Use of ^{18}F-fluorodeoxyglucose positron emission tomography coupled with computed tomography in early breast cancer management: consensus-based local recommendations by the Hong Kong Breast Cancer Foundation PET/CT Study Group

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ABSTRACT

Introduction: ^{18}F-fluorodeoxyglucose positron emission tomography coupled with computed tomography (PET/CT) has been incorporated into breast cancer management. In Hong Kong, PET/CT use is increasing. This study aimed to establish consensus-based recommendations on the use of PET/CT in the management of early breast cancer.

Methods: A literature search was conducted in September 2023 using the keywords "breast cancer" and "PET/CT" within PubMed to identify research articles related to the use of PET/CT in early breast cancer. Guidelines from major international cancer agencies were also reviewed. Ten recommendation statements were drafted. A two-round modified Delphi consensus process was conducted over a 3-month period (19 December 2023 to 29 February 2024).

Results: A total of 76 experts consented to participate in the first round, of whom 71 completed the second round and were included as members of the expert panel, yielding a second-round response rate of 93.4%. The panel comprised oncologists (n=30, 42.3%), surgeons (n=35, 49.3%), and radiologists (including nuclear medicine radiologists) [n=6, 8.5%]. Experts from the Hospital Authority (n=37, 52.1%) and the private sector (n=32, 45.1%) were well represented. Two experts (2.8%) were from one of the two local university medical faculties. Over 75% of expert panel members had at least 15 years of clinical experience. Of the ten statements, consensus was achieved on seven in the first round and one additional statement in the second round.

Conclusion: Through the consensus process, the proposed recommendations are expected to gain wider acceptance and recognition among local healthcare professionals as guidance for the use of PET/CT in early breast cancer management.

Hong Kong Med J 2025;31:Epub
https://doi.org/10.12809/hkmj2411789

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This article was published on 12 Nov 2025 at www.hkmj.org.

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New knowledge added by this study

- First-of-its-kind local consensus-based recommendations on the use of positron emission tomography coupled with computed tomography (PET/CT) in early breast cancer were established.
- The proposed recommendations were based on the largest and most up-to-date evidence, which reflected updated international guideline recommendations.
- The consensus-establishing process provided a platform for exchange and sharing among multidisciplinary teams in resolving controversial aspects of clinical practice.

Implications for clinical practice or policy

- Local recommendations on the use of PET/CT for early breast cancer patients have been proposed in light of the increasing availability of PET/CT facilities in Hong Kong.
- These consensus recommendations cover important and relevant clinical settings, including screening, preoperative assessment of multifocality, axillary staging, pretreatment staging, evaluation of tumour response and axillary nodal status in the neoadjuvant setting before surgery, re-staging in recurrence, and follow-up for surveillance.
- Through the consensus process, the proposed recommendations are expected to gain wider acceptance and recognition among local healthcare professionals as guidance on the use of PET/CT in early breast cancer management.

^{18}F-氟脫氧葡萄糖正電子電腦掃描在早期乳癌治療中的應用：香港乳癌基金會正電子電腦掃描研究小組基於共識的本地建議

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引言：^{18}F-氟脫氧葡萄糖正電子電腦掃描（PET/CT）已被引入乳癌治療。在香港，正電子電腦掃描的使用日益增加。本研究旨在建立就早期乳癌治療中使用正電子電腦掃描的共識建議。

方法：我們在2023年9月在PubMed使用關鍵字「乳癌」（breast cancer）和「正電子電腦掃描」（PET/CT）進行文獻檢索，以識別與PET/CT在早期乳癌中的應用相關的研究文章，並參照主要國際癌症機構的指南起草了十項建議聲明。其後於2023年12月19日至2024年2月29日期間進行了為期三個月的兩輪修訂版德爾菲共識程序。

結果：共有76位專家同意參與第一輪共識程序，其中71位完成第二輪並被納入為專家小組。第二輪的回覆率為93.4%。小組成員包括腫瘤科醫生（n=30，42.3%）、外科醫生（n=35，49.3%）和放射科醫生（包括核子醫學放射科醫生）[n=6，8.5%]。來自醫院管理局（n=37，52.1%）和私營機構（n=32，45.1%）的專家皆有良好代表性。另有兩位專家（2.8%）來自本地兩所大學醫學院。超過75%專家小組成員擁有至少15年臨床經驗。十項聲明中，七項在第一輪達成共識，另有一項在第二輪達成共識。

