Clinicians' Perspective On Oligometastatic Disease: A National Survey.

Mette Felter (✉ mette.van.overeem.felter@regionh.dk)

Copenhagen University Hospital - Herlev and Gentofte <https://orcid.org/0000-0002-1069-5999>

Mirjana Josipovic

Copenhagen University Hospital - Rigshospitalet

Eva Serup_Hansen

Copenhagen University Hospital - Herlev and Gentofte

Poul Geertsen

Copenhagen University Hospital - Herlev and Gentofte

Claus Behrens

Copenhagen University Hospital - Herlev and Gentofte

Azza Ahmed Khalil

Århus Universitetshospital: Aarhus Universitetshospital

Gitte Fredberg Persson

Herlev Hospital Department of Oncology: Herlev Hospital Onkologisk Afdeling

Research Article

Keywords: Oligometastatic disease, oligo-progressive disease, SABR, SBRT, Stereotactic body radiotherapy, Survey

Posted Date: August 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-797444/v1>

License: This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published at Acta Oncologica on August 25th, 2022. See the published version at <https://doi.org/10.1080/0284186X.2022.2114380>.

Abstract

Background:

A clear definition of oligometastatic disease (OMD) does not exist. The number of metastases is the most used parameter to select patients for ablative treatments. We conducted a nationwide survey to assess the clinically working physician's perception and definition of the OMD concept.

Material and methods:

An 18-items questionnaire was prepared using an online survey tool and sent to 461 physicians working at nine different oncology centres. Both clinical- and medical oncologists were invited, specialists as well as trainees.

Results:

A total of 102 physicians from seven different centres completed the survey (response rate 22%). The majority (93%) of responders expected cure or long-term survival could be achieved with an ablative strategy for selected patients with OMD. Up to three metastases (43% of responders) in up to two organs (44% of responders) was the preferred threshold the responders were willing to treat when applying an ablative strategy for patients with OMD. Only 7% were willing to treat up to five metastases. There was no apparent disagreement between responders engaged/not engaged in RT planning. Among cancer types, patients with colorectal-, breast-, lung-, prostate-, and kidney cancer were considered most suitable for an ablative treatment strategy.

Conclusions:

Most responders expected that an ablative treatment strategy could be beneficial in selected patients with OMD. In general, there was agreement on the selection criteria for OMD regarding the number of metastases, number of organs, anatomical sites and cancer types.

Background

Since the introduction of the term 'oligometastatic disease' (OMD) in 1995 by Weichselbaum and Hellman [1], the concept has been controversial. The development of targeted therapies and immune checkpoint inhibitors to control micrometastatic disease in combination with new, more precise local therapies lead us to believe that a more aggressive approach to patients with limited metastatic disease may be meaningful.

The selection of patients with truly OMD is complex, and a clear definition does not exist. The oligometastatic state likely differs between cancer types and is best defined biologically [2]. However, in the absence of a robust biological signature to identify patients with true OMD, other surrogate signatures have been applied. The most used categorizing of OMD relies on the number of radiographically

visualized metastatic sites. Several attempts have been made to find a threshold for the number of metastatic lesions that reflects patient survival and defines an OMD state. Retrospective data analyses [3,4] and surveys [5-10] have been conducted to seek consensus in the number of metastases and involved organs to define OMD from a clinical point of view. In recent randomized phase-2 studies, evaluating an ablative treatment strategy for patients with limited cancer disease, OMD has been defined as the presence of 1- 5 metastatic lesions, and mainly patients with lung-, prostate-, colorectal-, and breast cancer have been included in these protocols [11-15]. The studies have shown promising results, including overall survival (OS) benefits and have renewed hopes that OMD may be controlled with ablative treatment strategies, e.g. stereotactic body radiotherapy (SBRT).

Efforts are continuously being made to standardize patient selection. The European Organization for Research and Treatment of Cancer (EORTC) has recognized the critical role of imaging, and expert recommendations are available to standardize the selection process [16,17]. In 2020, EORTC published a consensus report on the characterization and classification of oligometastatic disease [18]. The aim was to establish a comprehensive system of OMD characterization factors, describing biological and clinical processes underlying the development of OMD independently of the primary tumour. The proposed classification is under prospective evaluation in the OligoCare study (NCT03818503).

A recently established Danish National Research Centre for Radiotherapy (DCCC RT, <https://www.straaleterapi.dk/en>) has initiated multiple research initiatives, including a group investigating ablative strategies for OMD treatment, the IP15 group– Oligometastatic Disease. One of the initiatives has been to explore the current pattern of care regarding OMD.

