Imaging Standardization in Metastatic Colorectal Cancer: A Joint EORTC-ESOI-ESGAR Expert Consensus Recommendation

Marcus Unterrainer, Christophe M. Deroose, Ken Herrmann, Markus Moehler, Lennart Blomqvist, Roberto Cannella, Caroline Caramella, Damiano Caruso, Manil D. Chouhan, Timm Denecke, Carolina De la Pinta, Lioe-Fee De Geus-Oei, Audrius Dulskas, Michel Eisenblätter, Kieran G. Foley, Sofia Gourtsoyianni, Frederic E. Lecouvet, Egesta Lopci, Monique Maas, Markus M. Obmann, Daniela E. Oprea-Lager, Joost J.C. Verhoeff, Ines Santiago, Sylvain Terraz, Melvin D'Anastasi, Daniele Regge, Andrea Laghi, Regina G.H. Beets-Tan, Volker Heinemann, Florian Lordick, Elizabeth C. Smyth, Jens Ricke, Wolfgang G. Kunz, on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Imaging Group, the European Organisation for Research and Treatment of Cancer (EORTC) Gastrointestinal Tract Cancer Group, the European Society of Oncologic Imaging (ESOI) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR).

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A Joint EORTC-ESOI-ESGAR Expert Consensus Recommendation

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Abstract

Background: Treatment monitoring in metastatic colorectal cancer (mCRC) relies on imaging to evaluate the tumor burden. Response Evaluation Criteria in Solid Tumors (RECIST) provide a framework on reporting and interpretation of imaging findings yet offer no guidance on a standardized imaging protocol tailored to mCRC patients. Imaging protocol heterogeneity remains a challenge for the reproducibility of conventional imaging endpoints and is an obstacle for research on novel imaging endpoints.

Patients and methods: Acknowledging the recently highlighted potential of radiomics and artificial intelligence (AI) tools as decision support for patient care in mCRC, a multidisciplinary, international, and expert panel of imaging specialists was formed to find consensus on mCRC imaging protocols using the Delphi method.

Results: Under the guidance of the European Organisation for Research and Treatment of Cancer (EORTC) Imaging and Gastrointestinal Tract Cancer Groups, the European Society of Oncologic Imaging (ESOI) and the European Society of Gastrointestinal and Abdominal Radiology (ESGAR), the EORTC-ESOI-ESGAR core imaging protocol was identified.

Conclusion: This consensus protocol attempts to promote standardization and to diminish variations in patient preparation, scan acquisition and scan reconstruction. We anticipate that this standardization will increase reproducibility of radiomics and AI studies and serve as a catalyst for future research on imaging endpoints. For ongoing and future mCRC trials, we encourage principal investigators to support the dissemination of these imaging standards across recruiting centers.

Introduction

The imaging assessment of tumor burden plays a key role in the clinical evaluation and management of almost all solid tumors. A standardized and structured documentation in the change of tumor burden has been pivotal for the implementation of imaging endpoints in the scientific evaluation of cancer therapeutics, namely the Response Evaluation Criteria in Solid Tumors (RECIST) published 2009 in the latest version 1.1 [1]. Tumor regression as captured by an objective response is routinely used to serve as a measure of drug activity in phase II trials, progression-free survival as an, albeit imperfect, surrogate for overall survival.

In metastatic colorectal cancer (mCRC), therapy monitoring is routinely performed with computed tomography (CT) imaging [2]. It is well documented that intralesional metastatic changes visible to the human eye precede size-based changes during response and progression [3]. Beyond the subjective assessment, new imaging features can be quantified using modern image analysis (termed radiomics). The use of radiomics and artificial intelligence (AI) harbors great potential for early response assessment [4], and have been extensively studied in mCRC [5-8].

However, one of the biggest obstacles for applicability in trials and for generalizability towards clinical practice is the intra- and inter-institutional heterogeneity of imaging procedures. This heterogeneity significantly impacts radiomics stability and reproducibility and limits external applications of AI algorithms [4, 9]. These issues arise largely from modifiable parameters such as contrast phases, contrast timing, and image reconstruction. These equally affect the CT component of positron emission tomography (PET)/CT examinations [10].

In a European effort across multiple oncology and imaging societies including several national comprehensive cancer centers, we conducted a Delphi consensus finding survey with the goal to standardize the imaging procedures for patients with metastatic colorectal cancer.

Methods

Panel Composition

For the abovementioned issue, we established a panel of European experts involved in the management of mCRC patients. Panelists were actively recruited under auspices of the EORTC Imaging Group, the EORTC Gastrointestinal Tract Cancer Group, the ESOI and the ESGAR and their chairpersons or presidents, respectively. Panelists were invited based on the clinical expertise, publication records and society guideline involvement with special emphasis on mCRC. Involvement of different European countries was sought. The expert panelists involved in this initiative are presented in Table 1, the country representation is shown in Figure 1.

Delphi Consensus Process

We conducted a prospective, multi-step, modified, non-anonymous Delphi consensus approach to assess imaging properties and specifications regarding mCRC imaging among European mCRC experts [11, 12]. Two local facilitators from LMU Munich (MU & WGK) edited the questionnaires and moderated the consensus finding process. Questionnaires were edited by Google forms (https://www.google.com/forms/about/) and access links were directly forwarded to the expert panelists to initiate every poll. This study received endorsement by the EORTC.

The first step collected general information regarding local specifications and panelists in order to identify common practice and distinct differences among European centers. In the next two steps, further imaging specification regarding CT and PET/CT imaging in mCRC were assessed. The results of each round were forwarded to the panelists to further foster consensus and to influence opinion-forming among the expert panelists (Supp. Files 1 to 3). The composition of the panel was not anonymous; however, individual answers were not

attributable to individual expert panelists. The final aim was to reach consensus regarding a potential mCRC imaging protocol for imaging standardization. In case of questions with binary answers, an agreement of 70% was considered a consensus. In questions with multiple choice character, an agreement of at least 50% was considered consensus. A schematic of the applied Delphi process is displayed in Figure 2.

Trial Registration

This prospective survey was registered on clinicaltrials.gov (registry number NCT04656782) and can be accessed using this link: https://clinicaltrials.gov/ct2/show/NCT04656782.

