

# Oncologist Perspectives on Rare Cancer Care: A Nationwide Survey

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## Purpose

In response to the challenges and difficulties imposed by rare cancers, multi-stakeholder initiatives dedicated to improving rare cancer care was launched, and several recommendations were made by professional societies. However, these primarily reflect the view of the advocates and supporters, and may not represent the views of the “average” clinician or researcher. In this study, we sought to investigate perceived difficulties with regard to rare cancer care and potential solutions endorsed by oncologists.

## Materials and Methods

A representative sample of 420 oncologists recruited in 13 cancer centers participated in a nationwide survey.

## Results

Oncologists faced various difficulties in treatment of patients with rare cancers, including the lack of clinical practice guidelines (65.7%) and personal experience (65.2%), lack of approved treatment options (39.8%), and reimbursement issues (44.5%). They were generally supportive of recent recommendations by multi-stakeholder initiatives as well as professional societies for development of clear clinical practice guidelines (66.0%), flexible reimbursement guidelines (52.9%), and a national rare cancer registry (47.4%). However, there was only moderate endorsement for referrals to high-volume centers (35.5%) and encouragement of off-label treatments (21.0%).

## Conclusion

Insights into the general attitudes of oncologists gained through our nationwide survey of representative samples would be helpful in development of clinical practices and public health policies in rare cancer treatment and research.

## Key words

Rare diseases, Cancer, Oncologists, Attitude, Recommendation

## Introduction

Rare cancers are not rare at all. Despite the relatively low incidence of each type of cancer, rare cancers combined account for 20%-30% of cancer cases and deaths [1,2]. Every year, more than 500,000 people are diagnosed with a rare form of cancer in the European Union, and more than 4 million are living with the diagnosis of rare cancer [3,4]. Survival rates for rare cancers are lower than those for common cancers (5 years; 47% vs. 65%). Therefore, rare cancers pose a significant burden and should be recognized as a public health priority [5,6].

Patients and their families, as well as clinicians, researchers, and policy makers involved in cancer care are faced with the profound challenges and difficulties imposed by these forms of cancer. In fact, it is estimated that thousands of patients with these “forgotten cancers” are paying a high price as a result of repeated misdiagnosis and receiving inappropriate treatment [7]. Some may need to travel long distances in order to obtain the necessary treatment, while many struggle to find information about their disease and find their consultation time insufficient [7,8]. Clinicians also face unique challenges resulting from the lack of sufficient evidence [7], and researchers face challenges from insufficient funding or low number of research subjects [7]. From the perspective of policy makers, the disproportionate occurrence of such forms of cancer in younger and minority populations [1], unequal access to quality care, and geographic variation in survival rates create additional challenges in terms of health disparities [5,6].

Important steps or measures have recently been taken toward improving rare cancer care. Several workshops held in the United States and the EU promoting epidemiological research on rare and understudied cancer are notable examples of recent progress in this area [2,9]. Consequently, a multi-stakeholder initiative dedicated to improving rare cancer care was launched [4], and several recommendations were made by professional societies [9]. These initiatives and recommendations reflect the joint effort of research communities, clinicians, policy makers, patients, and industry partners, and workshop attendees are often advocates and supporters of proposed recommendations and thus may not represent the views of the “average” clinician or researcher.

In addition, several recommendations lack firm scientific evidence or support, and may be up for debate. For example, it remains unclear as to whether patients with rare cancers treated in high volume centers show better survival [10]. In addition, there is some evidence that the public do not have a societal preference for treating rare diseases over common ones, implying that the degree of rarity of a disease does not justify prioritization (e.g., the special market access status of

orphan drugs) [11]. Moreover, proponents assert that incentives promoting use of orphan drugs have resulted in market failures [12]. Experts also disagree on whether current incentives for research focusing on rare diseases are adequate [13].

To the best of our knowledge, there are no currently available quantitative data on the experiences and opinions of physicians involved in cancer care. Therefore, in this study involving nationally representative samples of oncologists, we sought to investigate perceived difficulties with regard to rare cancer care and potential solutions endorsed by oncologists.

## Materials and Methods

### 1. Study design and subjects

This study was part of a nationwide survey conducted in order to explore views regarding medical care and treatments among physicians involved in cancer care. Physicians in the National Cancer Center and 12 government-designated regional cancer centers across Korea participated in the survey. The study was approved by the Institutional Review Board of the National Cancer Center, Korea.

