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Oligometastatic Prostate Cancer: Results of a Dutch Multidisciplinary Consensus Meeting

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Abstract

Background: Oligometastatic prostate cancer (OMPC) is a heterogeneous disease state that is imperfectly understood, and its clinical implications are unclear.

Objective: To determine the consensus of a Dutch multidisciplinary expert panel on biological aspects, treatment goals, and management of OMPC in daily clinical practice.

Design, setting, and participants: The study comprised a modified Delphi method including an explorative survey with various statements and questions, followed by a consensus meeting to discuss and determine the agreement with revised statements and related items. The panel consisted of 34 Dutch representatives from urology, medical and radiation oncology, radiology, nuclear medicine, and basic research.

Outcome measurements and statistical analysis: Agreement was determined with statements (five-point scale). Consensus was defined as $\geq$75% panel agreement with a statement.

Results and limitations: Consensus existed for 56% of statements. The panel agreed that OMPC comprises a limited metastatic spread in the hormone-sensitive setting, in both the synchronous and the metachronous presentation. Limited metastatic spread was believed to involve three to five metastases and a maximum of two organs. Prostate-specific membrane antigen positron emission tomography/computed tomography scan was currently perceived as the most accurate diagnostic imaging modality. Although there was a consensus that targeted treatment of all metastases in OMPC will delay further dissemination of the disease, opinions on specific treatment regimens were divided. Panel outcomes were limited by the lack of scientific evidence on OMPC.

Conclusions: A multidisciplinary panel reached a consensus that OMPC is a specific disease state requiring a tailored treatment approach. OMPC registries and clinical studies should focus on both the biology and the clinical parameters in relation to optimal treatment strategies in synchronous and metachronous OMPC.

Patient summary: A group of Dutch medical specialists agreed that prostate cancer patients having few metastases may benefit from a new therapeutic approach. Clinical studies need to determine which treatment is best for each specific situation.

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1. Introduction

The concept of "oligometastatic disease" was first described in 1995 by Hellman and Weichselbaum [1] to identify a subgroup of metastatic patients with a limited number of clinically detectable metastases. It has been proposed as an intermediate stage between localised and widespread disease, which might be amenable to focal metastasis-directed therapies (MDTs), with the aim of preventing further disease spread, delaying systemic therapy, and potentially improving overall survival [1,2]. However, the biology of oligometastatic disease is not yet well understood, and knowledge about the genomic and molecular events involved in disease progression is largely lacking [3,4]. Furthermore, there is no consensus on the definition of oligometastatic prostate cancer (OMPC) [5]. Most commonly, OMPC has been defined by specific cut-offs for the number of metastases and involved sites, but there may also be other relevant variables such as the time and onset of metastasis (synchronous [de novo, within 3 mo of primary diagnosis] versus metachronous [recurrent]), and hormone-sensitive versus castration-resistant disease state [6,7]. In addition, the detection of metastases is highly dependent on the imaging modality used [8]. Finally, the evidence on treatment of OMPC is very limited. Most studies investigating local therapy and MDT for OMPC are retrospective and intervention focused [9,10]. Only few prospective studies evaluated the role of local treatment to the prostate in de novo (low burden) metastatic patients and MDT in patients with oligorecurrent disease [11–15]. To determine the state of the art on OMPC and its clinical implications for the Netherlands, a multidisciplinary consensus meeting was organised.

2. Patients and methods

2.1. Study design

The study comprised a two-phase modified Delphi approach in which an expert panel was firstly asked to complete an explorative survey on various statements and questions related to OMPC. During a subsequent 2-d consensus meeting, survey outcomes were discussed in light of the available scientific evidence, and panellists were asked to indicate their agreement with the (revised) statements. This approach combines elements from the Delphi method, Nominal Group Technique, and consensus development techniques [16].

2.2. Panel composition and selection of participants

Selection criteria were formulated by the initiating scientific committee (N.M., S.A., M.L., and H.P.), and included clinical and scientific expertise in the field of OMPC, representation of principal disciplines involved, geographic spread, and availability to participate in the consensus meeting. The panel ("Dutch Oligometastatic Prostate Cancer Working Group") consisted of 11 urologists, seven medical oncologists, five radiation oncologists, four radiologists, five nuclear medicine physicians, and two basic scientists.