Results

Panel Characteristics

Twenty-five expert panelists were included to ensure broad representation among European centers. Prerequisites for inclusion were activity in a respective imaging society / oncology-related society and board certification in imaging specialties or oncology-related specialties. Panelists were recruited from 13 European countries with most representatives being from both the Netherlands and Italy (4 expert panelists each). In total, 14/25 were radiologists, 5/25 nuclear medicine physicians, 3/25 both radiologists and nuclear medicine physicians, 2/25 radiation oncologists and 1/25 a colorectal surgeon. Most panelists have a clear clinical focus on reporting standard morphological imaging using CT and MRI (19/25, 76%) and 6/25 (24%) have a primary focus on hybrid imaging, e. g., using PET/CT. The panelist responses from the final consensus survey round are listed in Table 2.

General Information and Institutional Specifications

Among the panelists' institutions, a broad majority participate in imaging for RCTs (22/25, 88%) and most institutions currently include patients in RCTs involving mCRC (16/25, 64%). 18/25 panelists experienced the need of imaging protocol adaptations due to the specific requirements of the respective sponsor, even 4/25 (16%) experience imaging protocol changes in at least 50% of clinical trials. Among the participating panelists' institutions there was a median number of 5 (range, 1-15) CT scanners and a median number of 2 (range, 0-4) PET/CTs. Predominant vendors of CT scanners were (multiple answers possible) Siemens Healthineers (56%), Philips Healthcare (48%) and GE Healthcare (48%); predominant vendors of PET/CT scanners were (multiple answers possible) Philips Healthcare (40%), Siemens Healthineers (36%) and GE Healthcare (28%). Regarding PET/CT and CT imaging protocols, only

44% of centers apply a homogenously aligned protocol. Within their own department, 28% of panelists have experienced diverging imaging protocols across CT scanners, e. g., due to diverging slice thickness or diverging reconstruction algorithms. However, 56% of panelists experienced diverging imaging protocols across CT scanners among different institutions. 92% of institutions are experienced with radiomics analyses; here, 72% of panelists have experienced problems during data processing due to diverging protocols across CT scanners. 100% of expert panelists reported that imaging harmonization could be useful for multicenter imaging studies and Europe-wide standardized protocols could facilitate radiomics and AI research. Hence, 24/25 (96%) expert panelists are willing or probably willing to incorporate a potential standardized imaging protocol.

CT Scan Acquisition

The vast majority of 84% do not give oral contrast for mCRC CT staging purposes, even 88% of expert panelists do not consider oral contrast as essential part of mCRC staging. 92% of included centers give intravenous contrast for CT imaging; here, <5% of scans must be performed without contrast agent due to contraindications (96% of cases), in 1 center, 10-15% of cases were performed without contrast agent. In an open question regarding contrast agent dosage, most frequent contrast dosages applied were 1.5 mg/kg for most, 1.0 mg/kg for some cases (24%), 1.5 mg/kg for all cases (16%) and 1.0 mg/kg for most, 1.5 mg/kg for some cases (12%); all values indicate per patient body weight. In an open question regarding contrast agent concentration, most frequent contrast concentrations applied were 300 mg / mL contrast agent (32%) and 350 mg / mL contrast agent (32%).

mCRC staging does not regularly include neck studies in 96% of centers. If neck studies were included, mostly venous phase (56%) or late arterial phase (36%) were obtained. Thoracic

studies were most commonly performed in the venous phase (56%), the second most common acquisition was in the late arterial phase (36%). Most centers use the venous phase for abdominal CT imaging (88%), whereas late arterial phases were not common (20%) (multiple answers possible in case of multiphase approach). Image acquisition is performed in a monophasic approach in 56% of the included centers.

CT Scan Acquisition Consensus Round:

92% of the expert panelists agreed that oral contrast application is not an essential part of a standard mCRC CT imaging protocol. The application of intravenous contrast agent was deemed mandatory by all experts (100%). A majority (76%) agreed that a dosage of 1.0 - 2.0 mg / kg bodyweight of contrast agent should be applied on CT imaging (followed by < 1.0 mg / kg bodyweight (16%)). A majority (88%) argued in favor of an iodine concentration of 200 - 400 mg / mL contrast agent followed by < 200 mg / mL contrast agent (12%) regarding CT imaging. Thoracic and abdominal series should be acquired in a monophasic approach (72% agreement).

Neck studies are not a mandatory part of mCRC CT imaging (92%), but thoracic studies are a mandatory part of mCRC imaging (96% agreement) and should be performed using a venous phase (64% agreement). Abdominal studies are mandatory (100% agreement) and should be performed using a venous phase (100% agreement).

CT Scan Reconstruction

Regarding CT reconstruction, 76% of included centers do apply dedicated soft tissue reconstructions and 80% use dedicated lung reconstruction algorithms, whereas a dedicated bone reconstruction algorithm is only used in 40% of the centers. The most applied slice thickness is 3 mm for soft tissue reconstructions (36%) followed by 1 mm (20%). Using

dedicated lung reconstructions, 48% used 1 mm slice thickness, followed by 2 mm slice thickness (24%), whereas the most applied slice thickness for bone reconstructions, when applied, was 2 mm (24%) and 1 mm (20%).

CT Scan Reconstruction Consensus Round:

All panelists agreed that a dedicated soft tissue reconstruction should be applied (100%); also, a majority of 84% argued in favor of applying a dedicated lung reconstruction algorithm and 60% in favor of a bone reconstruction algorithm. A majority of 52% voted in favor of 3 mm slice thickness for soft tissue reconstructions, 64% argued for 1 mm slice thickness for lung reconstructions and 56% for 2 mm slice thickness regarding bone reconstructions on CT imaging, if applied. Thoracic studies should include axial soft tissue reconstructions (84% agreement) and axial lung reconstructions (84% agreement), but no axial bone reconstruction (64% agreement). Abdominal imaging should include an axial soft tissue reconstruction (96% agreement). A bone reconstruction was not considered mandatory by the majority of panelists (60% agreement).

