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Original Article

Radiation Oncologists' Perspectives on Oligometastatic Disease: A Korean Survey Study

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Purpose Perspectives of radiation oncologists on oligometastatic disease was investigated using multi-layered survey.

Materials and Methods Online survey on the oligometastatic disease was distributed to the board-certified regular members of the Korean Society for Radiation Oncology. The questionnaire consisted of four domains: five questions on demographics; five on the definition of oligometastatic disease; four on the role of local therapy; and three on the oligometastatic disease classification, respectively.

Results A total of 135 radiation oncologists participated in the survey. The median length of practice after board certification was 22.5 years (range, 1 to 44 years), and the vast majority (94.1%) answered affirmatively to the clinical experience in oligometastatic disease management. Nearly two-thirds of the respondents considered the number of involved organs as an independent factor in defining oligometastasis. Most frequently perceived upper limit on the numerical definition of oligometastasis was 5 (64.2%), followed by 3 (26.0%), respectively. Peritoneal and brain metastasis were nominated as the sites to be excluded from oligometastastic disease by 56.3% and 12.6% of the participants, respectively. Vast majority (82.1%) agreed on the role of local treatment in the management of oligometastatic disease. Majority (72%) of the participants acknowledged the European Society for Radiotherapy and Oncology (ESTRO)–European Organisation for Research and Treatment of Cancer (EORTC) classification of oligometastatic disease, however, only 43.3% answered that they applied this classification in their clinical practice. Underlying reasons against the clinical use were 'too complicated' (66.0%), followed by 'insufficient supporting evidence' (30.0%), respectively.

Conclusion While most radiation oncologists supported the role of local therapy in oligometastatic disease, there were several inconsistencies in defining and categorizing oligometastatic disease. Continued education and training on oligometastatic disease would be also required to build consensus among participating caregivers.

Key words Oligometastasis, Radiotherapy, Surveys and questionnaires

Introduction

Notorious hallmarks of malignancy include the capacity to disseminate throughout the body, which is definitely undesirable and typically leads not only to the compromised life quality but also the shortened life span of the victims. From a traditional oncological perspective, it has usually meant that there had been, though not be discovered yet, already metastatic involvement of multiple sites or organs, once any systemic metastasis is detected. In this context, the role of metastasis-directed local therapy used to have quite limited importance [1,2]. However, in 1995, Hellman and Weichselbaum [3] raised an argument that there existed an intermediate state between localized and systemic disease, and first proposed the term "oligometastasis" and suggested that "some patients should be amenable to curative local therapeutic strategies." Several attempts to administer local treatment to the patients with limited metastatic burdens have yielded more or less favorable outcomes. Notably, two studies on surgical resection of hepatic metastasis originating

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from colorectal cancer showed that a significant proportion of the patients could achieve long-term survival outcomes [4,5]. In addition, a larger retrospective study, which included over 5,000 patients with lung metastases from various primary sites, reported favorable 5-, 10-, and 15-year overall survival rates following complete lung metastasectomy, when compared to incomplete surgery (36%, 26%, and 22% vs. 13%, 7%, and 7%, respectively) [6]. Endorsed with these evidences, the perception of oligometastatic status emerged from the conceptual level to more realistic clinical category among the oncology communities [7,8]. Though supported by the evidences, the application of aggressive local treatment modalities to the patients with systemic metastasis used to encounter hesitancy and resistance by many cautious oncologists [9]. There have been many prospective trials, small and large, which evaluated the role of aggressive local treatment approaches, and most of them were in accordance to the fact that there is a certain role of local therapy in addition to the standard of care policy [10]. Moreover, there have been a few enthusiastic efforts to define and classify the oligometastatic status [8,11], but concrete and reliable guidelines on the definitions, diagnostic work-ups, and treatment strategies still remain to be determined.

Although local treatment has shown its efficacy in treating the oligometastatic patients, significant proportion of them ultimately have experienced progression of disease [10]. Consequently, the need for non-invasive ablative local treatment, as the alternative to surgical resection, has arisen. Modern radiation therapy (RT) techniques, such as stereotactic body radiotherapy (SBRT) and intensity-modulated radiotherapy, have enabled precise targeting of metastatic foci and reduced risk of toxicities by minimizing the bystander exposure to the normal organs. Many radiation oncologists have endeavored to explore the efficacy and suitable indications of local treatment for oligometastatic disease, and a few recently reported randomized studies confirmed that the consolidative local RT improved the oncologic outcomes in the oligometastatic patients [12-14]. This study is a survey-based research conducted by the K-OWG (Korean-Oligometastasis Working Group), a research group affiliated with the Korean Cancer Society, to investigate the perception of oligometastatic disease and treatment trends using the questionnaires to board-certified radiation oncologists in Korea.