2.3. Explorative survey

The survey was prepared by the scientific committee together with a researcher experienced in consensus methodology (H. S.). Based on key publications on OMPC [4,5,7,8,10,13,17,18], guideline recommendations [19,20], and clinical expertise, 26 statements and questions on key areas of OMPC (biology, definition/diagnosis, treatment, and treatment goals) were formulated. Panel members were encouraged to provide detailed feedback and suggestions for improvement of the items included. Based on this feedback, statements and questions were revised by the scientific committee.

2.4. Consensus meeting

The meeting took place in Utrecht (the Netherlands) on 22–23 March 2019 and was divided into four parts related to the key areas. Each part was introduced by a state-of-the-art lecture presented by an (inter)national expert, to ensure that participants could start from the same level of scientific evidence. Thereafter, the survey results were discussed and revised statements were presented. The discussion was led by the scientific committee members and an advising nonvoting methodologist. Where needed, the statements were further adapted. Subsequently, all items were anonymously (re)rated using an online voting system. For the 18 statements included, a five-point Likert scale (1 = strongly disagree, 5 = strongly agree) was used; for eight additional questions an adapted multiple-choice format was applied. All items included the option "can't judge" in case the expert lacked experience for a specific question or felt unable to vote for any other reason.

2.5. Statistical analysis

Frequency tables were used to describe the outcomes on the various statements and questions. Consensus (good agreement) was defined as the situation in which $\geq$75% of the panellists chose the same option. If 50–74% of panellists chose the same option, this was deemed fair agreement. Those who selected the option "can't judge" were excluded from the agreement calculations.

3. Results

3.1. Biology

Table 1 shows the panel results regarding the biology of OMPC. There were a consensus that MDT delays further disease dissemination (statement 3) and a fair agreement that OMPC is a distinct biological state compared with polymetastatic disease (statement 1), is associated with limited genetic intermetastatic heterogeneity (statement 2), and is not limited to the hormone-sensitive setting (statement 4).

3.2. Definition and diagnosis

There was a consensus that OMPC defines a limited metastatic spread in the hormone-sensitive setting, in both

Table 1 – Panel results on statements regarding the biology of OMPC.

Statement		No. of answers (no. of valid answers)[a]	Agree[b] (%)	Neutral[b] (%)	Disagree[b] (%)
1.	Oligometastatic disease in prostate cancer represents a distinct biological state in comparison with polymetastatic disease	33 (32)	69	3	28
2.	Oligometastatic disease in prostate cancer is associated with limited genetic intermetastatic heterogeneity	34 (20)	65	15	20
3.	Targeted treatment of all metastases in oligometastatic disease will delay further dissemination of disease	32 (31)	**78**	19	3
4.	Oligometastatic disease exists only in the hormone-sensitive setting	34 (31)	23	6	71

OMPC = oligometastatic prostate cancer.
The bold values represent statements for which =75% of the panellists chose the same option.
[a] Valid answers: "can't judge (unqualified to answer)" excluded.
[b] Agree = categories "agree" + "strongly agree"; disagree = categories "disagree" + "strongly disagree". % = percentages of valid answers.

Table 2 – Panel results on statements regarding definitions and diagnostics of OMPC.

Statement		No. of answers (no. of valid answers)[a]	Agree[b] (%)	Neutral[b] (%)	Disagree[b] (%)
1.	OMPC defines a limited metastatic spread at diagnosis, in the hormone-sensitive setting	30 (30)	**100**	0	0
2.	OMPC defines a limited metastatic spread in the hormone-sensitive setting, following PSA relapse after definitive treatment of the prostate/regional nodes	33 (32)	**94**	3	3
3.	There should be different cut-offs in the number of metastases for different anatomical locations	33 (31)	61	0	39
4.	OMPC in the hormone-sensitive setting excludes the presence of visceral metastases	33 (33)	58	3	39

OMPC = oligometastatic prostate cancer; PSA = prostate-specific antigen.
The bold values represent statements for which =75% of the panellists chose the same option.
[a] Valid answers: "can't judge (unqualified to answer)" excluded.
[b] Agree = categories "agree" + "strongly agree"; disagree = categories "disagree" + "strongly disagree". % = percentages of valid answers.