18F-FDG PET/CT Scan Acquisition

The vast majority of panelists (96%) does not apply oral contrast for mCRC CT staging purposes and 96% of expert panelists do not consider oral contrast as an essential part of mCRC PET/CT imaging. 52% of included centers do apply intravenous contrast for PET/CT imaging; in only 44% of centers, contrast agent is omitted in <5% of cases. In open question regarding contrast agent dosage, most frequent contrast dosages (including ‘not available’) were 1.5 mg/kg for most, 1.0 mg/kg for some cases (12%), 1.5 mg/kg for all cases (8%), 1.0 mg/kg for all cases (8%) and 1.0 mg/kg for most, 1.5 mg/kg for some cases (8%). In an open question regarding contrast agent concentration (including ‘not available’), most frequent contrast

concentrations applied were 350 mg / mL contrast agent (28%) and 300 mg / mL contrast agent (16%).

Contrast agent for PET/CT imaging is mostly provided by Bayer in 28% of centers, by GE Healthcare in 20% of centers and by Bracco Imaging in 16% of included centers. Regarding different phases, most centers (96%) do not apply multiphase imaging on PET/CT for mCRC imaging. Image acquisition on PET/CT is performed in a monophasic approach in 68% of cases.

PET/CT Scan Acquisition Consensus Round:

100% of the expert panelists agreed that oral contrast application is not essential for standard mCRC CT imaging protocols. No consensus could be reached regarding the application of contrast agents for PET/CT imaging; 52% of the panelists deemed the application of contrast agents not mandatory for PET/CT imaging. A majority of 80% agreed that a dosage of 1.0 - 2.0 mg / kg bodyweight of contrast agent should be applied on PET/CT imaging (followed by < 1.0 mg / kg bodyweight (16%)), in case contrast agent is applied. A majority of 88% argued in favor for an iodine concentration of 200 - 400 mg / mL contrast agent followed by < 200 mg / mL contrast agent (12%) regarding PET/CT imaging. Thoracic and abdominal series should be acquired in a monophasic approach (72% agreement). Neck acquisitions are not a mandatory part of mCRC imaging (92% agreement), but thoracic series are a mandatory part of mCRC imaging (96% agreement) and should be performed using a venous phase (72% agreement), if contrast is applied. Abdominal series are mandatory (100% agreement) and should be performed using a venous phase (96% agreement) if contrast is applied.

PET/CT Scan Reconstruction

Regarding reconstruction of the CT component on PET/CT imaging, 60% of included centers do apply dedicated soft tissue reconstructions and 52% use dedicated lung reconstruction

algorithms, whereas a dedicated bone reconstruction algorithm is only used in 20% of the included centers. The most applied slice thickness is 2 mm and 5 mm for soft tissue reconstructions (20% each) followed by 3 mm (16%). Using dedicated lung reconstructions, 24% used 1 mm and 2 mm slice thickness, respectively, followed by 5 mm slice thickness (16%), whereas the mostly applied slice thickness for bone reconstructions on PET/CT imaging, in case it was applied, was 1 mm and 2 mm (16% each), respectively.

PET/CT scan reconstruction consensus round:

Regarding dedicated CT reconstruction algorithms please see CT section above. A majority of 52% voted in favor of 3 mm slice thickness for soft tissue reconstructions, 56% argued for 1 mm slice thickness for lung reconstructions and 60% for 2 mm slice thickness regarding bone reconstructions on PET/CT imaging. Thoracic PET/CT series should include axial soft tissue reconstructions (80% agreement) and axial lung reconstructions (84% agreement), but no bone reconstructions (68% agreement). Abdominal PET/CT imaging should include an axial soft tissue reconstruction (92% agreement), but no bone reconstruction (68% agreement).

Dual Energy or Spectral CT Imaging

Dual energy or spectral CT imaging is part of the clinical routine for mCRC imaging in only 32% of the included centers. Also, no expert panelists experienced sponsor requirements towards inclusion of dual energy or spectral CT imaging in RCT imaging protocols.

Dual Energy or Spectral CT Imaging Consensus Round: not a mandatory part of a potential core protocol (92% agreement).

Core Imaging Protocol

CT mCRC Core Imaging Protocol:

Patient Preparation and Acquisition: no oral contrast. Intravenous contrast dosage: 1.0 - 2.0 mg / kg bodyweight. Iodine concentration 200 - 400 mg / mL. Monophasic acquisition.

Thorax: Venous phase. Axial soft tissue reconstruction with 3 mm slice thickness. Axial lung reconstruction with 1 mm slice thickness. No bone reconstruction mandatory.

Abdomen: Venous phase. Axial soft tissue reconstruction with 3 mm slice thickness. No bone reconstruction mandatory.

Further phases, reconstructions etc. can be added with emphasis on local specifications and clinical necessities.

<u>PET/CT mCRC core imaging protocol</u>

Acquisition: no oral contrast. If intravenous contrast is applied, contrast dosage: 1.0 - 2.0 mg / kg bodyweight. Iodine concentration 200 - 400 mg / mL. Monophasic acquisition.

Thorax: unenhanced or venous phase if contrast is applied. Axial soft tissue reconstruction with 3 mm slice thickness. Lung reconstruction with 1 mm slice thickness. No bone reconstruction mandatory.

Abdomen: unenhanced or venous phase if contrast is applied. Axial soft tissue reconstruction with 3 mm slice thickness. No bone reconstruction mandatory.

Further phases, reconstructions etc. can be added with emphasis on local specifications and clinical necessities.

Imaging Scorecard

The main components of the consensus core protocol are summarized and illustrated in the Imaging Scorecard as provided in Figure 3. All questions and responses during the survey process are presented in Supplementary Files 1-3.

Discussion

In this European collaboration across multiple societies, we conducted a successful consensus finding survey on mCRC imaging applying the Delphi process. The survey included imaging specialists with a focus on mCRC from cancer centers across Europe as panelists. The first rounds during the survey illustrated the existing heterogeneity of CT imaging protocols. During the Delphi process, the imaging panelists agreed on standardizations for the imaging of patients with mCRC. This standardization covers patient preparation, scan acquisition and scan reconstruction; all of which are known factors that limit data reproducibility. Examples of imaging protocol heterogeneity in an mCRC trial are illustrated in Figure 4.

