OVARIAN CANCER AUSTRALIA

DECEMBER 2023

OPTIMAL TUMOUR TISSUE COLLECTION IN NEWLY DIAGNOSED, ADVANCED OVARIAN, FALLOPIAN TUBE AND PRIMARY PERITONEAL CANCER PATIENTS

"HRD testing is a game changer for women with ovarian cancer. It is great to see it becoming standard of care."

Associate Professor Orla McNally,
Consultant Gynaecological Oncologist

www.ovariancancer.net.au

The purpose and scope of the guidelines are to ensure equity of access and consistency in the rapidly changing area of molecular tumour testing in ovarian, fallopian tube, and primary peritoneal cancers.

These guidelines are focused on the upfront setting, with newly diagnosed advanced, high grade serous ovarian cancer patients, aiming to answer questions such as who should have their tumour tested, when should testing occur, and what constitutes adequate tumour tissue collection.

The target audience for these guidelines are all members of the multidisciplinary team involved in the diagnosis and treatment planning of newly diagnosed, advanced ovarian cancer patients.

DISCLAIMER

Please note these guidelines have been developed as a guide only. These guidelines have aimed to reach a consensus about what "optimal" looks like, whilst acknowledging not every health service will be resourced to implement these guidelines immediately.

PURPOSE AND SCOPE

Existing challenges regarding adequate tumour tissue for timely testing of newly diagnosed ovarian cancer patients are going to become more significant with the funding of HRD testing in Australia, and the growing need for a personalised approach to treatment. The current optimal care pathway for ovarian cancer doesn't capture the nuance and detail of the rapidly changing area of molecular tumour testing in ovarian cancer. To ensure equity of access and consistency, an advisory group has been formed to develop some consensus guidelines and recommendations regarding upfront tumour testing in newly diagnosed, advanced ovarian cancer patients.

These guidelines aim to answer questions such as: Who is the group we are considering in these guidelines? When should we be testing this group? What entails adequate tissue? Who is responsible for timely tissue collection?

Within scope of this project is gaining an understanding of what optimal care might look like when considering tumour tissue collection for an individual with suspected ovarian cancer, and some guidelines and recommendations to assist those caring for these individuals.

Not in scope is addressing the numerous challenges that exist at the local health service level around resourcing and addressing the known difficulties. These will vary between jurisdictions and any required changes to practice for the uptake of the recommendations will need to be managed at the local level.

Also, not within scope, but noted as related challenges that require addressing in a different context was guidelines around management of ovarian cancer patients at the time of recurrence, and the value of molecular testing and access to clinical trials at that time.

Target Audience:

The target audience for these guidelines are all members of the multidisciplinary team who may be involved in the diagnosis and treatment planning of newly diagnosed ovarian cancer patients. This includes the gynaecological oncologists, medical oncologists, pathologists, interventional radiologists, gynaecological Clinical Nurse Consultants and others.

Methods:

Key stakeholders have been engaged to assist in determining what optimal care might look like in this discussion. An advisory group comprising of the above target audience members was assembled to consider what the guidelines might include. Review of the international experience, and supporting guidelines was undertaken, and any available supporting evidence included. The draft guidelines were developed, and then circulated to a wider group of health professionals and stakeholders for review. Once consensus was reached, the guidelines were distributed to key stakeholder groups for endorsement and dissemination amongst their membership.

INTRODUCTION

The landscape of ovarian cancer in Australia is evolving, including the growing role of personalised medicine. Over 1800 Australians are expected to receive a diagnosis of ovarian cancer in the next year, and over 1000 are expected to die from the disease, due to the 5-year survival rate of just 49%.[1] Where the approach to treatment would historically be the same for these women, there is now variation and options available, dependent on several factors, some of which include histological subtype and the presence of a BRCA1 or BRCA2 gene fault.

The standard of care in high grade epithelial, non-mucinous ovarian cancer has evolved to now include germline BRCA1 and BRCA2 testing in addition to a broader panel of genes that predispose to ovarian cancer. If a germline BRCA1 or BRCA2 gene fault is not found, somatic BRCA1 and BRCA2 testing should be performed for patients with high grade serous cancer.[2] Maintenance therapies, such as the use of PARP inhibitors, have shown survival benefit in these patients with advanced high grade serous cancers.