the synchronous and the metachronous disease stage (Table 2, statements 1 and 2). There was fair agreement that different cut-off points are needed for the number of metastatic lesions in relation to location of OMPC (statement 3) and the exclusion of visceral metastases in the definition of OMPC (statement 4). Separate questions on the maximum number of metastases and locations that constitute OMPC revealed fair to good agreement. All panellists found that the maximum number of metastases (diagnosed by prostate-specific membrane antigen positron emission tomography/computed tomography [PSMA-PET/CT], excluding four or fewer pelvic lymph nodes) ranged between 3 and 5, more specifically, 52% voted for three, 14% for four, and 34% for five metastases. The maximum number of involved organs (irrespective of the number of metastases) was considered to be 2 by 89% of the panellists. An additional question on defining lag times for OMPC in the metachronous setting revealed that 82% found that it is not yet possible to define valid time cut-off points. A minority voted for a lag time of ≥3 mo (6%), ≥6 mo (9%), or ≥1 yr (3%). The perceived accuracy of several diagnostic imaging modalities for diagnosing OMPC (Fig. 1) was highest for PSMA-PET/CT scan.

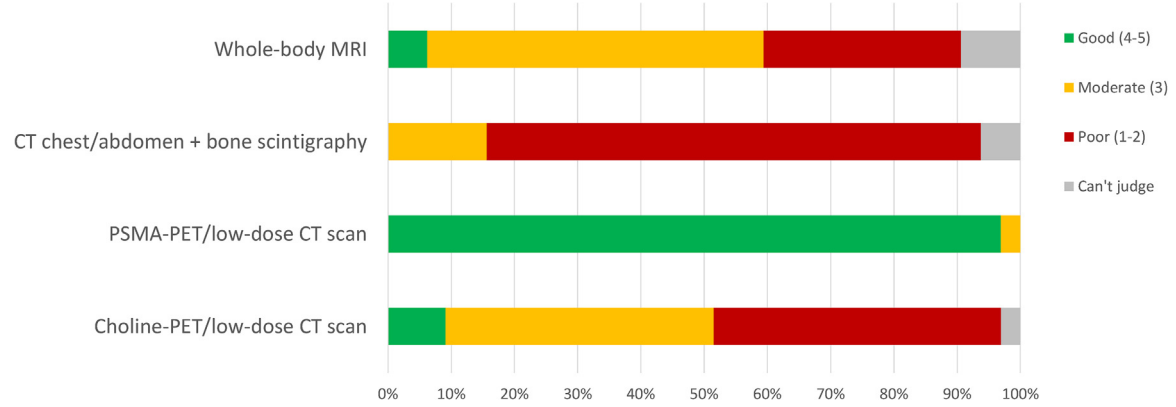

Fig. 1 – Perceived accuracy of different diagnostic modalities to assess (or diagnose) the presence (or occurrence) of OMPC, plotted against percentage of respondents. CT = computed tomography; Good = categories "very" + "extremely"; MRI = magnetic resonance imaging; OMPC = oligometastatic prostate cancer; PET = positron emission tomography; Poor = categories "not at all" + "slightly"; PSMA = prostate-specific membrane antigen.

Table 3 – Panel results on statements regarding treatment of OMPC.

Statement		No. of answers (no. of valid answers)[a]	Agree[b] (%)	Neutral[b] (%)	Disagree[b] (%)
1.	Patients with synchronous (de novo; pelvic lymph nodes ≤4 excluded) oligometastases should always be offered MDT when treatment to the local tumour is given	32 (32)	25	6	69
2.	Patients with metachronous (recurrent) asymptomatic oligometastases should always receive ADT with or without MDT	33 (29)	7	7	**86**
3.	OMPC, in the hormone-sensitive setting following definitive therapy to the prostate, should be treated only by MDT (without ADT) to all oligometastatic sites	30 (26)	42	4	54
4.	In patients with metachronous (recurrent) OMPC with exclusive nodal involvement, treatment choice is dependent on the level and number of lymph node metastases	29 (28)	**100**	0	0
5.	In patients with metachronous (recurrent) OMPC and exclusively nodal involvement after local treatment of the prostate with curative intent, lymph node–targeted treatment should be combined with ADT	31 (28)	7	7	**86**
6.	When oligometastasis-targeted therapy is considered, all visible metastatic lesions should be treated	31 (31)	**81**	0	19
7.	Chemotherapy has no role in the management of patients with oligometastases	30 (27)	**85**	0	15
8.	Oligometastasis-targeted therapy should be considered only for metastatic hormone-sensitive prostate cancer	29 (28)	57	4	39
9.	OMPC following failure to ADT (in castrate-resistant state) should preferably be treated by radical MDT	31 (29)	10	0	**90**

ADT = androgen-deprivation therapy; MDT = metastasis-directed therapy; OMPC = oligometastatic prostate cancer.
The bold values represent statements for which =75% of the panellists chose the same option.
[a] Valid answers: "can't judge (unqualified to answer)" excluded.
[b] Agree = categories "agree" + "strongly agree"; disagree = categories "disagree" + "strongly disagree". % = percentages of valid answers.