Of the 901 cancer care physicians invited to participate in the study, 680 agreed (75.5% participation rate) to do so and completed the study survey. Among them, those who directly see cancer patients for diagnosis and treatment were asked to answer questions regarding rare cancer issues, and 175 physicians who provided clinical support to oncologists (e.g., radiologists, pathologists, cardiologists, rehabilitation specialists, pain specialists, and psychiatrists) were excluded from the study. In addition, 30 oncologists who did not answer the questionnaire regarding rare cancer issues and 52 physicians who reported that they do not see rare cancer patients at all were also excluded from the study. Three additional oncologists were excluded from the analyses due to their high rates of missing responses ( $\geq 50\%$  of items on rare cancer questions), leaving 420 oncologists comprising the study's eventual sample.

### 2. Measures

We developed a questionnaire based on themes identified from various scientific and lay literature regarding rare cancer care [4,5,7,13-19]. Survey questions covered: (1) the proportion of rare cancer patients in participants' practices, (2) personal experiences of difficulties in treatment of rare cancers, and (3) participants' endorsements of potential solutions for improving rare cancer care (Appendix 1).

In our instructions to study participants, we addressed the current lack of a unified definition of rare cancer to ensure that they understood the survey's content: "Although there is presently no clear definition of 'rare cancer,' it is commonly defined as a cancer with an incidence of 5 per 100,000 [9]. Please answer the following questions, supposing that they do not apply to common cancers (e.g., cancers of the stomach, lung, liver, colon, breast, cervix, thyroid, prostate, gallbladder, and pancreas) but may apply to cancers with uncommon histologies in common cancer sites." The list of cancer types included in the questionnaire reflected cancer epidemiology in Korea [20].

Other issues related to rare cancer care that we explored through the survey included lack of clinical experience and need for referral [4,7,16,19], availability of approved drugs and need to promote off-label treatments [4,7,15,16,19], reimbursement issues [14,17,19], lack of research evidence and guidelines [4,5,19], research funding and clinical trials of pharmaceutical companies [18,19], support and incentives from the government [5,7,13,16,18], and the need for an (inter)national registry [4,16-18]. When answering the questions regarding difficulties faced by oncologists and solutions for improvement of care survey physicians were allowed to choose multiple answers that apply without limitation. In addition, a blank space was provided for them to share any personal experiences or opinions regarding rare cancer treatment. Data on participants' age, sex, specialty, years from board certification, and patient volume (average number of outpatients per week) were also collected.

### 3. Statistical analysis

Descriptive statistics were used to summarize participants' responses to the questionnaire. Chi-square tests were performed for comparison of responses according to participants' specialties and the proportions of rare cancer patients in their practices. Correlations between responses to the

**Table 1.** Characteristics of the oncologists (n=420)

Characteristic	No. (%)
Age (yr)	43.0±7.8
Time since board certification (yr)	12.0±7.8
Gender	
Male	335 (79.8)
Female	85 (20.2)
Specialty	
Surgical oncologists	240 (57.1)
Medical oncologists	152 (36.2)
Radiation oncologists	28 (6.7)
Patient volume (No. of outpatients/wk)	119.8±79.3

Values are presented as mean±SD or number (%).

items were further explored to determine associations between perceived barriers and recommendations. All statistical analyses were performed using Stata ver. 12.0 (StataCorp, College Station, TX), and a  $p < 0.05$  was considered statistically significant.

## Results

### 1. Characteristics of participants

The mean age of the oncologists was 43.0 years, and the average number of years since board certification was 12.0 years. Around 80% were male. The sample comprised surgical oncologists (57.1%), medical oncologists (36.2%), and radiation oncologists (6.7%) (Table 1). Overall, the proportions of rare cancer patients seen by the oncologists were < 1% for 38.3% and 1%-5% for 39.1%. Less than a quarter of

**Table 2.** Proportion of rare cancer patients by specialty

Variable	Total	Proportion of rare cancer patients			
		≤ 1% (n=161)	> 1%-≤ 5%	> 5%-≤ 50%	> 50% (n=22)
All	420	161 (38.3)	164 (39.1)	73 (17.4)	22 (5.2)
Surgical oncologist	240	93 (38.8)	91 (37.9)	45 (18.8)	11 (4.6)
Medical oncologist					
Adult	142	63 (44.4)	53 (37.3)	21 (14.8)	5 (3.5)
Pediatric	10	0	0	4 (40.0)	6 (60.0)
Radiation oncologist	28	5 (17.9)	20 (71.4)	3 (10.7)	0

Values are presented as number (%).

