REVIEW

The impact of COVID-19 on and recommendations for breast cancer care: the Singapore experience

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Abstract

The ensuing COVID-19 pandemic poses unprecedented and daunting challenges to the routine delivery of oncological and supportive care to patients with breast cancer. Considerations include the infective risk of patients who are inherently immunosuppressed from their malignancy and therapies, long-term oncological outcomes from the treatment decisions undertaken during this extraordinary period, and diverted healthcare resources to support a coordinated whole-of-society outbreak response. In this review, we chronicle the repercussions of the COVID-19 outbreak on breast cancer management in Singapore and describe our approach to triaging and prioritising care of breast tumours. We further propose adaptations to established clinical processes and practices across the different specialties involved in breast oncology, with references to the relevant evidence base or expert consensus guidelines. These recommendations have been developed within the unique context of Singapore's public healthcare sector. They can serve as a resource to guide breast cancer management for future contingencies in this city-state, while certain elements therein may be extrapolatable to other medical systems during this global public health emergency.

Key Words

- ▶ COVID-19
- ▶ breast cancer
- ▶ surgery
- ▶ systemic anti-cancer treatments
- ▶ radiotherapy
- ▶ palliative care

Endocrine-Related Cancer
(2020) **27**, R307–R327

Introduction

A novel infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and spread through human-to-human transmission first emerged in Wuhan, China, in December 2019 (Zhu *et al.* 2020). Coronavirus disease 2019 (COVID-19) can manifest as asymptomatic carriage, mild acute respiratory

illness or, worse, fulminant pneumonia complicated by acute respiratory distress syndrome. The World Health Organisation (WHO) declared it as a pandemic on 11 March 2020. By 23 April 2020, this contagion has infected more than 2.5 million individuals worldwide, resulting in over 175,000 deaths.

As one of the first affected countries outside of China, Singapore saw her first imported case on 23 January 2020. Following few local clusters of COVID-19, Singapore elevated the outbreak risk assessment from Yellow to Orange according to its colour-coded Disease Outbreak Response System Condition (DORSCON) framework on 7 February 2020. Adopting a multi-pronged surveillance and containment strategy executed through border control, contact tracing and quarantine measures, this densely populated Southeast Asian island nation initially curbed rapid transmission (Ng *et al.* 2020). Since mid-March 2020, the city-state experienced a resurgence of cases due to residents returning from overseas followed by local clusters. The government responded by implementing stricter measures to enforce physical distancing. These 'circuit breaker' measures lasted for 8 weeks (four incubation cycles of SARS-CoV-2) from 7 April 2020 onwards, and included closure of schools and non-essential workplaces in addition to a temporary ban on social gatherings, amounting to a partial lockdown of the city. As of 23 April 2020, there have been 12,075 infected persons and 12 deaths from COVID-19 in Singapore.

The optimal management of breast malignancy entails multidisciplinary cooperation from breast and oncoplastic surgeons, medical and radiation oncologists, palliative services, nursing and allied health professionals. The tremendous adverse impact of the COVID-19 epidemic on the Singapore healthcare system also extends to breast cancer care. This review aims to present the challenges to breast oncology practice in Singapore during this unfurling health crisis. We further set forth recommendations for care continuity planning in the face of resource constraints, which strive to safeguard patients and cancer care professionals against SARS-CoV-2 exposure while upholding therapeutic goals for patients with breast cancer.

Impact of COVID-19 on healthcare system and cancer care services in Singapore

The healthcare system

The Singapore medical system predominantly consists of a state-run public sector which administers subsidised healthcare to its 5.7-million population, co-existing with a private sector counterpart.

Singapore learnt important lessons from the Severe Acute Respiratory Syndrome (SARS) pandemic in 2003. Since then, systematic efforts to prepare public hospitals for

another respiratory disease outbreak included setting up the purpose-built National Centre for Infectious Diseases and National Public Health Laboratory; increasing the number of negative-pressure isolation beds and biosafety level 3 laboratories; stockpiling personal protective equipment (PPE); and training healthcare workers in the correct use of PPE (Wong *et al.* 2020). The DORSCON system was also developed to guide responses from the whole of government based on the local outbreak status and public health impact during a pandemic (Ministry of Health, Singapore 2014).