This consortium supports the use of a standardized core imaging protocol that will build the backbone for the imaging data in mCRC trials. This concept was introduced to facilitate the implementation of new imaging standards as institutional and individual preferences could affect their acceptance. This approach will give institutions the choice to fully switch to this proposed protocol or to keep existing protocols by adding the required image reconstructions. Notably, all imaging panelists indicated that their institutions are either committed or likely willing to implement this core imaging protocol. Notably, spectral imaging was not deemed mandatory among the participating experts.

The heterogeneity of imaging protocols remains a significant challenge for reproducibility of conventional as well as novel imaging endpoints [4]. As examples for the size-based RECIST1.1 criteria, CT acquisition and reconstruction parameters affect reproducibility of lymph node [13] and liver lesion size assessments [14]. Efforts by the International Biomarker Standardization Initiative (IBSI) have standardized the image post-processing and analysis [15], yet not addressed heterogeneity arising from imaging protocols. Regarding novel

imaging endpoints however, differences in CT acquisition and reconstruction parameters have been repeatedly shown to affect radiomics feature reproducibility [9, 16].

With this core imaging protocol, which reached consensus by the participating oncology and imaging societies, we expect to reduce protocol heterogeneity and pave the way for future research on modern imaging endpoints. The use of radiomics data has significant potential in treatment monitoring of mCRC [17]. Basic radiomics features of liver metastases predict a poor outcome at 2 months with the same performance as RECIST1.1 evaluation at 6 months in first-line mCRC treatment [5]. In another application, a radiomics signature outperformed existing biomarkers (KRAS-mutational status, tumor shrinkage) in predicting survival as well as in the detection of treatment-sensitivity to cetuximab [6].

The application of AI has significant potential for even further improvement in early response assessment. Deep learning methods enabled prediction of early on-treatment response using conventional CT imaging in mCRC patients [7]. The quantitative characterization of tumor morphological changes from pretreatment to follow-up CT scans significantly strengthened the association with patient survival and may be used for early on-treatment decision making. Notably, all these radiomics and AI studies excluded trial patients based on imaging protocol deviations (which were avoidable, i.e. not due to medical contraindications).

For patients with mCRC, robust assessment of such novel imaging endpoints will open avenues towards new trial designs. In the field of mCRC, there are no imaging response-adapted trial designs. The pioneering effort of response-adapted treatment guidance has been made in the management of Hodgkin's lymphoma, using positron-emission tomography for decisions on additive radiation [18] or treatment de-escalation [19]. In solid malignancies, response-adapted treatment de-escalation of immunotherapy has been successfully tested in a phase II

trial in metastatic melanoma [20]. Similar trial designs could pave the way for personalized treatment of mCRC patients based on reliable and robust imaging endpoints.

International efforts for standardization of imaging procedures in oncology have significantly increased over the past few years and consensus recommendations were either achieved with or without the use of dedicated methods (e.g. the Delphi process). Imaging recommendations are often part of guidelines that cover acquisition, interpretation, and reporting. Protocol recommendations with high adherence in clinical trials exist for prostate cancer screening [21], metastatic prostate cancer [22], breast cancer [23], endometrial cancer [24], multiple myeloma [25], and lung cancer [26].

Interpretation and reporting of mCRC imaging studies are covered by the RECIST1.1 criteria [1]. Yet there are no consensus recommendations available to standardize imaging protocols for mCRC patients. Dedicated recommendations for imaging protocol standardization have been previously published for primary brain tumors [27] and for brain metastases [28], which have been instrumental for successful AI applications [29]. Our protocol recommendations could thereby serve as a catalyst to accelerate such research efforts in mCRC.

Strengths of our study are the participation of leading oncology and imaging societies and adherence to the Delphi process. We thereby ensure that our recommendations represent the collective position of all key opinion leaders without individual overrepresentation. Our and other protocol recommendations cannot elude lack of inter-vendor standardization, yet this limitation represents a subordinate impact on radiomics feature assessment [15]. The time delays between contrast administration and different phase acquisitions could not be standardized as panelist responses were mostly given in ranges or as rough estimates. We did not include magnetic resonance imaging due to the technical complexity and very strong dependence on vendor-specific sequences. Among the panelists, there may be differences in

technical proficiency regarding CT and/or PET/CT imaging based on training. Overall, a Delphi process was considered a suitable approach for consensus finding in a set of European experts, as this approach enables an inclusion of a wide range of expertise among panelists. These can express their own opinion on questions more individually compared to the dynamic of a group discussion; however, certain limitations have to be listed, e. g. such as a potentially dominant influence of the facilitators or a high consumption of time and resources. Moreover, the process depends on expertise and motivation of the panelists [11, 12, 30, 31].

In conclusion, this group of imaging experts reached consensus through a Delphi survey on a standardized CT imaging protocol with easy-to-implement core components for patients with mCRC. We anticipate that this standardization will increase reproducibility of radiomics and AI studies and serve as a catalyst for future research on imaging endpoints. For ongoing and future mCRC trials, we encourage principal investigators to support the dissemination of these imaging standards across recruiting centers.

Conflict of Interest Statement

K.H. reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, all outside the submitted work. L.B. is a cofounder of Collective Minds Radiology. R.C. reports travel support by Bracco Imaging. T.D. reports honorary fees and travel support by Siemens, Canon, Bayer, b.e. imaging and research grants by Siemens Healthineers, Bayer, Guerbet, and b.e. imaging. E.L. reports receiving research grants from AIRC and from the Italian Ministry of Health, and faculty remuneration from ESMIT (European School of Multimodality Imaging and Therapy) and MI&T congressi. D.E.O.-L. received expert remuneration from EAU for participating in PET PSMA Consensus Meeting in January 2022. The remaining authors declare that they have no conflict of interest related to this study.