3.3. *Treatment*

Panel results on treatment of OMPC (Table 3) revealed a consensus that when considering MDT for OMPC, all visible metastases should be treated (statement 6). When considering MDT for OMPC, the panel disagreed that combination with androgen-deprivation therapy (ADT) is always required (statements 2 and 5). The panel agreed that chemotherapy is not indicated in OMPC (statement 7), and that treatment of nodal OMPC should be based on the level and number of metastases (statement 4). Other aspects showed more diverse answers. Panel results per discipline are available in the Supplementary tables. The importance of diagnostic measures for treatment choice (Fig. 2) was highest for the number and location of metastases. Prostate-specific antigen (PSA) kinetics was found to be especially relevant in the metachronous setting, while molecular or pathological characteristics were considered to be of less value.

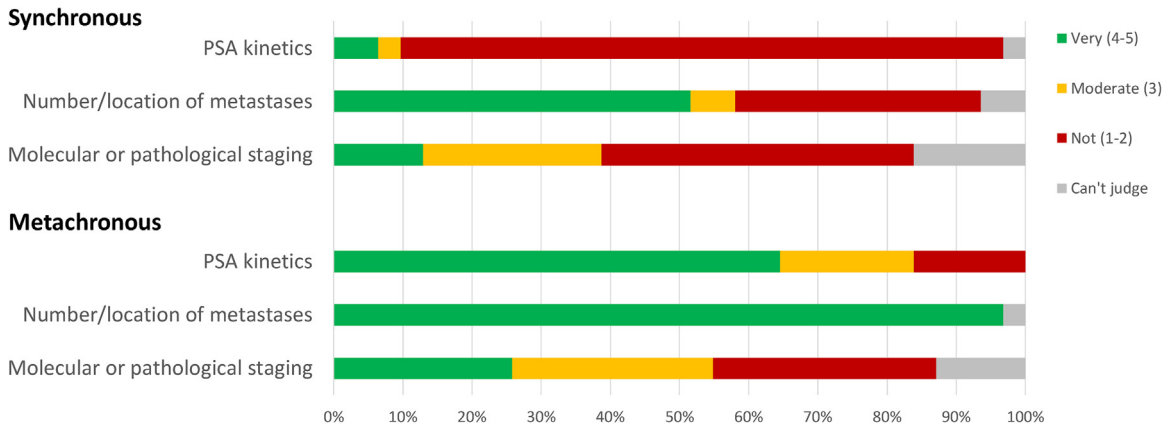

Fig. 2 – Perceived importance of different diagnostic measures for treatment decisions in patients with oligometastatic disease, plotted against percentage of respondents. Not = categories "not at all" + "slightly"; PSA = prostate-specific antigen; Very = categories: "very" + "extremely".

3.4. Treatment goals

Opinions on the primary treatment goal of OMPC showed considerable variation. For the hormone-sensitive synchronous setting, prolonged metastasis-free survival, improved quality of life, and delayed or reduced duration of systemic therapies each accounted for 25% of the voting. For the hormone-sensitive metachronous setting, delayed or reduced duration of systemic therapies (40%) and improved quality of life (32%) were most frequently mentioned as the primary treatment goal. Improved overall survival scored relatively low in both the synchronous (8%) and the metachronous (8%) setting. There was a consensus that toxicity should be weighted heavily against the potential benefit of targeted therapy (100%).

4. Discussion

This work aimed to determine the consensus of a Dutch multidisciplinary expert panel on biological aspects, treatment goals, and management of OMPC in daily clinical practice.

4.1. Biology

About two-thirds of the experts agreed that OMPC represents a distinct biological state compared with polymetastatic disease. Understanding the biology behind oligometastatic disease may help identify patients potentially benefitting from ablative treatment of limited metastases [4].