Materials and Methods

Online survey was performed from March to April 2022 and was distributed to the board-certified radiation oncologists, all of whom were the regular members of the Korean Society for Radiation Oncology (KOSRO). All respondents answered voluntarily, and the informed consent form was obtained from all of them. The questionnaires were developed and revised by seven radiation oncologists of the K-OWG committee. The survey consisted of four domains: five questions on the demographics of respondents; five on the definition of oligometastatic disease; four on the role of local therapy in treating oligometastatic disease; and four on the acknowledgment of the oligometastatic disease classification formulated by the European Society for Radiotherapy and Oncology (ESTRO) and European Organisation for Research and Treatment of Cancer (EORTC), respectively (Table 1) [8]. The survey included both multiple choices and open questions. The Survey Monkey (Palo Alto, CA) platform was used, and this research was conducted according to the principles of the Declaration of Helsinki and locally applicable requirements.

Results

1. Demographics

The total number of participants of this survey study was 135, among 356 radiation oncologists requested to participate. Among them, 127 respondents (94.1%) answered that they had experience of treating the oligometastatic patients, and the average number of oligometastasis cases managed per year was 1-5 in 27 (20%), 6-10 in 40 (29.6%), 11-20 in 31 (23.0%), 21-30 in 22 (16.3%), and > 31 in 15 (11.1%), respectively. The median years of clinical practice as a board-certified radiation oncologist was 22.5 years (range, 1 to 44 years). The average numbers of new patients treated per month by the respondents, were < 19 in 30 (22.2%), 20-29 in 38 (27.9%), 30-39 in 36 (26.7%), and ≥ 40 in 31 (23.0%), respectively. The most common subspecialties of the respondents were breast cancer (n=64, 47.4%), colorectal cancer (n=57, 42.2%), lung cancer (n=53, 39.3%), head and neck cancer (n=52, 38.5%), and prostate cancer (n=51, 37.8%), respectively (Table 2).

2. Definition of oligometastasis

There were five questions on the definition of oligometastasis. Regarding the number of involved organs, 39 (31.7%) and 38 (30.9%) respondents answered "2 or less" and "3 or less," respectively, whereas 36 (29.3%) responded that they did not consider the number of organs involved as an independent factor (Table 1). As for the upper limit of number of metastatic foci, 79 respondents (64.2%) answered "5 or less" and 32 (26.0%) did "3 or less," respectively. Other unlisted responses included "the disease burden that could be included in a single RT target volume should be defined as oligometastatic disease," and "oligometastasis should be defined comprehensively considering the location of metastases and

Table 1. Survey results of the definition, role of local therapy, classification of oligometastatic disease (n=135)

	No. (%)
Definition	
Q1. What do you think is an upper limit of the number of involved organs to be regarded as oligometastasis?	
Do not consider	36 (29.3)
2 or less	39 (31.7)
3 or less	38 (30.9)
5 or less	8 (6.5)
Others	2 (1.6)
No answer	12
Q2. What do you think is an upper limit of the number of metastases to be regarded as oligometastasis?	
Do not consider	6 (4.9)
3 or less	32 (26.0)
5 or less	79 (64.2)
10 or less	4 (3.3)
Others	2 (1.6)
No answer	12
Q3. What do you think is an upper limit of the size of metastatic tumors to be regarded as oligometastasis?	
Do not consider	62 (50.4)
2 cm or less	6 (4.9)
3 cm or less	23 (18.7)
5 cm or less	31 (25.2)
10 cm or less	0
Others	1 (0.8)
No answer	12
Q4 . Would there be an exclusive organ not to be regarded as oligometastasis? If so, please name any?	
Do not consider	30 (24.4)
Exclude brain metastasis	13 (10.6)
Exclude peritoneal seeding	71 (57.7)
Others	9 (7.3)
No answer	12
Q5. Are there other factors need to be considered for defining oligometastatic disease? (open question)	
Performance status or expected survival	25 (18.5)
Primary tumor control	11 (8.1)
Disease-free interval	10 (7.4)
Others	5 (3.7)
No answer	84 (62.2)
Role of local therapy	
Q1. Do you think there is a role for local therapy in oligometastatic disease?	
Yes	101 (82.1)
No	1 (0.8)
Not proven	3 (2.4)
Depends on cancer subtypes	18 (14.6)
No answer	12