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Author Contribution

M.U., C.M.D., J.R. and W.G.K. contributed to the conception, design and planning of the study. M.U., C.M.D., M.M., A.L., R.B.-T., F.L., E.C.S., J.R. and W.G.K. contributed to conduct of the data. C.M.D., K.H., L.B., R.C., D.C., M.D.C., T.D., C.D.L.P., L.-F.D.G.-O., A.D., M.E., K.G.F., S.G.,

F.L., E.L., M.M., M.O., D.E.O.-L., J.J.C.V., I.S., S.T., M.D., D.R., and J.R. participated in the acquisition of the survey data. M.U., C.M.D., M.M., L.-F.D.G.-O., F.L., D.E.O.-L., A.L., R.B.-T., V.H., F.L., E.C.S., J.R. and W.G.K. contributed to the interpretation of the results. M.U. and W.G.K. drafted the manuscript. All authors critically reviewed or revised the manuscript for important intellectual content and approved the final version to be submitted. This final manuscript received endorsement by the EORTC.

Figures

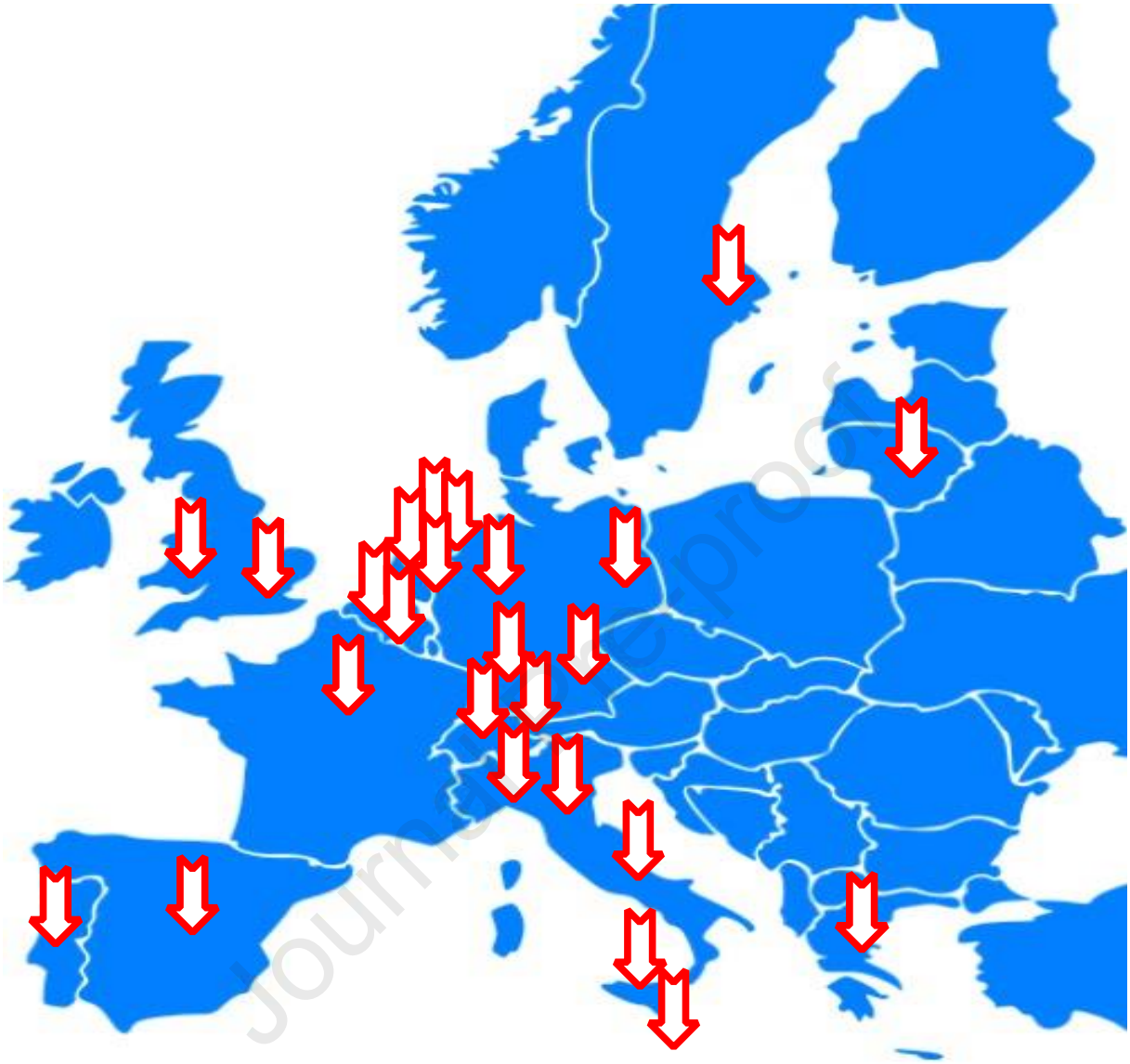

Figure 1. Schematic Country Representation in the Panel

Each arrow indicates the location of the participating panelists' affiliations on this schematic.