With the introduction of funded HRD testing in Australia (a test that requires more tissue than somatic BRCA1 and BRCA2 testing); and the growing need for engagement with translational research programs to match identified mutations with a targeted trial; there is a place for consensus guidelines around what optimal care might look like when considering adequate upfront tissue collection for newly diagnosed, advanced ovarian cancer patients.

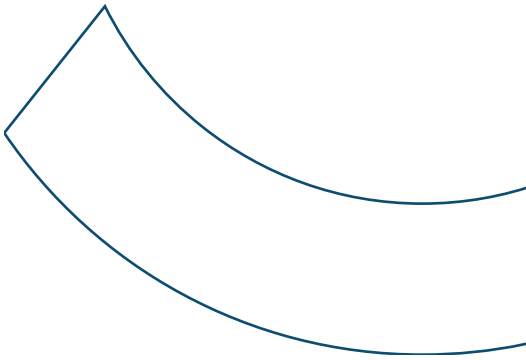
[1] Australia, C. (2019, December 18). Ovarian cancer statistics in Australia. https://www.canceraustralia.gov.au/cancer-types/ovarian-cancer/statistics

[2] Konstantinopoulos, P. A., Norquist, B., Lacchetti, C., Armstrong, D., Grisham, R. N., Goodfellow, P. J., Kohn, E. C., Levine, D. A., Liu, J. F., Lu, K. H., Sparacio, D., & Annunziata, C. M. (2020). Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. Journal of Clinical Oncology, 38(11), 1222–1245. https://doi.org/10.1200/jco.19.02960

Current landscape of molecular testing in ovarian cancer, standard of care testing and access to maintenance therapies in Australia:

Whilst many women are already having tissue collected at diagnosis, at either primary surgery or with biopsy samples taken prior to commencing neoadjuvant chemotherapy, there are cases where cytology alone or limited tissue is obtained for diagnosis prior to commencing neoadjuvant chemotherapy. We are then reliant on tissue taken at interval debulking surgery. There is a high rate of quality control fail with these samples.[3] If tissue is collected early on for diagnostic purposes, the amount of tissue needs to be sufficient for somatic BRCA testing, HRD testing and ideally enough to allow for further molecular testing in the clinical trial/research space.

There is growing use of neoadjuvant chemotherapy in the management of newly diagnosed ovarian cancer.[4,5] There is a risk in these cases that patients relying on tissue samples obtained at the time of interval debulking surgery may not have enough tissue of sufficient quality to facilitate genetic and molecular testing.[6] Somatic BRCA testing and PARP inhibitor access for somatic BRCA mutations were funded by MBS and PBS in 2020.[7] We know that it has taken some time for the uptake of somatic BRCA testing to increase, and we are still missing some eligible patients. Such shifts in practice aren't immediate, and there is a place for guidelines to assist and support with the rollout of any new technologies or treatments to ensure optimal care is afforded to all with ovarian cancer in a timely manner.



[3] Capoluongo, E., Ellison, G., López-Guerrero, J. A., Penault-Llorca, F., Ligtenberg, M. J. L., Banerjee, S., Singer, C., Friedman, E., Markiefka, B., Schirmacher, P., Büttner, R., van Asperen, C. J., Ray-Coquard, I., Endris, V., Kamel-Reid, S., Percival, N., Bryce, J., Röthlisberger, B., Soong, R., & de Castro, D. G. (2017). Guidance Statement On BRCA1/2 Tumor Testing in Ovarian Cancer Patients. Seminars in Oncology, 44(3), 187–197. https://doi.org/10.1053/j.seminoncol.2017.08.004

[4] Farrell, R., Liauw, W., & Brand, A. (2018). Ovarian Cancer Surgery in Australia and New Zealand: A Survey to Determine Changes in Surgical Practice Over 10 Years. 28(5), 945–950. https://doi.org/10.1097/igc.0000000000001247

[5] Ovarian Cancer Registry The OvCR Annual Report. (2020). https://ngor.org.au/wp-content/uploads/2018/05/NGOR_AnnualReport_2021_F_WEB.pdf