(Continued to the next page)

disease-free interval as well as number of lesions." As for the size criteria, 62 respondents (50.4%) answered that they did not consider the size, and 31 (25.2%) chose "5 cm or less," 23 (18.7%) did "3 cm or less," and six (4.9%) did "2 cm or less," respectively. Regarding the sites of metastasis, 71 respondents (57.7%) answered that the peritoneal metastasis should be excluded, 13 (10.6%) did that brain metastasis should be excluded, and two did that pleural metastasis should be excluded from the definition of oligometastasis, respectively. Thirty respondents (24.4%) answered that they did not con-

Table 1. Continued

	No. (%)
Q1-1. If it depends on cancer types, in which cancer do you think there is a role of local therapy? (multiple choice)	
Lung cancer	10 (52.6)
Colorectal cancer	14 (73.7)
Prostate cancer	11 (57.9)
Breast cancer	14 (73.7)
Head and neck cancer	6 (31.6)
Gastrointestinal cancer	5 (26.3)
Others	1 (5.3)
No answer	118
Q2. If so, in what aspects do you think local therapy has a role? (multiple choice)	
Overall survival	70 (59.3)
Progression-free survival	87 (73.7)
Quality of life	81 (68.6)
Chemotherapy-free interval	88 (74.6)
Others	4 (3.4)
No answer	17
Q3. What would be an appropriate endpoint to evaluate the role of local therapy? (multiple choice)	
Overall survival	53 (43.1)
Progression-free survival	83 (67.5)
Local control	95 (77.2)
Depends on cancer subtypes	29 (23.6)
Others	7 (5.7)
No answer	53
Classification and clinical application	
Q1. Are you aware of ESTRO/EORTC classification as following? (Genuine OMD, Repeat OMD, Induced OMD, Oligorecurrence, Oligopersistence, Oligoprogression)	
Yes	88 (72.1)
No	34 (27.9)
No answer	13
Q2. Do you use ESTRO/EORTC classification in clinical practice?	
Yes	39 (43.3)
No	51 (56.7)
No answer	45
Q3. If not, what is the reason against clinical use?	
Insufficient supporting evidence	15 (30.0)
Too complicated	33 (66.0)
Others	2 (4.0)
No answer	85
Q4. Among the ESTRO/EORTC classifications of oligometastasis, in which case do you think there may be a role of local therapy? (multiple choice)	
Genuine oligometastatic disease	65 (79.3)
Repeat oligometastatic disease	36 (43.9)
Induced oligometastatic disease	40 (48.8)
Oligorecurrence	72 (87.8)
Oligopersistence	54 (65.9)
Oligoprogression	57 (69.5)
No answer	53

EORTC, European Organisation for Research and Treatment of Cancer; ESTRO, European Society for Radiotherapy and Oncology; OMD, oligometastatic disease.

Table 2. Demographics of respondents

	No. (%)
Years of practice as board-certified radiation oncologist	
1-5	27 (20.0)
6-10	40 (29.6)
11-20	31 (23.0)
21-30	22 (16.3)
> 31	15 (11.1)
No. of new patients (per person per month)	
< 19	30 (22.2)
20-29	38 (28.1)
30-39	36 (26.7)
≥ 40	31 (23.0)
Oligometastasis cases per year	
< 10	45 (35.4)
10-19	39 (30.7)
20-29	23 (18.1)
≥ 30	20 (15.7)
Subspecialties (multiple options)	
Lung	53 (39.3)
Colorectal	57 (42.2)
Prostate	51 (37.8)
Breast	64 (47.4)
Head and neck	52 (38.5)
Gastrointestinal	46 (34.1)
Gynecologic	40 (29.6)
Others	24 (17.8)

sider the site of metastasis as independent factor. In an open question on any other considerations beyond the aforementioned, 25 radiation oncologists (18.5%) answered that performance status or expected survival should be additionally considered, 11 (8.1%) did that the status of primary tumor control should be considered, and 10 (7.4%) did that disease-free interval should be taken into account, respectively. Other answers included "available systemic treatment option," "sufficient diagnostic studies including positron emission tomography–computed tomography," "differentiation of new primary tumor," "patients' symptom," and "feasibility of local therapy," respectively.