結論：透過共識程序，建議中的推薦指引有望在本地醫療專業人員之間獲得更廣泛的認同和接納，作為在早期乳癌治療中使用PET/CT的參考指引。

Introduction

Diagnostic imaging plays an important role in the screening, diagnosis, staging, and follow-up of patients affected by breast cancer. Mammography and breast ultrasound are the current standards of care for screening, diagnosis, and surveillance. For patients with locally advanced disease, guidelines recommend contrast-enhanced computed tomography (CT) scans and bone scans to detect distant metastases. In recent years, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography coupled with CT (PET/CT) has been introduced as an important imaging modality in oncological care. It is a powerful tool that combines the spatial resolution of a CT scan with information regarding biological processes within the scanned region. Positron emission tomography coupled with CT has the potential to identify malignant disease that may otherwise be missed or classified as benign based on size or morphological features in conventional imaging modalities.

In 2021, the Hong Kong Breast Cancer Foundation (HKBCF) analysed the utilisation of PET/CT among patients enrolled in the Hong Kong Breast Cancer Registry since 2007. Among the 4154 patients studied, the utilisation rate of PET/CT was 40.4% (online supplementary Fig 1). There was an increasing trend in PET/CT scan use for breast cancer staging over the past two decades. The overall utilisation of PET/CT increased from 23.3% in 2006-2010, to 48.5% in 2011-2015, and to 61.6% in the 2016-2021 cohort across all cancer stages (online supplementary Fig 2). This trend largely reflected the increasing availability of PET/CT facilities in Hong Kong. Over the past two decades, multiple PET/CT scanning facilities have been established in both the public and private sectors, making the service more accessible. Overall, usage of PET/CT was correlated with higher pathological stages of disease. Notably, PET/CT was used in up to 13.8% of stage 0 cases and 21.0% of stage I cases (online supplementary Fig 3).

Given the relatively high costs, concerns regarding radiation exposure, and the possibility of false-negative results, it is important to provide local recommendations on which groups of patients would benefit from the use of PET/CT in breast cancer. Through this study, we aimed to develop a local guideline regarding the use of PET/CT for early breast cancer to assist healthcare professionals in making evidence-based recommendations.

Methods

The objective of this study was to develop local recommendations on how to utilise PET/CT in the screening, diagnosis, staging, treatment response assessment, and surveillance of early breast cancer. A study group consisting of five members from the HKBCF (first, second, third, fifth and sixth authors) was convened. Study Group members were involved in performing the literature search, constructing the Delphi survey, analysing data, interpreting findings, and providing final approval of the recommendations.

To construct the survey, a literature search was performed in September 2023 by the Study Group using the keywords "breast cancer" and "PET/CT" in PubMed to identify research articles related to the use of PET/CT in early breast cancer. Systematic reviews and randomised controlled trials were prioritised to form the evidence base for the proposed statements. Guidelines from major international cancer agencies, including the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology, were reviewed. Ten statements were drafted based on the literature and international guidelines.

Delphi consensus process

A two-round modified Delphi consensus process was conducted over a period of 3 months (19 December 2023 to 29 February 2024). Surveys were developed using Google Forms, a web-based development tool. Responses provided by individual participants were anonymised to protect confidentiality. This study

did not involve any patients as participants. Only individuals who took part in the first round were invited to participate in the second round.

Experienced physicians with an interest in breast cancer, working in the medical faculties of The University of Hong Kong and The Chinese University of Hong Kong, the Hospital Authority, and the private sector, were identified by the Study Group and invited to participate in the Delphi process. Additionally, members of the Hong Kong Breast Cancer Registry Steering Committee, the Hong Kong Breast Oncology Group, and the Hong Kong Society of Breast Surgeons were invited. Emails were sent to all potential participants by the Study Group to confirm their interest in participating.

After providing informed consent, participants were directed to an online survey for completion. In the first round, participants were provided with a summary of evidence corresponding to each of the ten statements in the survey (online Appendix 1). Participants were asked to indicate the extent of their agreement or disagreement on a five-point Likert scale ('Completely agree', 'Agree', 'Neutral', 'Disagree', and 'Completely disagree') for each statement. Respondents who selected 'Disagree' or 'Completely disagree' were asked to provide reasons for their choice in a free-text field within the survey. In accordance with published recommendations, statements that achieved agreement ('Completely agree' or 'Agree') from more than 75% of participants were considered to have reached consensus.