**Table 3.** Difficulties faced by oncologists in the treatment of patients with rare cancers

Difficulty	All respondents No. (%)	By oncologist specialty (%)			p-value	By proportion of rare cancer patients (%)				p-value
		Surgical oncologist (n=240)	Medical oncologist (n=152)	Radiation oncologist (n=28)		≤ 1% (n=161)	> 1%-≤ 5%	> 5%-≤ 50%	> 50% (n=22)	
Insufficient personal experience with regard to rare cancer treatment	274 (65.2)	64.6	64.5	75.0	0.532	78.9	65.2	46.6	27.3	< 0.001
Insufficient approved treatment options	167 (39.8)	31.7	59.9	0.0	< 0.001	40.4	36.0	41.1	59.1	0.213
Issues regarding reimbursement	187 (44.5)	36.3	63.2	14.3	< 0.001	41.0	43.9	49.3	59.1	0.333
Insufficient research evidence on rare cancer treatments	227 (54.1)	50.4	55.9	75.0	0.04	57.1	57.9	43.8	36.4	0.059
Lack of standard treatment guidelines	276 (65.7)	69.2	60.5	64.3	0.211	67.1	68.3	67.1	31.8	0.008
Insufficient investment and clinical trial opportunities from pharmaceutical companies	77 (18.3)	14.6	27.0	3.6	0.001	16.2	16.5	20.6	40.9	0.035
Insufficient research funding from the government	72 (17.1)	15.8	20.4	10.7	0.327	11.8	17.1	24.7	31.8	0.024

oncologists answered that rare cancer patients constituted > 5% of the patients in their practice, except for pediatric medical oncologists, 60% of whom noted that rare cancer patients comprised the majority of their patient population (Table 2).

## 2. Difficulties faced by oncologists in rare cancer care

Difficulties reported by more than half of the respondents included lack of standard treatment guidelines (65.7%), insufficient personal experience with rare cancer treatments (65.2%), and lack of evidence regarding rare cancer treatments (54.1%). Relatively little clinical experience was higher for those who rarely see rare cancer patients ( $p < 0.001$ ). Reimbursements for drug treatments (44.5%), and unavailability of sufficient approved treatment options (39.8%) were also commonly reported, particularly by medical oncologists ( $p < 0.001$ ). Less than 20% of participants felt that investments from pharmaceutical companies and clinical trials were lacking (18.2%), or that more research funding from the government was needed (17.1%), although oncologists who frequently saw rare cancer patients were more likely to endorse these measures as solutions for better rare cancer care ( $p < 0.05$ ) (Table 3).

## 3. Potential solutions for improvement of rare cancer care

More than half of our study participants noted the need for development of clinical practice guidelines (66.0%), and more flexible reimbursement guidelines for treatment of rare cancers (52.9%). More than 30% of respondents felt that the establishment of a national registry (47.4%), a referral system to high volume centers for accumulating treatment experience (35.5%), research incentives (33.8%), and government initiative and support for research in rare cancer (30.2%) would improve patient care. Only a small proportion of respondents endorsed solutions involving off-label treatments for rare cancers (21.0%) and legislation mandating budget allocations for development of drugs for treatment of rare cancers (13.1%) (Table 4). Correlations between perceived barriers and recommendations are shown in Table 5.

## Discussion

To the best of our knowledge, our study was the first to investigate the consensus among oncologists regarding rare

**Table 4.** Potential solutions for improvement of rare cancer care

Potential solution	All respondents No. (%)	By oncologist specialty (%)			p-value	By proportion of rare cancer patients (%)				p-value
		Surgical oncologist (n=240)	Medical oncologist (n=152)	Radiation oncologist (n=28)		≤ 1% (n=161)	> 1%-≤ 5%	> 5%-≤ 50%	> 50% (n=22)	
Referrals to high volume centers to enable the accumulation of rare cancer treatment experience	149 (35.5)	37.9	31.6	35.7	0.442	42.2	35.4	27.4	13.6	0.02
Encouragement of off-label treatment for rare cancers	88 (21.0)	15.8	30.9	10.7	0.001	18.6	18.9	30.1	22.7	0.195
Flexible reimbursement guidelines for rare cancer treatment	222 (52.9)	49.2	63.2	28.6	0.001	49.7	48.8	64.4	68.2	0.052
Encouraging research on rare cancers through incentives	141 (33.6)	33.8	34.9	25.0	0.594	29.8	33.5	42.5	31.8	0.303
Development of clinical practice guidelines for rare cancers	277 (66.0)	66.3	66.5	60.7	0.832	62.1	74.4	63.0	40.9	0.005
Legislation mandating the allocation of funds for the development of rare cancer drug treatments	55 (13.1)	11.7	17.1	3.6	0.09	12.4	12.2	15.1	18.2	0.818
Increase government research funding for the development of rare cancer treatments	127 (30.2)	29.6	32.2	25.0	0.704	28.0	25.6	43.8	36.4	0.031
Development of national registry for the registration of rare cancer patients	199 (47.4)	45.0	48.7	60.7	0.266	51.6	43.9	42.5	59.1	0.28

cancer patient care. The strengths of our study include its nationally representative samples of oncologists with various specialties and experiences in treatment of rare cancers, which enabled a comparison of responses across subgroups.