[6] Zalaznick, H., Clegg, B., Cogan, E. S., Perry, M. J., Trost, J. G., Mancini-DiNardo, D., Gutin, A., Lanchbury, J. S., & Timms, K. (2022). Rates of homologous recombination deficiency across different subtypes of ovarian cancer and in pre- and post-neoadjuvant chemotherapy tumor samples (139.5). 166, S86–S87. https://doi.org/10.1016/s0090-8258(22)01365-8

[7] Health, A. G. D. of. (n.d.). 1554 - Testing of tumour tissue or blood to detect somatic or germline BRCA1 or BRCA2 gene mutations, in a patient with newly diagnosed, advanced (FIGO stage III-IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy). Www.msac.gov.au; Australian Government Department of Health. Retrieved July 13, 2023, from http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1554-public

EMERGENCE OF HRD TESTING IN AUSTRALIA

Homologous Recombination Deficiency (HRD) testing assists in identifying patients beyond those with a germline or somatic BRCA mutation who might benefit from PARP inhibitor therapy. In doing so, this can also guide treatment planning for those who are determined to be Homologous Recombination Proficient and who may benefit more from non-PARPi treatment options.[8]

Determining the HRD status of patients does pose challenges, including the amount of tissue required being more than that needed for diagnostics and somatic BRCA testing, however obtaining adequate tissue must be a priority moving forward with data supporting the benefits of PARP inhibitor first line maintenance treatment in this population. Cytology specimens such as cell blocks are currently unsuitable for HRD testing. If we are unable to successfully identify the HRD status for a patient, we risk them missing out on therapy that can potentially reduce their risk of recurrence and/or death.

HRD testing has been recommended for funding by Medical Services Advisory Committee (MSAC) and the PARP inhibitors Olaparib and Niraparib recommended for expanded listing by Pharmaceutical Benefits Advisory Committee (PBAC) for newly diagnosed, advanced, high grade epithelial, non-mucinous ovarian, fallopian tube and primary peritoneal patients who have are determined to be HRD-positive. As of 1st January 2024, the first of these PBS listings has occurred. Whilst many newly diagnosed patients have accessed HRD testing through research and compassionate access programs, this is a final step to equitable and affordable access in Australia.

[8] Miller, R. E., Leary, A., Scott, C. L., Serra, V., Lord, C. J., Bowtell, D., Chang, D. K., Garsed, D. W., Jonkers, J., Ledermann, J. A., Nik-Zainal, S., Ray-Coquard, I., Shah, S. P., Matias-Guiu, X., Swisher, E. M., & Yates, L. R. (2020). ESMO recommendations on predictive biomarker testing for homologous recombination deficiency and PARP inhibitor benefit in ovarian cancer. Annals of Oncology, 31(12), 1606–1622. https://doi.org/10.1016/j.annonc.2020.08.2102

RECOMMENDATIONS

Recommendation One:

As with the introduction of somatic BRCA1 and BRCA2 testing, HRD testing does not replace the need for germline testing where indicated.[9,10] It is recommended that each health service have a local process to ensure germline testing isn't missed.

This process (requesting of tests, and the order in which they are requested) can differ depending on the way in which the patient comes into the multi-disciplinary team, and the agreed process at the local level, but it is important that germline testing isn't missed with the new inclusion of HRD testing.[3]

Recommendation Two:

It is recommended that the Multi-Disciplinary Team (MDT) incorporate discussion and planning for upfront tissue collection when the patient with suspected ovarian cancer is first presented to MDT, to ensure tissue collection occurs before the commencement of neoadjuvant chemotherapy, where possible.

The success rate of samples decreases after commencement of neoadjuvant therapy, especially when an individual has a good response to their neoadjuvant chemotherapy.[3] Low tumour DNA percentages lead to a higher inconclusive rate, and therefore pre-chemotherapy biopsies are optimal.[11]

The most preferable method for tissue collection for diagnosis and molecular testing is laparoscopic biopsy, followed next by core biopsies. Whilst some patients will not be appropriate for laparoscopic biopsy, where a patient is clinically able to undergo laparoscopic biopsy, this is most preferable. Data has demonstrated however that core biopsies can also yield enough tissue and is an appropriate option for those not able to have a laparoscopic biopsy.