Since the infancy of the COVID-19 outbreak, hospital infection prevention and control policies, modified workflows and suspect case definitions have been communicated through daily emails to staff. Clear guidance has been laid for the use of PPE tiered by the type of clinical care setting, while emergency departments and inpatient wards have been re-organised with designated care areas for patients with suspected and confirmed COVID-19. Patient transfers between acute hospitals are minimised and restricted to cases which are clinically indicated. Visitors in public hospitals and outpatient clinics are curtailed and screened for temperature, symptoms and travel history before permitted entry.

Public healthcare workers undergo temperature surveillance twice daily. Staff leave is restricted and overseas travel is prohibited. Staff members who develop fever or respiratory symptoms are seen at designated staff clinics or the emergency department; unwell staff are discouraged from going to work (Lee *et al.* 2020, Ngoi *et al.* 2020).

Only essential healthcare services in the public and private sectors remain functional during the 'circuit breaker' period. Supply chains supporting these services also continue to operate.

As the number of local infections rose in April 2020, swab testing for patients meeting criteria became decentralised from public hospitals to include selected primary healthcare clinics.

Cancer care services

During the 'circuit breaker' period in Singapore, hospital-based cancer care services, inpatient hospices and home palliative care are considered as essential and remain operational. Otherwise, cancer screening and surveillance services, including the national mammographic screening programme, are categorised as non-essential and have temporarily halted.

As border controls tightened, non-resident referrals and visits to cancer clinics have ceased. Non-urgent clinic

appointments such as for cancer surveillance are deferred, while telephonic and telemedicine consultations, where appropriate, are used in lieu of face-to-face reviews. Outpatient pharmacies have also switched from on-site dispensation to home delivery of medications.

Cross-institution movement of clinicians is restricted during DORSCON Orange and the 'circuit breaker' period. Tumour boards, radiopathology conferences and other intradepartmental or multidisciplinary meetings are conducted via secure videoconferencing platforms. Furthermore, clinical teams at cancer centres have split or segregated in inpatient and ambulatory settings on a rotational or full-term basis. One such segregated-team model is described separately (Ngoi *et al.* 2020).

Recommendations for adaptations to breast oncology practice in Singapore during the COVID-19 pandemic

Principal considerations and conceptual framework

The principal considerations in approaching breast cancer care during the COVID-19 pandemic are:

1. Safety: balancing the need to visit cancer care facilities for treatment against patients' risk of exposure to SARS-CoV-2 and between immunosuppression induced by cancer treatment(s) and infection risk
2. Clinical urgency for therapeutic intervention(s)
3. Efficacy of anti-cancer treatment(s): these relate to the desired treatment outcomes and magnitude of treatment benefit
4. Availability of healthcare personnel and resources to safely deliver anti-cancer treatment(s)
5. Quality of life and access to care throughout the patient's care trajectory

It is widely accepted that cancer patients can have weakened immunity secondary to their underlying neoplasm or anti-cancer treatments. In particular, receipt of chemotherapy (within the past three months) or ongoing extensive radiotherapy, leucopaenia, age above 60 years, hospital admission and frequent hospital visits are putative risk factors that predispose cancer patients to SARS-CoV-2 infection (Pentheroudakis *et al.* 2020, Yu *et al.* 2020), making mitigating and infection prevention measures for these vulnerable subgroups paramount. Moreover, early reports suggest an association between a history of cancer or its treatments and serious complications from COVID-19 (Liang *et al.* 2020,

Zhang *et al.* 2020), with a preliminary case fatality rate of 5.6% among infected cancer patients in China (Zhou *et al.* 2020). For the majority of curative and treatment-naïve metastatic cases of breast cancers, the probable survival benefit of cancer treatment(s) generally outweighs the risk of death from COVID-19.