The lack of standard treatment guidelines was the most common difficulty in treating rare cancers noted by oncologists, regardless of their specialty. In addition, development of clinical practice guidelines for rare cancers was the most frequently endorsed item for improvement of rare cancer care. Agencies including the National Comprehensive Cancer Network (NCCN) and National Institute for Health and Care Excellence (NICE) are publishing more clinical guidelines on cancers, which currently do not yet cover most rare cancers. The lack of established guidelines for rare cancer treatment often leaves oncologists with no clear direc-

tion in treating patients with rare cancers and in making treatment decisions based on empirical evidence [19]. Indeed, the World Health Organization (WHO) [5] and European Society for Medical Oncology (ESMO) [9] have suggested implementing guidelines for medical and psychosocial care.

Insufficient personal experience in rare cancer treatment was the second most common difficulty faced by oncologists, and was related to endorsement of referrals to high volume centers ( $\gamma=0.23$ ,  $p < 0.001$ ). Centralization of diagnosis and multidisciplinary treatment at specialized centers have been advocated by professional societies [9], government bodies [21], and even insurers [19,22], who assume that such measures will improve outcomes [3,9,10]. However, among our study participants, the endorsement of referrals to high



**Table 5.** Correlations between perceived barriers and recommendations

Variable	Insufficient personal experience	Insufficient treatment options	Reimbursement issues	Insufficient research evidence	Lack of standard treatment guidelines	Insufficient investment and clinical trial opportunities	Insufficient research funding from the government
Referrals to high volume centers	0.24**	-0.05	-0.10*	0.07	0.01	-0.07	-0.03
Encouragement of off-label treatment	0.02	0.20**	0.25**	0.09	0.09	0.22**	0.09
Flexible reimbursement guidelines	-0.09	0.35**	0.45**	0.02	-0.05	0.23**	0.24**
Encouraging research on rare cancers	-0.02	0.15**	0.13	0.15**	0.01	0.28**	0.35**
Development of clinical practice guidelines	0.19**	-0.03	0.00	0.11*	0.41**	-0.08	0.01
Legislation mandating the allocation of funds for the development of drug treatments	-0.01	0.19**	0.19**	0.15**	0.01	0.35**	0.37**
Increase government research funding	-0.02	0.09	0.13**	0.12*	-0.01	0.34**	0.44**
Development of national registry	0.04	0.04	0.05	0.21**	0.05	0.11*	0.16**

\* $p < 0.05$ , \*\* $p < 0.01$ .

volume centers was relatively low (35.5%), particularly among those who saw a higher proportion of rare cancer patients ( $p=0.02$ ). In the blank space in which they could express their views and offer suggestions, several oncologists proposed that rare cancer treatments be administered in regional cancer centers rather than in centralized venues, and suggested the need for information sharing, registry establishment, and collaborative research. Further studies are warranted regarding the optimal degree of centralization in treatment of rare cancers, and the full potential of information technology/telemedicine [21] as a viable alternative to centralization.

Insufficient approved treatment options and issues pertaining to reimbursement were also frequently reported, both of which were found to be inter-related ( $\gamma=0.51$ , data not shown). These two barriers were also strongly related to their endorsement for encouragement of off-label treatment for rare cancer treatment and relief of reimbursement guidelines for rare cancer treatment ( $\gamma=0.20-0.45$ ,  $p < 0.001$ ). Medical oncologists, whose main treatment modalities were anti-cancer drugs, were more likely to perceive these as being obstacles to quality rare cancer patient care and called for necessary improvements. Clinical trials on rare disease treatment are rarely conducted due to the lack of commercial

incentives [23]. When conducted, trials are likely to be underpowered due to a small number of available patients. Therefore, off-label anti-cancer drugs are often requested by patients or family caregivers [24], are justified or regarded as essential in certain conditions when there is compelling biological plausibility as to their efficacy, and were supported by professional guidelines and US reimbursement policies [14,25]. In our study, while the need for flexible reimbursement guidelines was acknowledged by over half of the oncologists, only about 20% agreed with the idea of promoting off-label medication use. Such seemingly discrepant attitudes were also reported in a US survey; while 61% of oncologists expressed their belief that off-protocol treatment use should be discouraged among patients, only 31% agreed that such treatments should not be available [24]. This implies that while oncologists prefer greater flexibility in cancer drug use/treatments [14,19], they also feel uncomfortable trying unproven therapies. In fact, professional oncology societies have called for timely production of "standard medical compendia" enlisting off-label uses judged to be legitimate [25].