With many patients in Australia undergoing neoadjuvant chemotherapy prior to interval debulking surgery, there is variation in which specialist the patient will meet first e.g. medical oncologist or gynaecological oncologist. Therefore, it is important each multidisciplinary team and health service have an established pathway and process for tissue collection prior to commencement of chemotherapy, where able.

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[9] Vergote, I., González-Martín, A., Ray-Coquard, I., Harter, P., Colombo, N., Pujol, P., Lorusso, D., Mirza, M. R., Brasiuniene, B., Madry, R., Brenton, J. D., Ausems, M. G. E. M., Büttner, R., Lambrechts, D., & European experts' consensus group. (2022). European experts consensus: BRCA/homologous recombination deficiency testing in first-line ovarian cancer. Annals of Oncology: Official Journal of the European Society for Medical Oncology, 33(3), 276–287. https://doi.org/10.1016/j.annonc.2021.11.013

[10] Konstantinopoulos, P. A., Norquist, B., Lacchetti, C., Armstrong, D., Grisham, R. N., Goodfellow, P. J., Kohn, E. C., Levine, D. A., Liu, J. F., Lu, K. H., Sparacio, D., & Annunziata, C. M. (2020). Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. Journal of Clinical Oncology, 38(11), 1222–1245. https://doi.org/10.1200/jco.19.02960

[11] Zalaznick, H., Clegg, B., Cogan, E. S., Perry, M. J., Trost, J. G., Mancini-DiNardo, D., Gutin, A., Lanchbury, J. S., & Timms, K. (2022). Rates of homologous recombination deficiency across different subtypes of ovarian cancer and in pre- and post-neoadjuvant chemotherapy tumor samples (139.5). 166, S86–S87. https://doi.org/10.1016/s0090-8258(22)01365-8

Recommendation Three:

It is recommended that samples be sent for HRD testing as soon as diagnostic tissue confirms a diagnosis of advanced high grade epithelial, non-mucinous ovarian, fallopian tube and primary peritoneal cancers. This allows adequate time for a result to be returned before the completion of first line chemotherapy, to guide possible PARP inhibitor maintenance therapy.

Whilst HRD testing is still relatively new to many laboratories in Australia, work undertaken internationally has helped identify some guidance for surgeons and interventional radiologists as to what aspects can increase the chance of a viable sample. Existing international laboratory guidance on HRD testing recommends:

- Samples with high neoplastic content and high tumour cellularity, avoiding necrotic tissue, inflammatory cells and fibrosis[13]
- Where feasible, 14G or 16G core biopsies are preferable, with at least 18G used.[12]
- A minimum of 2 cores is required, but ideally 4 samples would be obtained[14] (3 cores as a minimum should be taken if using 18G) These should be in different blocks.

CYTOLOGY AND HRD TESTING

Ascitic fluid isn't currently routinely used for HRD testing in Australian laboratories. If laparoscopic or core biopsies aren't feasible options for a patient, it is worth considering alternatives such as cytology. We suggest reaching out to your laboratory to discuss whether they could use ascitic fluid. Cytology fluid as ascitic cell blocks may be an option if there is adequate neoplastic content.

HRD testing has been occurring in the research setting for some time, and the team at ANZGOG are kindly willing to discuss any cases where it is seeming difficult to obtain a HRD result. Please consider reaching out to them for additional support if you are unable to obtain a sample for your patient.

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[12] Heitz, F., Beyhan Ataseven, Staniczok, C., Carsten Denkert, Rhiem, K., Schmutzler, R. K., Heikaus, S., Malak Moubarak Moubarak, Welz, J., T Dagres, Vasilios Vrentas, Mareike Bommert, Schneider, S., Concin, N., & Harter, P. (2022). 2022-RA-1402-ESGO Implementing HRD testing in routine clinical practice among patients with primary high-grade advanced ovarian cancer. https://doi.org/10.1136/ijgc-2022-esgo.706

[13] Souza da Silva, R., Pinto, R., Cirnes, L., & Schmitt, F. (2022). Tissue management in precision medicine: What the pathologist needs to know in the molecular era. Frontiers in Molecular Biosciences, 9. https://doi.org/10.3389/fmolb.2022.983102

[14] Corr, B., Behbakht, K., & Spillman, M. (2013). Gynecologic Biopsy for Molecular Profiling: A Review for the Interventional Radiologist. Seminars in Interventional Radiology, 30(04), 417–424. https://doi.org/10.1055/s-0033-1359738

CONCLUSION

HRD testing is available to Australian patients with advanced, high grade epithelial, non-mucinous ovarian cancer. We are now able to identify an additional group who can benefit from maintenance PARP inhibitor therapy.