Following participant voting, the Study Group compiled and prepared the results from the first round. Statements that did not reach consensus were reviewed and amended based on participant feedback. For the second round, statements that did not reach consensus, or were newly created or modified based on participant feedback, were sent as a survey to the same participants. Participants were shown the results of the first round and informed where amendments had been made to statements in the second round.

Consensus statement disclaimer

The recommendations provided in this publication reflect the majority opinion of the expert panel. Although the recommendations are intended to guide clinical decision-making, they should not be regarded as the sole indications for utilising PET/CT in early breast cancer management. These consensus-based recommendations are designed to provide guidance for oncologists, surgeons, general practitioners, radiologists, and other physicians involved in the care of patients with early breast cancer. Treatment decisions for individual patients should ultimately be made at the discretion of the treating clinician, in conjunction with the patient's unique needs and through shared decision-making.

Results

Two Delphi consensus rounds were completed. Among the 270 invited experts, 76 consented to participate in the first round, of whom 71 completed the second round and were included as members of the expert panel (online Appendix 2). The response rate for the second round was 93.4%. The panel comprised oncologists (n=30, 42.3%), surgeons (n=35, 49.3%), and radiologists (including nuclear medicine radiologists) [n=6, 8.5%]. Experts from the Hospital Authority (n=37, 52.1%) and the private sector (n=32, 45.1%) were well represented. Two experts (2.8%) were from one of the two medical faculties of the local universities. Over 75% of expert panel members had at least 15 years of clinical experience.

Of the ten statements, consensus was achieved on seven in the first round. Three statements were returned to the expert panel for rating in the second round, of which one achieved consensus (Fig). The results of the final consensus on the recommendation statements after the two-round Delphi consensus process are listed in the Table.

Discussion

In recent years, driven by increasing demand and easier access to PET/CT services, there has been a substantial increase in the use of PET/CT for breast cancer patients. Currently, there are 33 PET/CT machines across public, private, and academic institutions in Hong Kong. While PET/CT has the capability to enhance the detection of occult malignant disease, it also carries the risk of identifying false-positives and incidental findings,

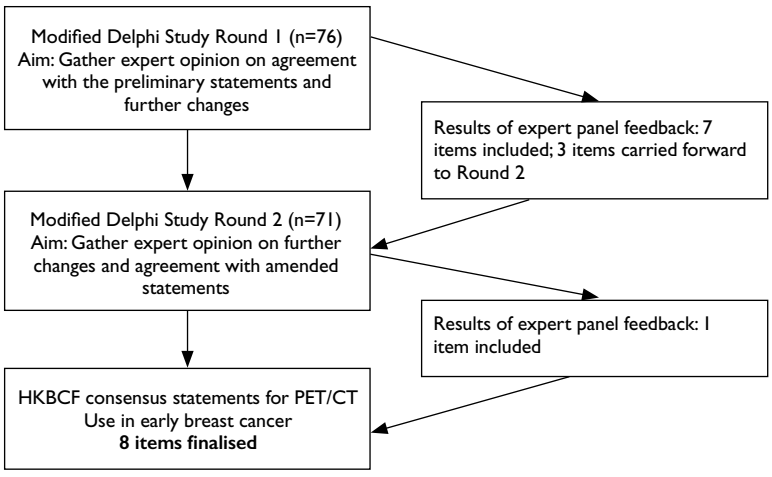

FIG. Modified Delphi process
Abbreviations: HKBCF = Hong Kong Breast Cancer Foundation; PET/CT = positron emission tomography coupled with computed tomography

TABLE. Results of the final consensus on the recommendation statements after a two-round Delphi consensus process