3. Role of local therapy

To the question "Do you think there is a role for local therapy in oligometastatic disease?," 101 respondents (82.1%) answered in affirmative, while 18 (14.6%) did that "it depends on the cancer subtypes," respectively. To the sub-question of "In which subtypes do you think there is a role of local therapy?," 52.6%, 73.7%, 57.9%, and 73.7% of the respondents answered lung cancer, colorectal cancer, prostate cancer, and breast cancer, respectively. To the question "In what aspects do you think local therapy has a role?," "increasing overall survival," "increasing progression-free survival," "enhancing quality of life," and "increasing chemotherapy-free interval" was chosen by 59.3%, 73.7%, 68.6%, and 74.6% of the respondents, respectively. To the question "Which one do you think is the appropriate endpoint to evaluate the role of local therapy in oligometastatic disease?," "local control" was the most frequent answer (77.2%), followed by "progression-free survival" (67.5%), and "overall survival" (43.1%), respectively. Other answers included "chemotherapy-free interval" and "quality of life."

4. Classification and clinical application

To the question that asked awareness of the ESTRO/EORTC classification of oligometastatic disease (e.g., genuine oligometastatic disease, repeat oligometastatic disease, induced oligometastatic disease, oligorecurrence, oligopersistence, oligoprogression) [8], 88 respondents (72.1%) replied "yes." However, only 39 respondents (43.3%) answered that they applied the ESTRO/EORTC classification in their clinical practice. The most common reason for not using of this classification was "too complicated for clinical use" in 33 respondents (66.0%), followed by "insufficient supporting evidence" in 15 (30.0%), respectively. Other answer included "disagreement among multidisciplinary caregivers." To the question "Among the ESTRO/EORTC classifications of oligometastasis, in which case do you think there is a role of local therapy?," "oligorecurrence" and "genuine oligometastatic disease" were chosen by 87.8% and 79.3% of the respondents, respectively, while "repeat oligometastatic disease" and "induced oligometastatic disease" were chosen by 43.9% and 48.8%, respectively.

5. Statistical analysis based on respondents' demographics

The differences in responses based on the demographics of the respondents (number of new patients, year of practice, number of oligometastasis cases, and subspecialty) are depicted in S1 Table. Regarding the upper limit of number of involved organs, radiation oncologists who were working in the high-volume centers (new patients ≥ 30 per month), had longer clinical career (≥ 10 years), and those who treat more oligometastasis cases (≥ 10 per month) tended to choose "do not consider" more frequently, with 31.3%, 29.7%, and 28.0%, respectively. As for the size criterion, the respondents working in the high-volume centers and those with shorter career were more likely to select "do not consider" more frequently (55.2% and 53.7%, respectively). The radiation oncologists working at the high-volume centers (74.6%) and those with shorter career (70.1%) were familiar with the ESTRO/EORTC classification, more frequently. Seventy-seven per-

cent of lung cancer specialists and 63.3% of prostate cancer specialists were aware of the classification, respectively. As for the application of classification in clinical practice, the radiation oncologists working in the high-volume centers and those treating more oligometastasis cases (≥ 10 per month) showed more affirmative responses than others, accounting for 35.8% and 32.9%, respectively. However, none of the aforementioned differences were statistically significant.

Discussion

Although it is generally agreeable that oligometastasis carries a better prognosis than polymetastatic disease, the biologic profile that can distinctively define oligometastatic status has not been established concretely [8,15]. Therefore, the definition of oligometastatsis is still based on the clinical perspectives. In the ESTRO-ASTRO consensus report, "up to 5" and "up to 3" oligometastatic lesions were the most commonly-used quantitative definitions, and the maximum number could be limited by the feasibility of curative metastasis-directed treatment [11]. In a similar context, 64% of physicians answered that they used "5 or less" as a quantitative definition for oligometastasis, and 26% answered that they used "3 or less" in the current study. Other response mentioned the feasibility of RT to include all disease burden.

According to the results based on the demographics, the radiation oncologists affiliated in the high-volume centers were more likely to be generous regarding the number of involved organs or tumor size, and they were also more familiar with the EORTC/ESTRO classification. Those with shorter career (practice years < 10) tended to have a stricter definition of oligometastatic disease, and they were more familiar with EORTC/ESTRO classification than more experienced counterparts. It could be because radiation oncologists with shorter career tend to follow guidelines while those with longer career tend to rely on their experience or institutional policies. Additional demographic analysis revealed that the radiation oncologists with 6-10 years of experience treated oligometastatic disease patients most frequently (S2 Table). Currently, the subspecialty of radiation oncologists was determined by the institutional circumstances or in-house rules, which were more likely based on where the cancer originated or spread. In order to stay up-to-date in this rapidly evolving situation, the designation of radiation oncologists who specialize in oligometastatic disease regardless of the origin, much or less similar to the surgical oncologist, who focus on the site to be managed, could be considered.