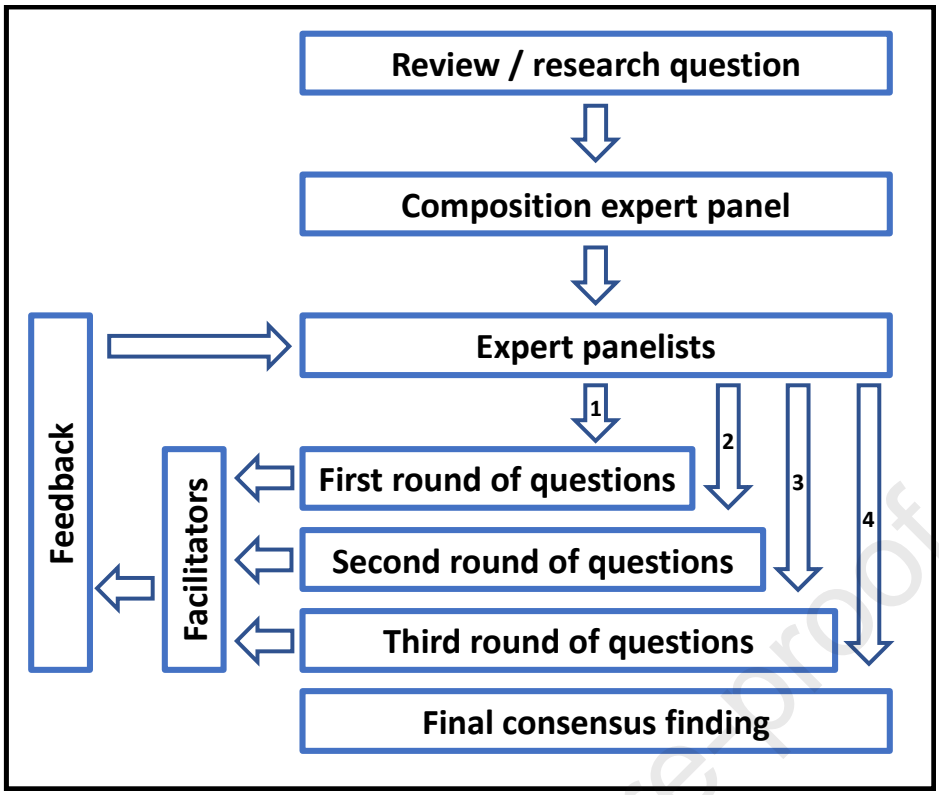

Figure 2. Schematic of the Applied Delphi Approach.

This figure illustrates the different steps and feedback mechanisms of the applied Delphi approach.

Core Protocol Parameters	Requirement	Conformity
Patient Preparation		
Intravenous Contrast in CT Exams	Required	[ ]
Intravenous Contrast in PET-CT Exams	Optional*	[ ]
Intravenous Iodine Concentration	200-400 mg / mL	[ ]
Intravenous Contrast Dosage	1.0-2.0 mg / kg§	[ ]
Oral Contrast in CT / PET-CT Exams	Not Required#	[ ]
Scan Acquisition		
Monophasic Acquisition	Required	[ ]
Contrast Phase Acquisition Chest	Venous	[ ]
Contrast Phase Acquisition Abdomen	Venous	[ ]
Scan Reconstruction		
Soft Tissue Kernel - Orientation	Axial	[ ]
Soft Tissue Kernel - Slice Thickness	3 mm	[ ]
Lung Kernel - Orientation	Axial	[ ]
Lung Kernel - Slice Thickness	1 mm	[ ]
Protocol Extension		
Additional Reconstructions	As Per Institution	N/A
Additional Contrast Phase Acquisition	As Per Institution	N/A
This core imaging protocol is endorsed by:	EORTC, ESOI, ESGAR	

Figure 3. Imaging Scorecard for Implementation of the Consensus Core Protocol

This figure illustrates the core components of this panel's consensus recommendation on imaging in mCRC patients. The imaging scorecard was developed to facilitate implementation of the standardized protocol in cancer and imaging centers that participate in accrual for randomized controlled trials. * If PET/CT is the only exam at a certain timepoint, intravenous contrast as would be needed to ensure compatibility with the RECIST1.1 requirements [1]; this does not apply if the PET/CT is performed in close temporal proximity of a dedicated CT. §

Value refers to per patient body weight. # Oral contrast may be considered if lesion conspicuity in diffuse peritoneal disease is expected to impact response assessment.

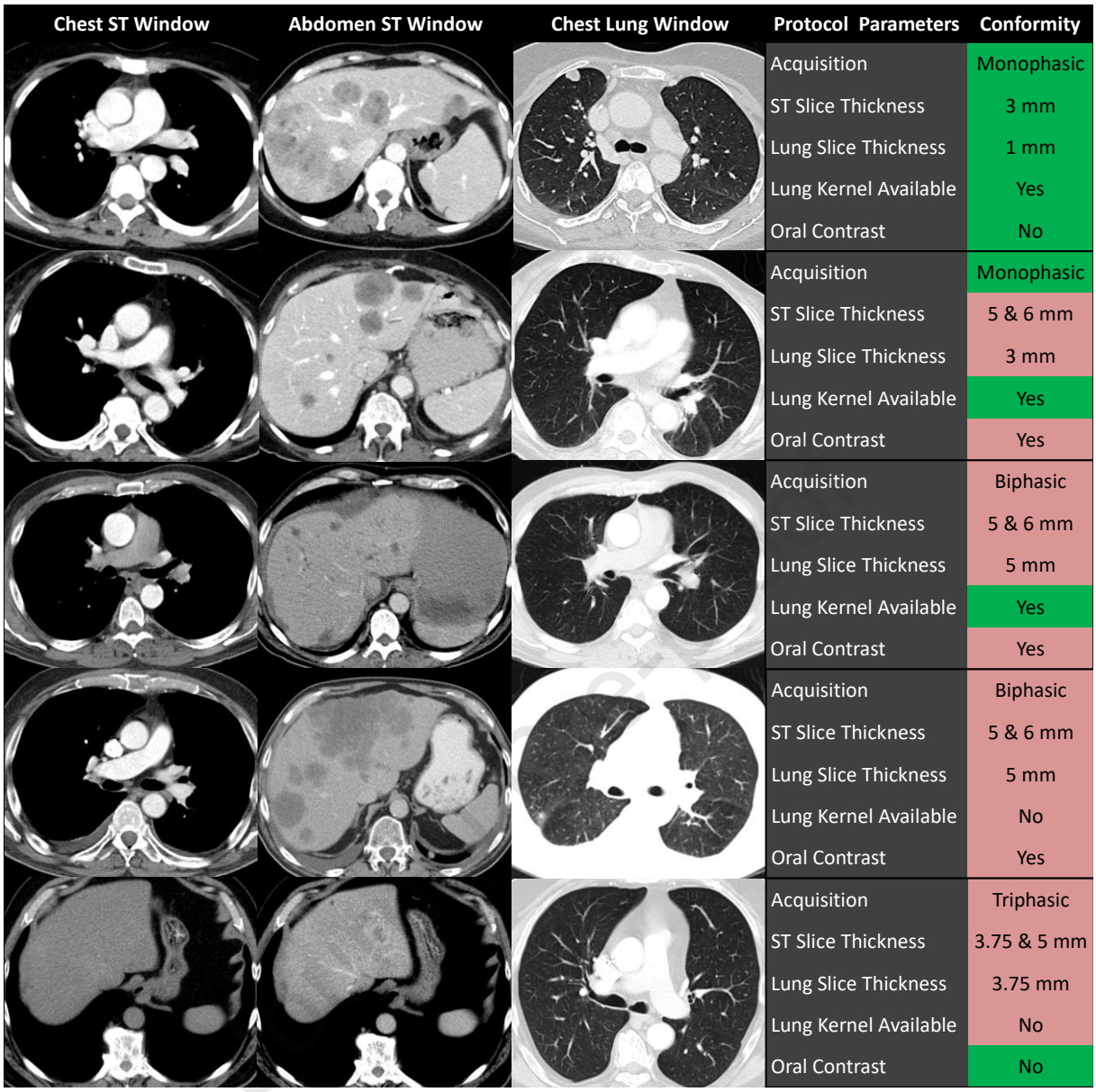

Figure 4. Examples of Imaging Protocol Heterogeneity in a Randomized Controlled Trial