These guidelines are a first step to ensuring access to upfront HRD testing for as many eligible Australians as possible. HRD testing in the advanced ovarian cancer setting informs access to maintenance treatment options, and therefore every effort must be made to obtain a viable sample in a timely manner.

Maintenance treatment options in advanced ovarian cancer have evolved significantly over the past few years, and we know treatment is becoming more personalised. Prioritising the collection of adequate tumour tissue upfront does not only play an important role in HRD testing for ovarian cancer, but also in the translational research and clinical trials space. Patient tissue samples are required for many clinical trials, and highlighting the importance of increasing how much tissue is collected, and the timing of tissue collection, plays a role in ensuring tissue availability doesn't become a barrier to clinical trial participation and research access for patients.

ACKNOWLEDGEMENTS

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We thank the health professionals who kindly gave their time and expertise to assist in the development of these guidelines:

- A/Prof Lyndal Anderson
- Dr George Au-Yeung
- Dr Bryan Barry
- Dr Abdallah Bessayah
- Dr Allison Black
- Dr Michael Burling
- Prof Anna De Fazio AM
- Dr Michelle Harrison
- A/Prof Orla McNally
- Ms Anne Mellon
- Prof Clare Scott AM

We are grateful to the following organisations for their support and endorsement of these guidelines, and for their broader leadership in the gynaecological oncology space. Please see their supporting letters included in the appendix:

- Australia New Zealand Gynaecological Oncology Group (ANZGOG)
- Australian Society Gynaecological Oncologists (ASGO)
- Ovarian Cancer Research Foundation (OCRF)
- Royal Australian and New Zealand College of Radiologists (RANZCR)

APPENDIX 1

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E enquiries@anzgog.org.au
anzgog.org.au

12 December 2023

Bridget Bradhurst
Acting Chief, Support and Advocacy
Ovarian Cancer Australia
Queen Victoria Women's Centre,
Level 1, 210 Lonsdale St,
MELBOURNE 3000

Email: Bridget.bradhurst@ovariancancer.net.au

Support for Ovarian Cancer Australia's Guidelines for Optimal Tumour Tissue Collection in Newly Diagnosed, Advanced Ovarian, Fallopian Tube and Primary Peritoneal Cancer Patients.

ANZGOG is the peak, national gynaecological cancer research organisation for Australia and New Zealand, with 1300 members representing the various gynaecological cancer clinical specialities along with pre-clinical and allied health members. Our mission is to improve outcomes and quality of life for everyone with a lived experience of gynaecological cancer by conducting and promoting clinical trials and multidisciplinary research.

ANZGOG commends Ovarian Cancer Australia on the OCA Optimal Tumour Tissue Collection in Newly Diagnosed, Advanced Ovarian, Fallopian Tube and Primary Peritoneal Cancer Patients guidelines and are pleased to note the contribution by a number of ANZGOG members in their professional and institutional roles.

These guidelines are focused on the upfront setting, with newly diagnosed advanced, high grade serous ovarian cancer patients, aiming to answer questions such as who should have their tumour tested, when should testing occur, and what constitutes adequate tumour tissue collection.

As the target audience for these guidelines are to be all members of the multidisciplinary team involved in the diagnosis and treatment planning of newly diagnosed, advanced ovarian cancer patients, ANZGOG is pleased to be able to help with awareness of this guideline via our regular member ALERTS and website.

ANZGOG supports the development of these guidelines by Ovarian Cancer Australia and welcomes the opportunity to contribute to any future professional guidelines as they are identified.