Insufficient research evidence was also among the most commonly perceived difficulties in rare cancer care. Rare cancers typically receive little scientific attention [1] and have

suffered from difficulties in patient accrual as well as underfunding due to being low in priority. Therefore, platforms for collaborative research and sustained funding mechanisms have been advocated, including registries or research networks at the national or multinational level [17,18], federal or government funding for rare disease research projects [9,13,18], and financial support from industry partners for clinical research or regulatory registration activities for specific rare diseases [18].

Among such potential solutions, the development of a national rare cancer registry was supported by nearly half of the oncologists, implying that they agree with the idea that registries constitute key instruments increasing empirical evidence on rare diseases [16]. In contrast, only a small proportion of oncologists mentioned insufficient research funding or clinical trials as difficulties. In addition, endorsement for incentives for rare cancer research and government funding was only moderate, and oncologists generally opposed the enactment of legislation mandating pharmaceutical companies allocate funds for rare cancer treatment. These were also not expected in advance. However, we found no negative free statements on the idea and found many others supporting such ideas. In addition, these solutions were often endorsed by oncologists who frequently saw rare cancer patients. Therefore, we supposed that the low endorsement rates reflected low personal needs for such measures rather than objections to these ideas.

There were several limitations to the current study. First, we did not provide specific lists of rare cancers, as definitions vary from one set of guidelines to another and can differ according to the determining criterion [1-3,9]. Therefore, the proportion of patients with rare cancers in their practice estimated by the oncologists may not be accurate. Second, the majority of survey respondents did not frequently see rare cancer patients, and thus might not have clear opinions regarding many issues in rare cancer care. However, in the real world they would be the first physicians whom patients with rare cancers see and therefore their opinions were critical in development of national policies and strategies. Third, the experiences of oncologists in treatment of rare cancers as well as their attitudes towards treatments would be specific to each country as these are largely determined by health care delivery and reimbursement systems.

## Conclusion

In summary, oncologists faced various difficulties in treatment of patients with rare cancers, including the lack of clinical practice guidelines and personal experience, lack of approved treatment options, and reimbursement issues. They were generally supportive of recent recommendations by multi-stakeholder initiatives as well as professional societies for development of clear clinical practice guidelines, flexible reimbursement guidelines, and a national rare cancer registry. However, there was only moderate endorsement for referrals to high-volume centers or encouragement of off-label treatments. Insights into the general attitudes of oncologists gained through our nationwide survey of representative samples would be helpful in development of clinical practices and public health policies in rare cancer treatment and research.

## Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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## Appendix

### Appendix 1. Questionnaire

Although there is presently no clear definition of 'rare cancer,' it is commonly defined as a cancer with an incidence of 5 per 100,000. Please answer the following questions, supposing that they do not apply to common cancers (e.g., cancers of the stomach, lung, liver, colon, breast, cervix, thyroid, prostate, gallbladder, and pancreas) but may apply to cancers with uncommon histologies in common cancer sites.

#### 1. What is your estimation of the proportion of rare cancer patients in your patient pool?

Approximately (            )%

#### 2. Please indicate all the difficulties you face in the treatment of patients with rare cancers.

- ① Insufficient personal experience with regard to rare cancer treatment
- ② Insufficient approved treatment options
- ③ Issues regarding reimbursement
- ④ Insufficient research evidence on rare cancer treatments
- ⑤ Lack of standard treatment guidelines
- ⑥ Insufficient investment and clinical trial opportunities from pharmaceutical companies
- ⑦ Insufficient research funding from the government

#### 3. Please freely describe the difficulties you faced during the care of rare cancer patients.

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#### 4. Please indicate all the potential solutions you think would be helpful for the improvement of rare cancer care.

- ① Referrals to high volume centers to enable the accumulation of rare cancer treatment experience
- ② Encouragement of off-label treatment for rare cancers
- ③ Flexible reimbursement guidelines for rare cancer treatment
- ④ Encouraging research on rare cancers through incentives
- ⑤ Development of clinical practice guidelines for rare cancers
- ⑥ Legislation mandating the allocation of funds for the development of rare cancer drug treatments
- ⑦ Increase government research funding for the development of rare cancer treatments
- ⑧ Development of national registry for the registration of rare cancer patients

#### 5. Please freely describe your own opinion if any to improve the rare cancer treatment difficulties you faced during the care of rare cancer patients.

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