Several studies have attempted to unravel the genetic and molecular landscape of (oligo)metastatic disease [4]. The lack of research concerning the genetic signature of OMPC is reflected in the large number of experts who opted for “can’t judge” when asked about this aspect. In metastatic prostate cancer, metastasis-to-metastasis spread is found to be common, through either de novo monoclonal seeding of daughter metastases or polyclonal seeding between metastatic sites [17,21]. This cross-metastatic site seeding is often associated with heterogeneous tumour clones with varying degrees of aggressiveness and resistance to therapy [22]. Therefore, limited metastatic disease may be eligible for MDT, with the aim of reducing further seeding of metastases. Indeed, about three-quarters of the experts agreed that targeted treatment of all metastases in oligometastatic disease would delay further dissemination of disease. In addition to cross-metastatic site seeding, metachronous metastatic prostate cancer could arise from any clone in the heterogeneous primary disease, not just the dominant one [18]. In other cancers, including colorectal cancer, heterogeneity of the primary tumour was found to be predictive for the metastatic potential and consequently clinical outcome of the patients [4,23]. Limited molecular data have been obtained from patients with oligometastatic cancer, but available data support differential genomic, transcriptomic, or regulatory networks, with heterogeneous outcomes within aggressive and nonaggressive oligometastatic cancer, or between oligo- and polymetastatic disease [4,24–26].

During the meeting, it was discussed that disease spread occurs on a continuous scale similar to population growth [4]. Therefore, it seems important to also invest in understanding whether biological processes such as growth speed and extent of spread are important determinants of patients’ outcome.

4.2. Definition and diagnosis

Opinions on the maximum number of metastases to define OMPC (diagnosed by PSMA-PET/CT, excluding four or fewer synchronous pelvic lymph nodes) varied between 3 and 5. In the Netherlands, four or fewer synchronous pelvic lymph nodes are still considered curative by combined hormonal therapy and pelvic radiotherapy, including the prostate [20], and are therefore excluded from the definition of OMPC. In addition, PSMA-PET/CT is commonly performed in daily clinical practice in the Netherlands for early screening of metastases and was therefore chosen to define a clinically relevant cut-off. During the Advanced Prostate Cancer Consensus Conference (APCCC) 2017 meeting, 66% of panellists opted for three or fewer metastases to be considered as a cut-off for the definition of oligometastases when using CT and bone scans, while 20% voted for five or fewer metastases [27]. Most studies use(d) three or five metastases as the cut-off. However, the imaging modality used differs between studies. In our panel, a consensus was reached on the number of involved organs, with 89% of the experts defining two organs as the maximum.

PSMA-PET/CT scan was considered the most accurate diagnostic tool to assess the presence or occurrence of oligometastatic disease by the panellists. Indeed, data show that PSMA-PET/CT is sensitive for detecting small metastases [28]. However, PSMA-PET/CT is currently recommended by the European Association of Urology (EAU) guidelines only for patients with biochemical recurrence following radical prostatectomy if the PSA level is $>$0.2 ng/ml and if the results will influence subsequent treatment decisions [19]. Although often routinely used for the detection of metastases, bone and CT scans have poor diagnostic accuracy for low-burden disease [29,30]. The value of whole-body magnetic resonance imaging in the setting of OMPC was scored as limited by the panellists.

4.3. Treatment

For the synchronous oligometastatic setting, only 25% of experts agreed that MDT should always be offered when treatment to the local tumour is given. In the APCCC 2017 consensus meeting, $>$60% of panellists voted for a treatment strategy including local ablative treatment of the primary tumour site and all metastases in patients with newly diagnosed OMPC [27]. The difference in consensus might be explained by the phrasing of our statement, as the majority of panellists hesitated on “always” and therefore disagreed. However, MDT of non-nodal and/or nodal disease

outside the pelvis is not the standard of care and should be considered experimental [19]. A recent meta-analysis of two prospective phase III trials in patients with de novo metastatic disease showed a 7% improvement in 3-yr overall survival when local radiotherapy to the prostate was added to ADT in case of a low disease burden [31]. Currently, no prospective randomised data are available showing a benefit of MDT in addition to local therapy in "de novo" oligometastatic setting. STAMPEDE is planning on a new arm randomising patients with low-volume disease to local therapy versus local therapy combined with MDT, with overall survival as the primary endpoint.