Clinical exigency, treatment intent (cure vs palliation of breast cancer), the anticipated extent of therapeutic benefit, disease biology and patient factors influence the prioritisation of cancer treatments during the COVID-19 era. Surgical emergencies (e.g. flap ischaemia, expanding haematoma) and oncological crises (e.g. visceral crisis, cord compression) are examples in breast oncology whereby expeditious interventions are warranted. It is crucial to involve patients closely in a shared decision-making process when the pandemic introduces another layer of complexity, taking into account their preferences for the risks and benefits of accepting vs deferring, interrupting or withholding anti-cancer treatment(s).

During DORSCON Orange and Red levels amidst a worsening COVID-19 outbreak, healthcare personnel and resources are likely to be diverted away from all fields of medicine and surgery, including those involved in breast oncology, to support Singapore's outbreak response efforts. This, along with other systems-level modifications in compliance of infection prevention protocols, will necessitate the rationalisation of limited resources and prioritisation of cancer care for different patient subpopulations.

A conceptual framework has been proposed by other authors for prioritising cancer radiotherapy and systemic treatments during the COVID-19 pandemic (Hanna *et al.* 2020). We adapted this to articulate our continuity planning strategy for breast cancer care in Singapore, incorporating the DORSCON system (Fig. 1). This construct encapsulates the priority and targeted availability of therapeutic interventions across the phases of the pandemic. We stress that these are guidelines which should not supersede treating oncologists' clinical judgement and patients' choice in personalising treatment plans.

Breast surgery

Breast surgeons are involved with the *diagnosis* and *treatment* of breast cancer. During this COVID-19 pandemic, healthcare resources (e.g. PPE, anaesthetic agents) and surgical manpower will be increasingly limited, and it is vital to avoid exposure of both patients and healthcare professionals to SARS-CoV-2.

Figure 1

As the COVID-19 outbreak becomes more widespread in Singapore, the outbreak risk assessment and the whole-of-government, whole-of-society responses have escalated from DORSCON Green through Yellow to Orange. The highest potential alert level is DORSCON Red. A set of intermediary measures referred to as 'circuit breaker' was instituted in April 2020 to prevent the transition from DORSCON Orange to Red (see main text). During DORSCON Orange and Red, less healthcare manpower and resources may be available for the provision of cancer care services because of resource diversion to support the outbreak response and/or logistical constraints to comply with infection control and prevention policies. Within this conceptual framework, the prioritisation of oncological interventions dictates resource commitment to sustain the availability of high-priority, time-sensitive therapies to breast cancer patients through more advanced phases of the outbreak. Across the continuum of DORSCON alert levels, we aim to maintain patients' quality of life and access to care through appropriate treatment selection, innovative models of care delivery (e.g. telemedicine), supportive care measures, and home hospice referral if indicated. Note that the span of the bars (availability of treatments) and the spacing in between them (ranked priority) are for illustrative purposes and not meant to be prescriptive. COVID-19, coronavirus disease 2019; DORSCON, Disease Outbreak Response System Condition.

Diagnosis

During DORSCON Orange and Red, we recommend concentrating our resources on the diagnosis and staging of breast cancers in symptomatic patients. This is to be achieved with the fewest possible patient visits to hospital.

Criteria for essential referrals are disseminated to primary care colleagues who serve as the first line of triage. Specialist outpatient consultations for new referrals remain available. The aim of the first clinic consultation is to identify patients at high suspicion of having breast cancer. This is aided by the use of bedside ultrasonography. Patients with high pre-test probability for malignancy have diagnostic mammographic and ultrasonographic assessments immediately after the clinic consult. These patients either undergo a biopsy by the surgeon within the same day or are scheduled for imaging-guided biopsy on a separate day. Patients at low suspicion of malignancy are reassured with imaging deferred by an appropriate time interval, ideally after de-escalation of DORSCON status. Staging scans for cancer diagnoses proceed as indicated and are coordinated on a same day if feasible.

This is followed by a single follow-up consultation to discuss the new diagnosis, stage and management plan.

Breast cancer screening in the general population and high-risk patients at hospitals and national screening centres have been suspended until further notice. Nonetheless, assessment clinics for recently screened patients still continue for those with abnormal mammographic findings. Percutaneous biopsies are performed on the day of assessment. Surgery of indeterminate or discordant lesions deemed likely benign have been postponed until DORSCON de-escalation to Green or Yellow.