Local treatment for oligometastasis was expected to improve the oncologic outcomes by interfering the metastatic cascade progression or reducing the disease burden [15,16]. In particular, several recent randomized trials consistently reported that the additional local treatment significantly improved overall survival or progression-free survival (PFS) [12,13,17-19]. In line with these results, 82% of the respondents answered that they supported the role of local treatment in oligometastatic disease. In a systematic review conducted by the investigators [10], local consolidative treatment was associated with improved overall survival (odds ratio [OR], 2.896; 95% confidence interval [CI], 2.337 to 3.528) and PFS (OR, 3.045; 95% CI, 2.356 to 3.937). However, there was a difference in the benefit of local treatment by the primary cancer types. For example, in colorectal cancer, the OR associated with benefit of local treatment was 4.453 (95% CI, 2.103 to 9.429), whereas it was 1.043 (95% CI, 0.336 to 3.240) for small cell lung cancer, which was statistically insignificant [10]. Another systematic review on SBRT for oligometastases by Nevens et al. [20] also concluded that survival was most significantly influenced by the primary cancer type, where survival was the most favorable in prostate cancer and the worst in non-small cell lung cancer. Similarly, we found a minor difference in responses regarding the benefit of local treatment based on their respective specialties: 83% of the prostate cancer experts and 73.5% of the breast cancer specialists supported the benefit, respectively.

The term oligometastasis literally refers to the limited number of metastatic lesions. However, oligometastasis is a concept that might include a range of diseases including the synchronous disease in the early phase of metastatic cascade or that with small residuals after near-eradication by active systemic treatments. Therefore, the ESTRO-EORTC group classified oligometastatic disease into nine categories incorporating various factors including the disease-free interval, time of diagnosis, and previous treatment, respectively [8]. Although this classification was finely tuned to span over various clinical scenarios, 56% of the physicians in the current survey failed to adopt this classification into their clinical practice with the most common reason of "complexity." Some respondents mentioned that it was difficult to use the classification in a multidisciplinary meeting, as there was disagreement among the caregivers, especially among non-radiation oncologists. Aforementioned recent systematic review reported that only 7.4% of the recruited oligometastasis studies (7 of 96) had sufficient information to apply full nine categories of EORTC/ESTRO classification [20]. Overall survival was not significantly different in comparison using three upper-level categorizations, among de novo, repeat, or induced oligometastasis. More intuitive and clinically applicable classification needs to be developed and verified. The studies are underway to decipher the biologic feature

of oligometastasis by examining the profiles such as circulating tumor DNA or tumor cells, and these results are highly expected to add the robustness to the definition of oligometastasis [12,19].

Innate limitation of the current study is that this survey targeted only the radiation oncologists. In fact, with wider adaptation of metastases-directed conformal RT, oligometastasis has been of great interest among the radiation oncologists. However, systemic treatment remains as the mainstay modality for oligometastasis. Considering that less explored chemotherapy-free interval could be the potential key benefit to be achieved by adding local treatments, the viewpoint of medical oncologists is indeed crucial. In addition, this study was conducted without considering cancer primary and pathology. Further survey may be needed to exploit disease-specific queries according to cancer types and collect opinions from the subspecialists on more practical point of view.

While most radiation oncologists supported the role of local therapy in oligometastatic disease, there were several inconsistencies in defining and categorizing oligometastatic disease. Because oligometastasis encompasses a diverse range of diseases, clinically applicable classification and cancer-specific approaches need to be developed and verified. Continued education and training through multidisciplinary conferences on oligometastatic disease would be also required to build consensus among participating caregivers.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Author Contributions

Conceived and designed the analysis: Rim CH, Cho WK, Lee JH, Kim YS, Suh YG, Kim KH, Chang AR, Chie EK, Ahn YC.
Collected the data: Rim CH, Cho WK.
Contributed data or analysis tools: Rim CH, Cho WK, Lee JH, Kim YS, Suh YG, Kim KH, Chang AR, Chie EK, Ahn YC.
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Conflicts of Interest

Yong Chan Ahn, the editor-in-chief of the Cancer Research and Treatment, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

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