Illustration of imaging protocol heterogeneity in patients with metastatic colorectal cancer included in the FIRE-3 randomized controlled trial [32]. ST refers to soft tissue, i.e. the windowing settings to evaluate mediastinal and visceral organs. The first and second column portray the available ST kernel reconstructions and the third column shows lung kernel reconstructions if available. The last column indicates conformity with the core imaging protocol according to this panel's consensus recommendation (green: compliant; red: non-compliant).

Tables

Table 1. Participating Expert Panelists

Name	Affiliation	City	Country
Lennart Blomqvist	Karolinska Institutet	Solna	Sweden
Roberto Cannella	Università degli Studi di Palermo	Palermo	Italy
Caramella Caroline	Institut de Cancérologie Gustave Roussy	Villejuif	France
Damiano Caruso	Sapienza University of Rome	Rome	Italy
Manil Chouhan	University College London, UCL Centre for Medical Imaging	London	United Kingdom
Melvin D'Anastasi	Mater Dei Hospital, Department of Medical Imaging, Malta	Msida	Malta
Timm Denecke	University of Leipzig	Leipzig	Germany
Christophe Deroose	University Hospitals Leuven	Leuven	Belgium
Audrius Dulskas	National Cancer Institute Vilnius	Vilnius	Lithuania
Lioe-Fee De Geus-Oei	Leiden University Medical Center	Leiden	Netherlands
Carolina de la Pinta	Hospital Universitario Ramón y Cajal	Madrid	Spain
Michel Eisenblätter	University of Freiburg	Freiburg	Germany
Kieran Foley	Cardiff University	Cardiff	United Kingdom
Sofia Gourtsoyianni	National and Kapodistrian University of Athens	Athens	Greece
Ken Herrmann	University of Essen	Essen	Germany
Frederic Lecouvet	Cliniques Universitaires Saint Luc, UCLouvain	Brussels	Belgium
Egesta Lopci	Humanitas Clinical and Research Center, University of Milan	Milan	Italy
Monique Maas	The Netherlands Cancer Institute	Amsterdam	Netherlands
Markus Obmann	University of Basel	Basel	Switzerland
Daniela Oprea-Lager	Amsterdam University Medical Center, Amsterdam (VUmc)	Amsterdam	Netherlands
Daniele Regge	Università degli Studi di Torino	Torino	Italy
Jens Ricke	University Hospital, LMU Munich	Munich	Germany
Ines Santiago	Champalimaud Foundation, Lisbon	Lisbon	Portugal
Sylvain Terraz	Université de Genève	Geneva	Switzerland
Joost Verhoeff	University of Utrecht	Utrecht	Netherlands

The panelists are listed in alphabetical order by last name.

Table 2. Panelist Responses from the Final Consensus Survey Round

Statement	Answer Option of Reference	Agreement	Consensus Reached
CT IMAGING			
In a mCRC consensus protocol, the application of oral contrast in CT scans should NOT be included as mandatory for mCRC staging?	Agree	92%	Yes
In a mCRC consensus protocol, the application of intravenous contrast in CT scans should be included as mandatory for mCRC?	Agree	100%	Yes
Which dosage of intravenous contrast (mg per kg bodyweight) should be implemented in a mCRC protocol for CT scans (in case intravenous contrast is applied)? *	1.0 - 2.0 mg / kg body weight	76%	Yes
Which iodine concentration (mg per mL intravenous contrast agent) should be included in a mCRC imaging protocol for CT imaging? *	200 - 400 mg / mL contrast	88%	Yes
Within a core imaging protocol, a dedicated soft tissue kernel should be used for reconstruction?	Agree	100%	Yes
Within a core imaging protocol, a dedicated lung tissue kernel should be used for reconstruction?	Agree	88%	Yes
Within a core imaging protocol, a dedicated bone tissue kernel should be used for reconstruction?	Yes	60%	No
The following slice thickness should be applied for soft tissue reconstructions on CT imaging in mCRC? *	3 mm	52%	Yes
The following slice thickness should be applied for lung tissue reconstructions on CT imaging in mCRC? *	1 mm	64%	Yes
The following slice thickness should be applied for bone tissue reconstructions on CT imaging in mCRC? *	2 mm	60%	Yes
Dual energy or spectral CT imaging in mCRC is NOT a mandatory part of a core mCRC imaging protocol?	Agree	92%	Yes
Thoracic and abdominal series should be acquired in a monophasic approach?	Agree	72%	Yes
Neck studies in mCRC CT staging should NOT be included in a core protocol as regular imaging studies?	Agree	92%	Yes
Thorax studies in mCRC CT staging should be included in a core protocol as regular imaging studies?	Agree	96%	Yes
Thorax studies in mCRC CT staging should include a venous phase as minimum requirement for a core protocol?	Agree	64%	No
Thorax studies in mCRC CT staging should include an axial soft-tissue reconstruction as minimum requirement for a core protocol?	Agree	84%	Yes
Thorax studies in mCRC CT staging should include an axial lung reconstruction as minimum requirement for a core protocol?	Agree	84%	Yes