A national survey aimed to assess the general perception and definition of the OMD concept broadly amongst physician working in the oncology departments. Furthermore, to explore the willingness to refer these patients for an ablative treatment strategy.

Materials And Methods

We designed an 18-item long questionnaire using an online survey tool. The target group was addressed Danish clinical- and medical oncologists, specialists as well as trainees. The survey consisted of multiple and single-choice questions covering different aspects of the clinical practice of handling and defining OMD. In addition, a text box was available for comments to each inquiry. A translated version of the complete questionnaire is given in Online Resource 1.

Data included demographic information, educational background, work aspects of the responders, and detailed questions about their perception and definition of the OMD concept. The responders were asked how many metastases in how many organs they were willing to treat with an ablative strategy, e.g. surgery, SBRT or other. They were also asked about referral patterns. If they referred patients with metastases outside CNS to SBRT and why they did or did not use this technique. In addition, they were asked if they thought all patients should be discussed at a tumour board before offering SBRT to patients with OMD.

The questionnaire was sent out to a relevant test group for comments and then revised accordingly. This was done twice to create the final version of the questionnaire. In the introduction to the questionnaire, we presented the responders to a predefined set of abbreviations.

- OMD = Oligometastatic disease (few metastases with or without the primary tumour).
- OPD = Oligo-progressive disease (progression of a few metastases with otherwise stable disease).
- Local treatment = ablative treatment (includes surgery, other invasive procedure, and SBRT).

The heads of departments of the eleven Danish oncology centres were contacted by email in spring 2020 and asked to give out the email addresses of their employed physicians. The request was resent if they did not respond immediately. Both clinical- and medical oncologists, as well as physicians in specialist training were invited.

The data were analysed using basic descriptive statistics, and results are generally presented as percentages of responders who have completed the survey. Information on the response rates for each question is reported in the Online Resource 2. The statistical program R (version 4.0.3) was used for the descriptive statistic and graphic design.

Results

The survey population

Two of the eleven heads of departments contacted, one with RT facilities and one without, never answered our request for email addresses of their employed physicians. Invitations to participate in the survey was sent to 461 physicians at nine different centres, six with radiotherapy (RT) facilities. A total of 102 physicians from seven different centres completed the survey, yielding a response rate of 22%. We received no responses from two centres, of which one has RT facilities. Characteristics of the survey population are presented in table 1. Most responders (67%) were specialists in clinical oncology, 25% were clinical oncology trainees, and 2% were specialists in medical oncology. The remaining 6% were specialised in palliative medicine or worked in unclassified positions. Five responders (5%) were from oncology departments without RT facilities. Most responders (95%) were from academic centres. More than half of the responders (58%) were engaged in the planning of RT as part of their clinical work, whereas 42% were only evaluating patients for the indication or not engaged in RT related work. The majority (81%) of the responders worked with at least one of the four following main organs-specific cancer groups: urogenital-, lung-, breast-, or gastrointestinal cancer. Two-thirds of the responders (66%) attended tumour board conferences (Table 1).

Definition and view on the oligometastatic state

The majority (93%) of the responders expected that cure or long-lasting disease control could be achieved for selected OMD patients when an ablative strategy (e.g. surgery, other invasive procedure or SBRT) was applied.

Up to three metastases were the preferred threshold the responders (43%) were willing to treat when applying an ablative strategy for patients with OMD, and only 7% were willing to treat up to five metastases (Fig. 1a). Fourteen responders (14%) answered that the number of metastases was not a determining factor. The most stated free text comment was that the decision should depend more on biological factors. The responders (44%) preferred a threshold of up to two involved organs when applying an ablative strategy for patients with OMD (Fig. 1b).

When the same questions were asked regarding patients with OPD, there was a tendency to set a lower threshold for the acceptable number of metastases to give ablative treatments. The responders were almost equally divided between accepting a threshold of one (25%), two (27%) or three (25%) metastases (Fig. 2a). The preferred limit of organs the responders were willing to treat with an ablative strategy in patients with OPD was one (42%) (Fig. 2b). For both OMD and OPD, there was no apparent disagreement between responders engaged or not engaged in the RT planning process (Fig. 1,2).

Among different cancer types, the responders found that patients with colorectal cancer (64%), breast cancer (60%), lung cancer (57%), kidney cancer (45%), and prostate cancer (45%) were most suitable for an OMD strategy with SBRT (Fig. 3).

The most accepted anatomical sites to apply SBRT as part of an ablative OMD strategy were CNS (86%), lung (76%), bone (55%), and liver (54%). For other soft tissue metastases, there were more discrepancies among the responders. For adrenal glands, 43% of the responders would treat, 22% would not, and 30% did not know. For lymph nodes, the corresponding answers were 36%, 40% and 20%, respectively.