Treatment

The principles adhered to by the surgical team during this pandemic are to maintain services for breast cancer resection, with considerate use of hospital resources, without compromise to oncological care and outcomes. This entails reducing the potential exposure of patients and healthcare professionals to SARS-CoV-2, as well as the pre-operative identification of COVID-19 infection.

At the time of writing, all surgical patients are screened with a questionnaire for travel history, contact and symptoms of COVID-19 before listing for surgery and prior to arrival on the day of operation (Chew *et al.* 2020). Patients who are screened negative clinically may proceed with their surgery. As we gain new knowledge on asymptomatic transmissions and learn of the increased and significant morbidity and mortality of patients who undergo surgery during the incubation period (Lei *et al.* 2020), pre-operative screening and testing of all patients for SARS-CoV-2 is under review.

Premised on the hypothesis of droplet and aerosol spread of SARS-CoV-2, we follow guidelines for precautions for operating room team members during the COVID-19 pandemic (Chew *et al.* 2020). In the rare situation of a breast cancer patient with COVID-19 requiring emergency surgery, the operation shall take place in a designated operating theatre with staff donning N95 masks and full-gear PPE (Ti *et al.* 2020). In view of rising community spread and number of asymptomatic carriers, all other patients are assumed to be potentially infected with SARS-CoV-2 until proven otherwise. To reduce the risk of viral transmission during aerosol-generating intubation and extubation, the anaesthetic team is gowned, gloved and masked (N95 or powered air-purifying respirator) with eye protection (goggles and face shield). All personnel not directly involved in intubation or extubation leave the operating theatre for 10 min before re-entry. This allows for at least two gas exchanges of the operating theatre and enhances safety in case the patient is an undiagnosed COVID-19 case. Surgeons perform breast surgery with standard surgical masks and face shields. Manpower in the operating theatre is kept to a minimum to avoid unnecessary exposure by healthcare workers.

Changes to other aspects of surgical practice have also been introduced to reduce the demands of hospital admissions. Where possible, cases are done as day surgeries. Same-day admission with an overnight stay post-operatively is otherwise recommended for mastectomies, axillary clearances with a surgical drain, and patients with medical comorbidities. Patients who require radiocolloid for sentinel lymph node biopsy undergo a 1-day protocol (instead of 2 days) to reduce hospital visits. For breast conserving surgeries, margin shaves of cavity are performed to reduce re-excision rates (Dupont *et al.* 2019). On-table ultrasound and specimen ultrasound and/or X-rays are also employed where appropriate (McCormick *et al.* 2004, Barellini *et al.* 2019).

Physiotherapists teach post-operative patients shoulder mobilisation before discharge. Videos for

rehabilitative exercises and teleconsultation with the therapist for follow-up have been made available.

As part of pandemic planning, we categorise procedures in breast disease-focused surgical oncology by three tiers of priority which are adapted from recommendations of the American Society of Breast Surgeons (Dietz *et al.* 2020), with tier A being the most urgent and C the least. Our proposed surgical recommendations according to priority and DORSCON status are shown in Table 1.

During DORSCON Orange and the 'circuit breaker' period, priority C operations have been deferred, whereas priority B surgeries that are still carried out include the following:

- resection of stage I–III breast cancers, ductal carcinoma *in situ* (DCIS), tumours post neoadjuvant systemic therapy, locoregional recurrences and Phyllodes tumours (borderline or malignant)
- re-excision of positive margins
- excision of discordant biopsies likely to be malignant
- immediate breast reconstruction

In the event of DORSCON Red and/or should resources become scarcer, the following priority B surgeries may have to be deferred:

- re-excision surgery
- immediate breast reconstruction: patients will be counselled for placement of a tissue expander, with a delayed definitive reconstruction upon de-escalation of DORSCON to Green or Yellow
- oncological surgeries for less aggressive tumours such as oestrogen receptor (ER) positive DCIS without associated mass (Dietz *et al.* 2020, Hwang *et al.* 2020) and cT1–2 N0–1 M0 luminal A-like tumours for which neoadjuvant endocrine therapy (ET) may be considered
- delayed sentinel lymph node biopsy for cancer identified on excisional biopsy

Systemic anti-cancer treatments

Physical distancing rules implemented from the 'circuit breaker' period onwards mandate a lower patient density at ambulatory chemotherapy units with proportionately fewer appointments available for the i.v. administration of systemic anti-cancer treatments (SACT). Reassignment of medical and nursing personnel to meet pressing demands of COVID-19 also decreases the volume of trained manpower to acutely manage hypersensitivity reactions in chemotherapy units. Broadly, our recommended adaptations for SACT and related supportive care are

Table 1 Recommendations for breast disease-focused surgical oncology according to priority of care and DORSCON status.