Initial statement	Percentage of participants who voted 'Strongly agree' or 'Agree' in Round 1	Consensus in Round 1	Revised statement	Percentage of participants who voted 'Strongly agree' or 'Agree' in Round 2	Consensus in Round 2
Recommendation 1: ^{18}F-FDG-PET/CT scan is not recommended for breast cancer screening.	96.1%	Achieved	N/A	N/A	N/A
Recommendation 2: ^{18}F-FDG-PET/CT scan is not recommended for staging patients with DCIS and clinical or pathological stage I breast cancer.	85.5%	Achieved	N/A	N/A	N/A
Recommendation 3: ^{18}F-FDG-PET/CT is not recommended to assess breast cancer multifocality.	85.5%	Achieved	N/A	N/A	N/A
Recommendation 4: ^{18}F-FDG-PET/CT is not recommended to guide axillary management in clinical N0 stage patients.	72.4%	Not achieved	**Revised Recommendation 4:** ^{18}F-FDG-PET/CT is not recommended to guide axillary management in patients with no evidence of axillary involvement on clinical examination, ultrasound and/or MRI, and planned upfront surgery.	88.7%	Achieved
Recommendation 5: ^{18}F-FDG-PET/CT is recommended over multimodality investigations (eg, contrast CT, MRI, and bone scan) for preoperative staging in clinical stage IIB or above to detect extra-axillary regional lymph nodes and distant metastases.	97.4%	Achieved	N/A	N/A	N/A
Recommendation 6: ^{18}F-FDG-PET/CT can be considered in selected patients with clinical stage IIA (T1N1 or T2N0) disease with high-risk histological features (eg, ER- or PR-negative, HER2-positive, and high Ki-67 level) to detect extra-axillary regional lymph nodes and distant metastases.	94.7%	Achieved	N/A	N/A	N/A
Recommendation 7: ^{18}F-FDG-PET/CT is not recommended to assess local tumour response to neoadjuvant systemic treatment in the breast to guide surgical planning.	57.9%	Not achieved	**Revised Recommendation 7:** ^{18}F-FDG-PET/CT is not recommended to assess whether the extent of tumour shrinkage in the breast after neoadjuvant systemic treatment is adequate to consider breast-conserving therapy.	71.8%	Not achieved
Recommendation 8: ^{18}F-FDG-PET/CT is not recommended to guide the decision for axillary lymph node dissection in patients with clinically node-positive disease who become clinically node-negative after neoadjuvant systemic therapy.	64.5%	Not achieved	**Revised Recommendation 8:** ^{18}F-FDG-PET/CT is not recommended to guide the decision for axillary lymph node dissection in patients with clinically node-positive disease who become node-negative on clinical examination and ultrasound and/or MRI after neoadjuvant systemic therapy.	64.8%	Not achieved
Recommendation 9: ^{18}F-FDG-PET/CT is recommended to screen for breast cancer recurrence in patients with suspicious symptoms or signs and/or elevated tumour markers.	96.1%	Achieved	N/A	N/A	N/A
Recommendation 10: Routine surveillance for breast cancer recurrence with ^{18}F-FDG-PET/CT is not recommended.	84.2%	Achieved	N/A	N/A	N/A

Abbreviations: ^{18}F-FDG-PET/CT = ^{18}F-fluorodeoxyglucose positron emission tomography coupled with computed tomography; CT = computed tomography; DCIS = ductal carcinoma in situ; ER = oestrogen receptor; HER2 = human epidermal growth factor receptor 2; MRI = magnetic resonance imaging; N/A= not applicable; PR = progesterone receptor

which could lead to unnecessary investigations and potentially delay curative-intent treatments. Although the utility of PET/CT in various breast cancer settings has been widely studied, there remains a lack of large prospective randomised studies comparing it with other imaging modalities. Given that PET/CT is costly and poses concerns about increased radiation exposure compared with other imaging techniques, such as contrast-enhanced CT scans, the development of local guidance and recommendations regarding its indications is clinically relevant and essential. To our knowledge, this consensus-based guideline is the first to provide practical recommendations on the use of PET/CT for breast cancer management.

Of the ten recommendation statements proposed, seven achieved consensus in the first round, suggesting that the indications for PET/CT in these areas are clear-cut and less controversial. These statements covered areas related to the screening, diagnosis, staging, and surveillance of breast cancer. Overall, the majority of local experts agreed that PET/CT should only be utilised in situations where patients have a high risk of distant metastases. This approach includes staging patients with advanced clinical stage disease or aggressive tumour biology and evaluating cancer survivors with suspicious clinical signs and symptoms suggestive of recurrence. Conversely, PET/CT should not be used in situations where the likelihood of detecting malignant disease is low, such as staging of ductal carcinoma in situ or stage I disease, screening asymptomatic women for breast cancer, and routine surveillance of cancer survivors. Increased ^{18}F-FDG avidity of malignant cells forms the basis of ^{18}F-FDG-PET in breast cancer imaging. Tumour characteristics that limit the sensitivity of ^{18}F-FDG-PET in breast cancer imaging include small tumour size, low tumour grade, low proliferation, high expression of hormone receptors (particularly luminal A phenotype), and lobular histological type.[1-3] Positron emission tomography coupled with CT therefore has limited sensitivity in detecting subcentimetre tumours,[4,5] micrometastases, and small lymph node metastases in a clinically negative axilla relative to sentinel lymph node biopsy (SLNB).[6,7] Additionally, the specificity of PET/CT is affected—some benign tumours and infectious or inflammatory conditions can demonstrate ^{18}F-FDG uptake.[8] Positron emission tomography coupled with CT has limited spatial resolution in assessing the multifocality of breast cancer.[9]