Referral pattern

Almost Two-thirds of responders (64%) indicated that they seldom referred patients to SBRT of metastases outside CNS. A comparable result was seen when posing the same question regarding referral to surgery. Here 65% answered that they seldom referred patients to surgery.

Ninety responders (88%) gave their indications for referring to SBRT. The most common reason was to gain local control (82%) and gain symptom relief (32%).

Sixteen responders gave their reasons for seldom or never referring patients for SBRT. The most common reason was that the responders (8%) knew too little about SBRT to choose this strategy. The lack of necessary equipment was never stated as a limitation in SBRT referral.

Most responders (60%) stated it was necessary to discuss all patients with OMD at a tumour board before referring them to SBRT (Fig. 4a), but only 25% described that this was the case in the daily clinical practice (Fig. 4b).

Discussion

The response rate in this survey was 22%, which was found acceptable comparing to other surveys using similar methodology [6, 7].

Clinicians generally agreed that an ablative strategy for selected patients with OMD could result in cure or long-lasting disease control. Up to three metastases in a maximum of two organs were the preferred threshold the responders were willing to treat when applying an ablative strategy for patients with OMD, and only 7% were willing to treat up to five metastases. Due to a small number of responders, analysis of agreement among different organ-specific specialists were not possible. For OPD, the picture was more blurred with a tendency to accept fewer metastases for an ablative treatment strategy when the patients were diagnosed with OPD compared to OMD. However, the responders agreed that ablative treatment could be an option for patients with OPD in selected cases. Our findings align with results from the large international survey from 2017, based on > 1000 responders from several international societies for radiation oncology. They found that most physicians (69%) were willing to target two to three oligometastatic lesions with SBRT in an individual treatment course [6]. However, in three other surveys, the threshold was higher. In the OLIGO-AIRO (The Italian Association of Radiotherapy and Clinical Oncology) survey [7], 78% of responders considered up to five metastases as the most appropriate definition of OMD, and in the “Elekta International Oligometastasis Consortium” survey [5], five out of seven responders recommended SBRT for up to five metastases in patients with OMD. In the AIRO-Lombardy survey (The Lombardy Section of the Italian Society of Oncological Radiotherapy) [8], 62% defined an oligometastatic state if the number of metastases was less or equal to five. In reference to the threshold of organs defining an OMD state, the OLIGO–AIRO survey [7] also found most of their responders (70%) willing to accept more than one involved organ when defining OMD. In contrast, the AIRO-Lombardy survey [8] found that their responders favoured limiting the threshold to one organ, but only with marginal support (54% versus 46%).

Among different cancer types, the responders in this survey opted that patients with colorectal-, breast-, lung-, kidney-, and prostate cancers were most suitable for an OMD strategy with SBRT. These findings are in concordance with the patient recruitment in recently published phase-2 studies [11–15]. The randomised phase 2 trial, SABR–COMET [14], recruited patients with a broad spectrum of different cancer types, and the four most frequent primary tumours were CRC (18%), lung cancer (18%), breast cancer (18%), and prostate cancer (16%), representing most common cancer types. However, rarer cancer types like kidney cancer may also benefit from an OMD strategy with SBRT [19, 20].

The responders agreed that metastases in the CNS, lung, bone, and liver were most suitable for an OMD strategy with SBRT. However, there were more discrepancies among the responders for other soft tissue metastases, as adrenal glands and lymph nodes. These findings differ from the OLIGO-AIRO survey results, where responders answered that lymph nodes (46%) were the site most susceptible for a local treatment. However, the following preferences matched the responses from our survey; bone (45%), lung (40%), brain (36%), and liver (7%) [7].

Most of the responders (60%) found it necessary to discuss patients with OMD at a tumour board, but only 25% described that this was the case in the daily clinical practice. In the OLIGO-AIRO survey, a similar part of the responders (66%) preferred an interdisciplinary discussion when managing patients with OMD [7].

The results across the different surveys depend not only on the responder's perception of the definition and treatment of OMD and the available ablative techniques. To a high degree, it reflects the selected responder group and the design of the survey questions. In the survey from the Elekta International Oligometastasis Consortium [5], responders were seven highly selected SBRT experts. In the OLIGO-AIRO survey [7] and in the large international survey [6], responders were members of large national and international radiation oncology societies. Our responders were less selected and consisted of both medical- and clinical oncologists as well as trainees. This may have impacted the responses. Several responders stated they did not know enough about SBRT to choose this strategy. The postgraduate six-year-long specialist training program in Denmark educates clinical oncologists to master both medical oncology for solid tumours and radiation oncology. However, a fraction of the oncologists is educated as medical oncologists or work merely within the medical oncology field. This was considered when we designed the survey, as aspects concerning the technical use of SBRT were not included.