Priority	Description	Clinical situation	DORSCON Green and Yellow	DORSCON Orange	DORSCON Red
A	Surgical emergencies which potentially threaten the patient's life or reconstructed breast if not expeditiously treated	Incision and drainage of a breast abscess	✓	✓	✓
		Evacuation of haematoma	✓	✓	✓
		Revision of ischaemic mastectomy flap	✓	✓	✓
		Revascularisation/revision of autologous tissue flap/autologous reconstruction	✓	✓	✓
B	Cancer treatments which can be delayed by short weeks without altering the clinical course	Patients completing NACT	✓	✓	✓ Tumours progressing on NACT and inflammatory BC take precedence
		Resectable TNBC and HER2+ tumours	✓	✓	✓
		Resectable HR+ HER2– tumours	✓	✓	✓ NACT is recommended for high-risk node positive or LABC
		Re-excision of positive margins	✓	✓	Offer neoadjuvant ET for cT1–2 N0–1 luminal A-like tumours Defer until de-escalation of DORSCON
		Resection of DCIS	✓	✓	✓
		• ER+ DCIS with an associated mass • ER- DCIS			
		Resection of ER+ DCIS without an associated mass	✓	✓	Defer if surgical resources do not allow. Consider neoadjuvant ET.
		Immediate breast reconstruction (autologous microsurgery free-flaps)	✓	✓	Defer. Counsel patients for tissue expander with delayed definitive reconstruction.
		Wide excision of borderline or malignant Phyllodes tumours	✓	✓	✓
		Discordant biopsies likely to be malignant	✓	✓	✓
		Excision of malignant recurrence	✓	✓	✓
		Delayed sentinel lymph node biopsy for cancer identified on excisional biopsy	✓	✓	Defer until de-escalation of DORSCON
		Excision of benign lesions, for example, fibroadenomas, nodules	✓	Defer until de-escalation of DORSCON	
C	Non-urgent surgeries which can be deferred for the entire duration of the outbreak	Microdocheotomy	✓	Defer until de-escalation of DORSCON	
		Discordant biopsies likely to be benign	✓	Defer until de-escalation of DORSCON	
		High-risk lesions, for example, atypia, papillomas	✓	Defer until de-escalation of DORSCON	
		Excision of screen-detected indeterminate lesions	✓	Defer until de-escalation of DORSCON	
		Prophylactic surgery for cancer and non-cancer	✓	Defer until de-escalation of DORSCON	
		Palliative toilet mastectomy	✓	Defer until de-escalation of DORSCON.	Continue palliative SACT and nursing care. Consider palliative RT.

✓, can proceed with the operation depending on institutional resource availability.

BC, breast cancer; DCIS, ductal carcinoma *in situ*; DORSCON, Disease Outbreak Response System Condition; ER, oestrogen receptor; ET, endocrine therapy; HER2, human EGF receptor 2; NACT, neoadjuvant chemotherapy; RT, radiotherapy; SACT, systemic anticancer treatments; TNBC, triple negative breast cancer.

designed to conserve resources which will be constrained by the pandemic while preserving standards of care as much as possible by minimising:

- the frequency of patient visits to outpatient units and unscheduled hospital admissions for the management of treatment-related adverse events
- the incidence of hypersensitivity reactions and febrile neutropaenia
- the utilisation of emergency, diagnostic and supportive services

During DORSCON Orange and Red in Singapore, we advocate the following strategies:

- Involve patients in shared decision-making, factoring in their acceptance for the commencement or continuation of SACT during the pandemic
- Consider alternative regimens, dose schedules (three/four weekly instead of one/two weekly) or formulations (oral or s.c. as opposed to i.v.) which are of equivalent or non-inferior efficacy to the conventional standard of care (i.e. no compromise to survival outcomes)
- Consider alternative agents for drugs that are prone to hypersensitivity reactions, for example, paclitaxel and carboplatin
- Consider primary prophylactic granulocyte colony-stimulating factor (G-CSF) for regimens associated with moderate to high risk for febrile neutropaenia
- Avoid elective admissions for diagnostic procedures and drug desensitisation unless absolutely necessary because of limited hospital beds
- Employ telemedicine options wherever possible
- Manage patients' expectations after modifications to cancer care delivery. Educate and empower patients to monitor and self-manage low-grade toxicities, for example, providing 'care packs' of symptomatic medicines and telephone helplines operated by specialist nurses to render supportive care advice

(i) Curative-intent treatments

The rationale for our recommendations in terms of (neo) adjuvant SACT (Table 2) is presented according to breast cancer subtypes subsequently. Additional guidelines for adjunctive supportive care are included in Table 2.

Triple negative breast cancer

Triple negative breast cancers (TNBC) generally have a more aggressive biology than other subtypes of breast cancer.

Neoadjuvant chemotherapy We recommend neoadjuvant chemotherapy (NACT) in the majority of tumours which are clinically 2 cm or greater in diameter (T2–4) or node positive, with the aim of downsizing and potentially improving the chance of breast conservation, as well as prognostication in the event of pathologic complete response (pCR) (Cortazar *et al.* 2014). The regimens of choice include sequential anthracycline and taxane (with or without platinum) for higher risk disease (Cardoso *et al.* 2019), as well as de-escalated anthracycline-sparing regimens like docetaxel and cyclophosphamide for lower risk disease (Jones *et al.* 2009). In cases of low clinical risk (cT1N0) or if the patient is considered at high inherent risk of chemotherapy-related toxicities, advocating primary oncological resection may optimise overall patient outcome and healthcare resource utilisation.

Adjuvant chemotherapy Post-NACT, patients who did not attain pCR should be offered adjuvant capecitabine based on survival benefit seen in the CREATE-X trial (Masuda *et al.* 2017). Patients who underwent primary breast surgery and have tumours greater than 0.5 cm in diameter should be offered adjuvant chemotherapy starting up to 6 weeks post-surgery (Cardoso *et al.* 2019), with shorter regimens preferred at DORSCON Orange/Red.

HER2+ breast cancer

In addition to chemotherapy principles highlighted previously, the addition of anti-human EGF receptor 2 (HER2) therapy has consistently shown to improve both disease-free survival (DFS) and overall survival (OS) in an adjuvant setting. In the neoadjuvant setting, addition of anti-HER2 therapy is also preferred in view of improved pCR rates that has both prognostic and therapeutic implications based on best evidence today. As such, anti-HER2 therapy should continue to be administered together with (neo)adjuvant chemotherapy wherever possible. Subcutaneous trastuzumab is favoured over the i.v. formulation to save chemotherapy chair time and decrease risk of exposure for both patients and healthcare workers (Jackisch *et al.* 2015, Gligorov *et al.* 2017).

Neoadjuvant SACT NACT in combination with anti-HER2 therapy is an excellent therapeutic option with high pCR rates (Cortazar *et al.* 2014) and should be considered if surgical resources are limited in the background of COVID-19. Patients with tumours which regressed

Table 2 Recommendations for SACT and supportive care of early breast cancer according to DORSCON status.