In contrast to its low sensitivity for detecting axillary nodal metastases, ^{18}F-FDG PET/CT demonstrates high sensitivity in detecting extra-axillary lymph node involvement, including internal mammary, infraclavicular, and supraclavicular nodes[10,11]; distant metastases; and other unsuspected synchronous malignancies during initial breast cancer staging, which can potentially lead to upstaging and ultimately modification of planned treatment.[12-14] The detection of extra-axillary lymph node involvement aids in selecting candidates for neoadjuvant chemotherapy and may guide subsequent radiotherapy planning to ensure adequate coverage of nodal involvement sites.[11,15,16] In contrast to stage 0 and stage I disease, where the likelihood of distant metastasis is low, there is a growing body of evidence that PET/CT may outperform conventional imaging (contrast-enhanced CT of the thorax, abdomen, and pelvis; and bone scan).[17,18] Furthermore, high-grade and poor-risk cancer subtypes may exhibit increased ^{18}F-FDG uptake, thereby enhancing the diagnostic yield of PET/CT in staging these tumours.[19-21] Our recommendations align with those of the NCCN[22] and the French working group,[23] which recently updated their guidance in this regard.

Controversies

The two recommendation statements that did not reach consensus after the Delphi rounds related to post–neoadjuvant therapy evaluation of tumour response to guide surgery to the primary tumour and axilla. In recent years, neoadjuvant chemotherapy has been increasingly used to downstage disease, facilitate surgery, and provide an opportunity for in vivo tumour response assessment to guide individualised treatment escalation or de-escalation after surgery. This approach has become the standard of care for patients with larger tumours who wish to undergo breast-conserving therapy and for stage II and III patients with aggressive tumour biology (eg, triple-negative and human epidermal growth factor receptor 2–positive breast cancer).[22] Current studies on post-neoadjuvant chemotherapy tumour response assessment have mainly focused on the prediction of pathological complete response.[24-27] Previous studies have shown that magnetic resonance imaging (MRI) may exhibit higher sensitivity, whereas PET/CT demonstrates higher specificity in predicting the pathological response after neoadjuvant chemotherapy, indicating the complementary value of combining these modalities to improve diagnostic performance.[28]

The method of assessing primary tumour response during neoadjuvant therapy has varied across clinical trials. For example, in the NeoSphere trial, which evaluated the addition of neoadjuvant pertuzumab to docetaxel and trastuzumab, clinical response was assessed via physical examination.[29] Other trials have supplemented clinical assessment with diagnostic imaging during treatment. In the PREDIX HER2 trial, which compared neoadjuvant docetaxel, trastuzumab and pertuzumab versus trastuzumab emtansine, investigators routinely utilised mammography, ultrasound, or MRI after

the second, fourth, and sixth cycles for response assessment.[30] Positron emission tomography coupled with CT was performed at baseline, then repeated after the second and final cycles at the investigators' discretion.[30] Currently, international guidelines vary in their recommendations of preferred assessment modality. The 2024 European Society for Medical Oncology guideline[31] recommends the use of MRI to assess local response if pretreatment MRI data are available. The NCCN guidelines[22] suggest that assessment should include physical examination and imaging studies, with the choice of imaging modality determined by a multidisciplinary team. The differing opinions within our expert panel reflect these variations in existing evidence and guidelines. Clinicians should individualise their assessment strategy based on the patient's clinical status and access to imaging modalities.