In Denmark, there is a broad access to radiotherapy and SBRT, although not all centres offer SBRT. This is reflected in the survey as none of the responders chose lack of human resources or lack of the necessary equipment as a reason for not referring to SBRT.

Most of our responders expected that cure or long-term survival could be achieved for selected patients with OMD. However, we still need clearer evidence of the clinical benefit of an ablative treatment strategy, and we lack tools to select these patients.

Conclusion

We found a general agreement on the selection criteria for an ablative treatment of OMD regarding the number of metastases, the number of organs, anatomical sites, and cancer types. The responders were willing to treat fewer metastases with an ablative strategy when the patients were diagnosed with OPD compared to OMD. Most responders expected that an ablative treatment strategy could be beneficial in selected patients with OMD and the responders showed a willingness to refer these patients to an ablative treatment.

Declarations

Funding: The work was supported by the Varian Medical System and The Danish National Research Center for Radiotherapy.

Financial interests: Gitte Fredberg Persson, Claus F. Behrens and Mette van Overeem Felter have received research support from Varian Medical System. Gitte Fredberg Persson, Azza Ahmed Khalil, Claus F.

Behrens and Mette van Overeem Felter have received research support from The Danish National Research Center for Radiotherapy. Claus F. Behrens have received research support from ViewRay outside this work.

Conflicts of interest/Competing interests: The authors have no conflicts of interest to declare that are relevant to the content of this article.

Availability of data and material (data transparency): Not applicable

Code availability (software application or custom code): Not applicable

Authors' contributions: All authors have equally contributed to writing and editing and agreed on submission of the final version. Material preparation, data collection and analysis were performed by Gitte Fredberg Persson, Azza Ahmed Khalil and Mette van Overeem Felter. The first draft of the manuscript was written by Mette van Overeem Felter and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval (include appropriate approvals or waivers): Not applicable

Consent to participate (include appropriate statements): Not applicable

Consent for publication (include appropriate statements): Not applicable

References

1. Hellman S, Weichselbaum RR. Oligometastases. *Journal of clinical oncology*. 1995;13(1):8–10.
2. Weichselbaum RR, Hellman S. Oligometastases revisited. *Nat Rev Clin Oncol*. 2011 Jun;8(6):378–82.
3. Singh D, Yi WS, Brasacchio RA, et al. Is there a favorable subset of patients with prostate cancer who develop oligometastases? *Int J Radiat Oncol Biol Phys*. 2004 Jan 1;58(1):3–10.
4. Steenbruggen TG, Schaapveld M, Horlings HM, et al. Characterization of Oligometastatic Disease in a Real-World Nationwide Cohort of 3447 Patients With de Novo Metastatic Breast Cancer. *JNCI Cancer Spectr*. 2021 Jun;5(3):pkab010.
5. Dagan R, Lo SS, Redmond KJ, et al. A multi-national report on stereotactic body radiotherapy for oligometastases: Patient selection and follow-up. *Acta Oncol*. 2016 May;55(5):633–7.
6. Lewis SL, Porceddu S, Nakamura N, et al. Definitive Stereotactic Body Radiotherapy (SBRT) for Extracranial Oligometastases: An International Survey of > 1000 Radiation Oncologists. *Am J Clin Oncol*. 2017 Aug;40(4):418–22.
7. Mazzola R, Jereczek-Fossa BA, Antognoni P, et al. OLIGO-AIRO: a national survey on the role of radiation oncologist in the management of OLIGO-metastatic patients on the behalf of AIRO. *Med Oncol*. 2021 Mar;24(5):48. 38(.