Thorax studies in mCRC CT staging should include an axial bone reconstruction as minimum requirement for a core protocol?	Agree	36%	No
Abdominal studies in mCRC CT staging should be included in a core protocol as regular imaging studies?	Agree	100%	Yes
Abdominal studies in mCRC CT staging should include a venous phase as minimum requirement for a core protocol?	Agree	100%	Yes
Abdominal studies in mCRC CT staging should include an axial soft-tissue reconstruction as minimum requirement for a core protocol?	Agree	96%	Yes
Abdominal studies in mCRC CT staging should include an axial bone reconstruction as minimum requirement for a core protocol?	Agree	40%	No
PET/CT IMAGING			
In a mCRC consensus protocol, the application of oral contrast in PET/CT scans should NOT be included as mandatory?	Agree	100%	Yes
In a mCRC consensus protocol, the application of intravenous contrast in PET/CT scans should be included as mandatory for mCRC	Agree	48%	No
Which dosage of intravenous contrast (mg per kg bodyweight) should be implemented in a mCRC protocol for CT scans (in case intravenous contrast is applied)? *	1.0 - 2.0 mg / kg body weight	80%	Yes
Which iodine concentration (mg per mL intravenous contrast agent) should be included in a mCRC imaging protocol for PET/CT imaging? *	200 - 400 mg / mL contrast	88%	Yes
The following slice thickness should be applied for soft tissue reconstructions on PET/CT imaging in mCRC? *	3 mm	52%	Yes
The following slice thickness should be applied for lung tissue reconstructions on PET/CT imaging in mCRC? *	1 mm	56%	Yes
The following slice thickness should be applied for bone tissue reconstructions on PET/CT imaging in mCRC? *	2 mm	60%	Yes
Neck studies in mCRC PET/CT staging should NOT be included in a core protocol as regular imaging studies?	Agree	56%	No
Thorax studies in mCRC PET/CT staging should be included in a core protocol as regular imaging studies?	Agree	96%	Yes
If contrast is applied, thorax studies in mCRC PET/CT staging should include a venous phase as minimum requirement for a core protocol?	Agree	84%	Yes
Thorax studies in mCRC PET/CT staging should include an axial soft-tissue reconstruction as minimum requirement for a core protocol?	Agree	84%	Yes
Thorax studies in mCRC PET/CT staging should include an axial lung reconstruction as minimum requirement for a core protocol?	Agree	84%	Yes

Thorax studies in mCRC PET/CT staging should include an axial bone reconstruction as minimum requirement for a core protocol?	Agree	32%	No
Abdominal studies in mCRC PET/CT staging should be included in a core protocol as regular imaging studies?	Agree	100%	Yes
Abdominal studies in mCRC PET/CT staging should include a venous phase as minimum requirement for a core protocol?	Agree	96%	Yes
Abdominal studies in mCRC PET/CT staging should include an axial soft-tissue reconstruction as minimum requirement for a core protocol?	Agree	92%	Yes
Abdominal studies in mCRC PET/CT staging should include an axial bone reconstruction as minimum requirement for a core protocol?	Agree	32%	No

* Multiple choice statement. The statements indicate questions that have evolved towards the final consensus survey round based on the panelists' feedback. The questions have hence already been adapted to incorporate the general view of the panel.

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Supplement

Supplemental File 1. Survey Questions and Responses of the First Round

Please find all information in the attached spreadsheet.

Supplemental File 2. Survey Questions and Responses of the Second Round

Please find all information in the attached spreadsheet.

Supplemental File 3. Survey Questions and Responses of the Third Round

Please find all information in the attached spreadsheet.

Highlights

- Across European cancer centers, imaging protocols show considerable heterogeneity.
- This European collaboration conducted a consensus finding survey on mCRC imaging.
- An imaging protocol scorecard is provided to facilitate implementation in trials.

Conflict of Interest Statement

K.H. reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, all outside the submitted work. L.B. is a cofounder of Collective Minds Radiology. R.C. reports travel support by Bracco Imaging. T.D. reports honorary fees and travel support by Siemens, Canon, Bayer, b.e. imaging and research grants by Siemens Healthineers, Bayer, Guerbet, and b.e. imaging. E.L. reports receiving research grants from AIRC and from the Italian Ministry of Health, and faculty remuneration from ESMIT (European School of Multimodality Imaging and Therapy) and MI&T congressi. D.E.O.-L. received expert remuneration from EAU for participating in PET PSMA Consensus Meeting in January 2022. The remaining authors declare that they have no conflict of interest related to this study.

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Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

K.H. reports personal fees from Bayer, personal fees and other from Sofie Biosciences, personal fees from SIRTEX, non-financial support from ABX, personal fees from Adacap, personal fees from Curium, personal fees from Endocyte, grants and personal fees from BTG, personal fees from IPSEN, personal fees from Siemens Healthineers, personal fees from GE Healthcare, personal fees from Amgen, personal fees from Novartis, personal fees from ymabs, all outside the submitted work. L.B. is a cofounder of Collective Minds Radiology. R.C. reports travel support by Bracco Imaging. T.D. reports honorary fees and travel support by Siemens, Canon, Bayer, b.e. imaging and research grants by Siemens Healthineers, Bayer, Guerbet, and b.e. imaging. E.L. reports receiving research grants from AIRC and from the Italian Ministry of Health, and faculty remuneration from ESMIT (European School of Multimodality Imaging and Therapy) and MI&T congressi. D.E.O.-L. received expert remuneration from EAU for participating in PET PSMA Consensus Meeting in January 2022. The remaining authors declare that they have no conflict of interest related to this study.

Author Contribution

M.U., C.M.D., J.R. and W.G.K. contributed to the conception, design and planning of the study. M.U., C.M.D., M.M., A.L., R.B.-T., F.L., E.C.S., J.R. and W.G.K. contributed to conduct of the data. C.M.D., K.H., L.B., R.C., D.C., M.D.C., T.D., C.D.L.P., L.-F.D.G.-O., A.D., M.E., K.G.F., S.G., F.L., E.L., M.M., M.O., D.E.O.-L., J.J.C.V., I.S., S.T., M.D., D.R., and J.R. participated in the acquisition of the survey data. M.U., C.M.D., M.M., L.-F.D.G.-O., F.L., D.E.O.-L., A.L., R.B.-T., V.H., F.L., E.C.S., J.R. and W.G.K. contributed to the interpretation of the results. M.U. and W.G.K. drafted the manuscript. All authors critically reviewed or revised the manuscript for important intellectual content and approved the final version to be submitted. This final manuscript received endorsement by the EORTC.