous metastatic renal cell carcinoma</td>
<td>Renal artery embolization with immunotherapy or tyrosine kinase inhibitor</td>
<td>No treatment (immunotherapy or tyrosine kinase inhibitor only) (n=128)</td>
<td>Overall survival, progression-free survival</td>
<td>81.3 Months</td>
<td>This study was supported by the Korean National Cancer Center Grants (No. 170290).</td>
</tr>
<tr>
<td>2017</td>
<td>Korea</td>
<td>58±11.5 (overall)</td>
<td></td>
<td>Nephrectomy with immunotherapy or tyrosine kinase inhibitor (n=54)</td>
<td></td>
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<tr>
<td>Onishi et al.</td>
<td>Inpatient and outpatient/</td>
<td>54 Poor performance or advanced-stage renal cell carcinoma</td>
<td>Renal artery embolization with chemotherapy, interferon-α or radiation (n=24)</td>
<td>No treatment (n=8)</td>
<td>Overall survival, symptom improvement</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>2001</td>
<td>Japan</td>
<td>66.2±8.2/65.2±13.5</td>
<td></td>
<td>Chemotherapy, interferon-a or radiation (n=22)</td>
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<td></td>
<td></td>
<td>46.8</td>
<td></td>
<td>T1/T2/T3/T4 (3/2/1/1 vs. 0/0/1/0)</td>
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</tbody>
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7. The Rationale for Recommendations for Angioembolization

The rationale for the recommendations to ‘suggest for’ rather than ‘suggest against’ is based on 2 factors. First, the balance between the desirable and undesirable effects favors angioembolization. Second, the cost and resources are not likely to be a barrier for clinicians to use angioembolization. Collectively, the guideline development group agreed that these observations warrant weak recommendations.

DISCUSSION

We developed the recommendations for angioembolization following the GRADE Working Group Standards. Based on a systematic review assessing the harms and benefits, the available evidence regarding patients’ values and preferences, costs, and resources associated with angioembolization, we suggest angioembolization for RCC patients with intractable symptoms compared to supportive therapies, including systemic treatment. (very low CoE, weak recommendation).

1. Why Does the Panel Rate the Recommendations as Weak?

The weak strength of the recommendation highlights the small magnitude of the desirable effects on overall survival and symptom improvement. The guideline development group had a high preference for angioembolization, and the cost of angioembolization contributed to a weak recommendation.

2. Comparison With Other Guidelines

The EAU guidelines suggest angioembolization for symptom control, including visible hematuria and flank pain, and RCC patients with intractable symptoms. The recommendations contained in these guidelines suggest angioembolization (very low CoE, weak recommendation) and are consistent with the EAU guidelines. In contrast to
the EAU guidelines, the American Urological Association guidelines [12], the European Society of Oncology guidelines [13], and the National Comprehensive Cancer Network guidelines do not mention the role of angioembolization in controlling intractable symptoms in RCC patients. The guideline development panel agreed with the EAU guidelines that angioembolization can be used to control intractable symptoms in RCC patients.

3. Strengths and Limitations

These guidelines have several strengths. First, an independent systematic review team conducted the review and meta-analysis on the efficacy of angioembolization in RCC patients following the rigorous methodology adopted by Cochrane to address evidence from nonrandomized trials and assessed the CoE using the GRADE methodology. In addition, domestic and foreign databases were searched for systematic data collection and utilization of vascular embolization. Although it had a very low CoE, this is the first guidelines using a systematic review and meta-analysis for comparative studies. We conducted regular guideline panel meetings led by a methodologist (MAH), who derived the efficacy of angioembolization using the GRADE evidence.

These guidelines also have limitations. First, long-term follow-up pain studies were lacking in both randomized controlled trials and nonrandomized studies. Second, even after searching the various domestic and foreign databases, only 4 studies focused on the effects of angioembolization were found. Third, the guideline development group members consisted exclusively of urologists and methodology experts, and no patients were included in the panel.

4. Implications for Clinical Practice

Palliative nephrectomy is one option to control treatment-refractory pain, hemorrhage, and severe tumor necrosis syndrome in RCC patients. However, for patients who are not surgical candidates or do not want to undergo traditional surgery, angioembolization is a safe and effective therapy.

Therefore, angioembolization is suggested to treat intractable symptoms in RCC patients who are not surgical candidates, and it is suggested that angioembolization will be helpful in clinical practice (very low CoE, weak recommendation).

NOTES

- Supplementary Materials: Supplementary Tables 1-4 and Fig. 1 can be found via https://doi.org/10.22465/juo.234600180009.
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