It has long been the standard of care to offer axillary lymph node dissection to patients with a clinically positive axillary lymph node to ensure adequate tumour clearance. However, given the introduction of neoadjuvant systemic therapies, ongoing studies are evaluating alternative approaches to axillary management to reduce the risk of arm lymphoedema. In patients who have converted from clinically node-positive to clinically node-negative disease after systemic therapy, SLNB and targeted axillary lymph node dissection are currently recommended by international guidelines (instead of routine axillary lymph node dissection).[22] Our Delphi study surveyed the views of local experts on whether PET/CT should be recommended as an additional imaging modality to screen for occult residual axillary disease. While recognising that PET/CT may yield false-positive results, some experts reported using PET/CT to guide whether axillary lymph node dissection could be undertaken directly without a positive SLNB, particularly in patients with initially bulky axillary disease. This approach aligns with the latest NCCN guidelines,[22] which caution against the use of SLNB in pre-chemotherapy clinical N2 stage disease. The statement that PET/CT is not recommended to guide the decision for axillary lymph node dissection in patients with clinically node-positive disease who become node-negative on clinical examination and ultrasound and/or MRI after neoadjuvant systemic therapy remains open. Further studies regarding the accuracy of PET/CT in this context may help resolve the controversy. The management approach for the axilla after neoadjuvant therapy is constantly evolving. For example, axillary radiation is currently being tested as an alternative to axillary lymph node dissection in the ongoing Alliance A011202 randomised trial among patients with a positive SLNB.[32] The timing and role of PET/CT will need to be re-evaluated within this ever-changing paradigm of axillary management in the neoadjuvant setting.

Positron emission tomography coupled with CT is often presumed to involve high radiation exposure. However, when used appropriately for breast cancer staging with low-dose, non-contrast CT, the radiation exposure can be considerably lower than that of whole-body, high-resolution contrast CT combined with a bone scan. Previous international guidelines have suggested that PET/CT can be performed in situations where standard staging studies are equivocal or suspicious.[22,31] Such a sequential approach may not be cost-effective in the clinical scenarios outlined by our expert panel and may expose patients to unnecessary radiation from multiple whole-body imaging examinations. The use of PET/CT as a one-stop assessment enables quicker evaluation of disease status and can facilitate earlier initiation of appropriate treatment.[33]

Strengths and limitations

A strength of our Delphi consensus study is that it involved a large group of experienced specialists representing multiple disciplines and both the public and private sectors. This consensus exercise provided a valuable platform in which clinical experiences, practices, ideas, and opinions were shared and exchanged anonymously. It also helped resolve controversial issues and achieve consensus, particularly in areas where high-level evidence is absent. Recommendations that have achieved consensus should receive wider acceptance and recognition when incorporated into clinical practice.

However, our study had notable limitations. First, expert panellists were invited by the Study Group, and thus the consensus results may not fully reflect the views of all local practitioners involved in treating breast cancer patients. Nevertheless, our sample size of more than 70 participants is considered large for Delphi studies, and we achieved balanced representation of participants from various backgrounds. Second, the initial statements were devised based on recently published articles selected by the Study Group, which could introduce bias compared with a formal systematic review. However, the Study Group prioritised reviewing meta-analyses and randomised controlled trials when drafting the initial statements to ensure they reflected the most up-to-date, high-level evidence.

Conclusion

Based on the results of this Delphi consensus study, the HKBCF PET/CT Study Group provides recommendations on the use of PET/CT for early breast cancer in areas of screening, diagnosis, staging, and surveillance. These recommendations are intended to guide the appropriate use of PET/CT in the local population across both public and private

healthcare settings. Breast cancer management is rapidly advancing, and the management paradigm is continually evolving as new evidence becomes available. As technology progresses, more innovative imaging modalities, such as PET/MRI and PET scans with new radiotracers, are expected to play an increasing role.[14,34,35] The Study Group will review and update these recommendation guidelines at regular intervals based on emerging evidence, particularly in relation to response assessment during and after neoadjuvant systemic therapy.

Author contributions

Concept or design: PSY Cheung, CC Yau, CCH Kwok, HCY Wong, CYH Wong.
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Analysis or interpretation of data: HCY Wong, CCH Kwok, LW Yuen.
Drafting of the manuscript: CCH Kwok, HCY Wong.
Critical revision of the manuscript for important intellectual content: CCH Kwok, HCY Wong, CYH Wong, CC Yau, PSY Cheung.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Acknowledgement

The authors thank all participants who contributed to this research.

Funding/support

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics approval

This research was approved by the Breast Cancer Research Centre Research Committee of the Hong Kong Breast Cancer Foundation. The requirement for informed consent from patients was waived by the Committee as patient data collection by the Hong Kong Breast Cancer Registry was approved by respective participating hospitals and centres. The present study does not involve patient participation and there was no new patient data collection.

Supplementary material

The supplementary material was provided by the authors and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2411789).

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