8. Jereczek-Fossa BA, Bortolato B, Gerardi MA, et al. Radiotherapy for oligometastatic cancer: a survey among radiation oncologists of Lombardy (AIRO-Lombardy), Italy. *Radiol Med*. 2019 Apr;124(4):315–22.
9. Aluwini SS, Mehra N, Lolkema MP, et al. Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting. *Eur Urol Oncol*. 2020 Apr;3(2):231–8.
10. Levy A, Hendriks LEL, Berghmans T, et al. EORTC Lung Cancer Group survey on the definition of NSCLC synchronous oligometastatic disease. *Eur J Cancer*. 2019 Nov;122:109–14.
11. Gomez DR, Tang C, Zhang J, et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. *J Clin Oncol*. 2019 Jun;20(18):1558–65. 37(.
12. Iyengar P, Wardak Z, Gerber DE, et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. *JAMA Oncol*. 2018 Jan;11(1):e173501. 4(.
13. Ost P, Reynders D, Decaestecker K, et al. Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol*. 2018 Feb;10(5):446–53. 36(.
14. Palma DA, Olson R, Harrow S, et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): a randomised, phase 2, open-label trial. *Lancet*. 2019 Apr 10.
15. Ruers T, Van Coevorden F, Punt CJ, et al. Local Treatment of Unresectable Colorectal Liver Metastases: Results of a Randomized Phase II Trial. *J Natl Cancer Inst*. 2017 Sep 1;109(9).
16. deSouza NM, Liu Y, Chiti A, et al. Strategies and technical challenges for imaging oligometastatic disease: Recommendations from the European Organisation for Research and Treatment of Cancer imaging group. *Eur J Cancer*. 2018 Mar;91:153–63.
17. Lecouvet FE, Oprea-Lager DE, Liu Y, et al. Use of modern imaging methods to facilitate trials of metastasis-directed therapy for oligometastatic disease in prostate cancer: a consensus recommendation from the EORTC Imaging Group. *Lancet Oncol*. 2018 Oct;19(10):e534–45.
18. Guckenberger M, Lievens Y, Bouma AB, et al. Characterisation and classification of oligometastatic disease: a European Society for Radiotherapy and Oncology and European Organisation for Research and Treatment of Cancer consensus recommendation. *Lancet Oncol*. 2020 Jan;21(1):e18–28.
19. Kothari G, Foroudi F, Gill S, et al. Outcomes of stereotactic radiotherapy for cranial and extracranial metastatic renal cell carcinoma: a systematic review. *Acta Oncol*. 2015 Feb;54(2):148–57.
20. Hoerner-Rieber J, Duma M, Blanck O, et al. Stereotactic body radiotherapy (SBRT) for pulmonary metastases from renal cell carcinoma-a multicenter analysis of the German working group "Stereotactic Radiotherapy". *J Thorac Dis*. 2017 Nov;9(11):4512–22.

Table

Table 1. Characteristics of the survey population.		
Survey population (<i>n</i> =102)	Possible answers	Respondents <i>n</i> [%]
Centres^a		
Centres with RT facility		
	Centre 1	27(26)
	Centre 2	24(23)
	Centre 3	17(17)
	Centre 4	17(17)
	Centre 5	
	Centre 6	0
	Centre 7	12(12)
Centres without RT facility		
	Centre 8	3(3)
	Centre 9	0
	Centre 10	2(2)
Organ specific specialty^a		
	Gastro-intestinal	15 (15)
	Urogenital	26(25)
	Lung	24(24)
	Breast	17(17)
	CNS	11(11)
	Malignant melanoma	10(10)
	Head and Neck	10(10)
	Other	7(7)
Educational background		

	Medical oncologist	2(2)
	Clinical oncologist	68(67)
	Clinical oncologist trainee (2.- 6. Year)	18(17)
	Clinical oncologist trainee (1. Year)	8(8)
	Unclassified position	2(2)
	Other	4(4)
Tumour board attendance		
	Yes	67(66)
	No	32(31)
	Other	3(3)
Engaged with RT planning		
	I don't work at all with radiotherapy.	10(10)
	I am only evaluating the indication for the use of radiotherapy.	30(29)
	I am working with the radiotherapy planning procedure, but less than one day a week.	16(16)
	I am working with the radiotherapy planning procedure at least one day a week.	33(32)
	I am working with the radiotherapy planning procedure all days of the week.	5(5)
	Other ^b	8(8)
RT; radiotherapy.		
^a Multiple-choice available.		
^b Others were grouped according to the answers. Three were categorised as not engaged in the RT planning process and five were categorised as engaged in the RT planning process.		

Figures

Figure 1

a) The preferred threshold of metastases (mets), the responders were willing to treat when applying an ablative strategy in patients with OMD, b) The preferred threshold of involved organs (org), the responders were willing to treat when applying an ablative strategy in patients with OMD.

Figure 2

a) The preferred threshold of metastases (mets), the responders were willing to treat when applying an ablative strategy in patients with OPD, b) The preferred threshold of involved organs (org), the responders were willing to treat when applying an ablative strategy in patients with OPD.

Figure 3

Cancer types the responders found most eligible for an ablative strategy.

Figure 4

The distribution of responses when the responders were asked a) If they found it necessary to discuss all patients at a tumour board before referring them to stereotactic radiotherapy, b) If all patients were

discussed at a tumour board before referring them to stereotactic radiotherapy?

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [ESM1.docx](#)
- [ESM2.docx](#)