For the metachronous setting, only 7% of experts agreed that asymptomatic patients should always receive ADT with or without MDT, and 42% agreed that patients should be treated with MDT (without ADT) at all metastatic sites. In the APCCC 2017 meeting, 12% of panellists opted for radical local treatment of all lesions without ADT [27]. This difference might be explained by recently published data, not available at the time of the APCCC 2017 meeting, showing a delay of androgen ablation when patients receive MDT [13]. EAU guidelines recommend immediate systemic treatment in asymptomatic and symptomatic metastatic patients [19]. Deferred castration can be discussed with well-informed asymptomatic metastatic patients provided the patient is closely monitored [19]. The evidence for treatment of men with oligorecurrent prostate cancer is scarce. Recently, two small prospective phase II studies evaluated MDT versus observation in asymptomatic patients in the oligorecurrent setting, with ADT-free survival as the primary endpoint [13,14]. Both trials, not powered for overall survival, found a modest delay in progression with limited toxicity [13,14]. A prospective phase I trial showed that stereotactic body radiotherapy was feasible and safe in a group of 33 oligorecurrent prostate cancer patients [15]. However, MDT in this setting should still be considered investigational [19]. In case of exclusively nodal involvement, only 7% of experts agreed that lymph node–targeted treatment should be combined with ADT, and all experts agreed that treatment choice is dependent on the level and number of lymph node metastases.

For both the synchronous and the metachronous setting, the number and location of metastases were considered the most important diagnostic measures to decide on treatment by the experts. Although clear evidence is lacking, the panel agreed that PSA kinetics, number and location of metastases (by imaging), and molecular or pathological characteristics should be taken into account during multidisciplinary meetings on management of a patient with OMPC, both in the hormone-sensitive and the castration-resistant setting.

Only 10% of experts agreed that OMPC should preferably be treated with radical MDT in the castrate-resistant state, suggesting that OMPC in castrate-resistant disease is of less value than in hormone-sensitive disease. However, since no consensus was obtained on the statement that MDT should *only* be considered for metastatic hormone-sensitive prostate cancer (57% agree, 39% disagree), its use in the castration-resistant setting remains an experimental option. Guidelines recommend life-prolonging systemic therapy combined with ADT as the standard of care, and symptomatic bone lesions should be treated by palliative radiotherapy [19]. Radical MDT is experimental and should be offered only in the context of clinical trials.

Finally, in the absence of prospective randomised trials, the panel believed that a large national registry is needed to prospectively collect data of patients treated for OMPC. Prospective initiatives, such as the registry trial Oligo-Care initiated by EORTC-ESTRO, will evaluate changing patterns of care of oligometastatic disease [32].

4.4. Treatment goals

There was no consensus on the primary treatment goal of MDT in clinical practice. This may (partly) be explained by the fact that current and on-going clinical trials on OMPC use different endpoints [3]. The panellists discussed that surrogate endpoints of overall survival are needed and are more relevant in the short term.

4.5. Limitations

The principal limitation of this study is related to the lack of scientific evidence, which necessitated relying on expert opinions for most of the topics discussed. Owing to a small number of panellists, analysis of agreement among different specialties was not feasible. The composition of the panel with the majority being urologists may have influenced the consensus on combining MDT (such as radiotherapy) with ADT. For full results per discipline, see the Supplementary tables.

5. Conclusions

OMPC was considered an important clinical concept, particularly in the hormone-sensitive disease state, but the consensus on its management in daily clinical practice was limited by scarcity of evidence from clinical studies. Further basic research is needed to establish oligometastatic disease as a distinct biological entity. In addition, PSMA-PET/CT was considered the best imaging modality. Management of OMPC should be standardised so that future clinical trials can be designed and compared properly. In the absence of clinical prospective studies, a large national registry is recommended to prospectively collect data of patients treated for OMPC.

Author contributions: Henk van der Poel had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Aluwini, Mehra, Lolkema, Oprea-Lager, Yakar, Stoevelaar, van der Poel.
Acquisition of data: Aluwini, Mehra, Lolkema, Oprea-Lager, Yakar, Stoevelaar, van der Poel.
Analysis and interpretation of data: Aluwini, Mehra, Lolkema, Oprea-Lager, Yakar, Stoevelaar, van der Poel.
Drafting of the manuscript: Aluwini, van der Poel, Stoevelaar.
Critical revision of the manuscript for important intellectual content: Aluwini, Mehra, Lolkema, Oprea-Lager, Yakar, van der Poel.

Statistical analysis: Stoevelaar.
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Other: None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euo.2019.07.010.

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