Yours sincerely

ALISON EVANS
ANZGOG | Chief Executive Officer

WomenCan fundraises for gynaecological cancer research conducted by AUSTRALIA NEW ZEALAND GYNAECOLOGICAL ONCOLOGY GROUP (ANZGOG)

Donations $2 and over are tax deductible in Australia
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APPENDIX 2

Australian Society of Gynaecologic Oncologists Inc.
Caring for women since 1986

Monday, November 20, 2023

Bridget Bradhurst
Ovarian Cancer Australia
Queen Victoria Women's Centre
Level 1, 210 Lonsdale St
Melbourne VIC 3000

Via email: Bridget.bradhurst@ovariancancer.net.au

Dear Bridget,

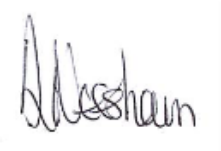
RE: ASGO Endorsement of HRD Guidelines

On behalf of ASGO members I am pleased to advise that we are delighted to endorse the HRD testing guidelines.

We all agree it is very important and certainly needs dissemination. Thank you for all the work done on this.

If you require any logos or further details from us, please do not hesitate to contact the ASGO secretariat via asgo@yrd.com.au or call 07 3368 2422.

Yours Sincerely,



Dr Deborah Neesham
Chair of ASGO

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APPENDIX 3

OVARIAN CANCER RESEARCH FOUNDATION

11 December 2023

Ms Bridget Bradhurst
Acting Chief, Support and Advocacy
Ovarian Cancer Australia
Queen Victoria Women's Centre
Level 1, 210 Lonsdale St
Melbourne VIC 3000

Via email: Bridget.bradhurst@ovariancancer.net.au

Dear Bridget,

RE: OCRF endorsement of Homologous Recombination Deficiency (HRD) Guidelines

On behalf of the Ovarian Cancer Research Foundation (OCRF), I wish to thank you for your valuable work developing the homologous recombination deficiency (HRD) testing guidelines and offer our endorsement and support of these important guidelines.

The OCRF understands the value of consensus guidelines in identifying additional patients that will benefit from maintenance therapies such as PARP inhibitors. We stress the importance of somatic BRCA and HRD testing to complement germline testing. We acknowledge the crucial nature of a discussion with the patient's multi-disciplinary team to collect upfront tissue for HRD testing prior to neoadjuvant chemotherapy, where possible, and of testing occurring immediately following a diagnosis of advanced high-grade epithelial, non-mucinous, ovarian, fallopian tube or peritoneal cancers.

We encourage the OCA to disseminate these guidelines widely and will communicate the same information to the OCRF community as well.

Yours sincerely,

Robin Penty
CEO

APPENDIX 4

The Royal Australian and New Zealand College of Radiologists®

The Faculty of Clinical Radiology

Bridget Bradhurst
Advocacy Manager
Ovarian Cancer Australia

Via email: Bridget.bradhurst@ovariancancer.net.au

16 November 2023

Dear Ms Bradhurst,

Re: OCA Optimal Tumour Tissue Collection in Newly Diagnosed, Advanced Ovarian, Fallopian Tube and Primary Peritoneal Cancer Patients.

The Royal Australian and New Zealand College of Radiologists (RANZCR) is committed to improving health outcomes for all, by educating and supporting clinical radiologists and radiation oncologists. RANZCR is dedicated to setting standards, professional training, assessment and accreditation, and advocating access to quality care in both professions to create healthier communities.

RANZCR creates a positive impact by driving change, focusing on the professional development of its members and advancing best practice health policy and advocacy, to enable better patient outcomes.

Thank you for inviting RANZCR to review these tumour testing guidelines. RANZCR commends Ovarian Cancer Australia on the OCA Optimal Tumour Tissue Collection in Newly Diagnosed, Advanced Ovarian, Fallopian Tube and Primary Peritoneal Cancer Patients guidelines and are pleased to note the role of the Interventional Radiologist has been recognised and included.

RANZCR would like to offer Ovarian Cancer Australia its support for these guidelines and welcomes the opportunity to contribute to any future professional documents.

Yours sincerely,

Rajiv Rattan

Dr Rajiv Rattan
Dean, Faculty of Clinical Radiology
RANZCR