Clinical situation	DORSCON Green and Yellow	DORSCON Orange	DORSCON Red
TNBC			
Neoadjuvant	No change to institutional standard	Higher risk (cT2–4 N1–3): q3w regimens preferred to dose-dense or weekly regimens <u>Preferred regimens:</u> AC x 4 – D x 4, TC x 4 <u>Other regimens:</u> AC x 4 – ddT x 4, AC x 4 – T x 12 Addition of carboplatin can be considered for selected patients who are expected to tolerate well Lower risk (cT1N0) or frailer patients: consider upfront surgery and adjuvant chemotherapy	Higher risk (cT2–4 N1–3): q3w regimens strongly recommended <u>Preferred regimens:</u> AC x 4 – D x 4, TC x 4 Addition of carboplatin is not advised given additional risk of myelosuppression Lower risk (cT1N0) or frailer patients: consider upfront surgery and adjuvant chemotherapy
Adjuvant	No change to institutional standard	<u>Post-NACT</u> <ul style="list-style-type: none"> pCR: no further systemic therapy residual disease: offer adjuvant capecitabine x 6–8 cycles <u>No NACT</u> <ul style="list-style-type: none"> Regimens as per NACT starting 4–6 weeks post-surgery Oral CMF x 6 is an option 	<u>Post-NACT</u> <ul style="list-style-type: none"> pCR: no further systemic therapy residual disease: offer adjuvant capecitabine x 6 cycles <u>No NACT</u> Oral CMF x 6 is an option
HER2+			
Neoadjuvant	No change to institutional standard	Higher risk (cT1c–4 N1–3): q3w preferred to dose-dense or weekly regimens Substitute i.v. trastuzumab with s.c. formulation <u>Preferred:</u> AC x 4 – DH(P) x 4, TCH(P) x 6 <u>Other regimens:</u> AC x 4 – weekly T x 12 + H(P)	Higher risk (cT1c–4 N1–3): q3w regimens strongly recommended Substitute i.v. trastuzumab with s.c. formulation Consider addition of pertuzumab only for cT3–4 N1–3 <u>Preferred:</u> AC x 4 – DH(P) x 4, TCH(P) x 6 Lower risk (cT1a/b N0) or frailer patients: consider upfront surgery and adjuvant therapy
Adjuvant	No change to institutional standard	Total 1-year anti-HER2 preferred Substitute i.v. trastuzumab with s.c. formulation <u>Post-NACT</u> <ul style="list-style-type: none"> pCR: complete adjuvant anti-HER2 residual disease: offer adjuvant T-DM1 in lieu of trastuzumab <u>No NACT</u> Shorter regimens preferred for pT1b N0/N1mi disease q3w preferred to weekly regimens Consider addition of pertuzumab only for node positive disease <u>Preferred:</u> TC x 4 + H, TCH x 6, AC x 4 – DH x 4 <u>Other regimens:</u> AC x 4 – weekly T x 12 + H, weekly T x 12 + H	Total 1-year anti-HER2 preferred Substitute i.v. trastuzumab with s.c. formulation <u>Post-NACT</u> <ul style="list-style-type: none"> pCR: complete adjuvant anti-HER2 residual disease: offer adjuvant T-DM1 in lieu of trastuzumab <u>No NACT</u> Shorter regimens preferred for pT1b N0/N1mi disease q3w regimens strongly recommended Addition of pertuzumab should not be routinely offered to node positive patients unless resources allow <u>Preferred:</u> TC x 4 + H, TCH x 6, AC x 4 – DH x 4 Omission of chemotherapy may be considered for HR+ HER2+ node negative tumours < 8 mm

(Continued)

Table 2 Continued.

Clinical situation	DORSCON Green and Yellow	DORSCON Orange	DORSCON Red
HR+ HER2– Neoadjuvant	No change to institutional standard	Higher risk (cT2–4 N1–3): If upfront operable, consider surgery If surgery is not feasible, NACT recommended if downsizing will improve surgical outcomes q3w preferred to dose-dense or weekly regimens <u>Preferred</u> : AC x 4 – D x 4, TC x 4 <u>Other regimens</u> : AC x 4 – ddT x 4, AC x 4 – T x 12 Lower risk (cT1–2 N0–1) or frailer patients: Upfront surgery and adjuvant therapy Post-menopausal patients with luminal A-like tumours ^a : consider trial of neoadjuvant ET	Higher risk (cT2–4 N1–3): If upfront operable, consider surgery If surgery is not feasible, offer NACT with q3w regimens <u>Preferred</u> : AC x 4 – D x 4, TC x 4 Lower risk (cT1–2 N0–1) or frailer patients: Upfront surgery and adjuvant therapy Post-menopausal patients with luminal A-like tumours ^a : offer trial of neoadjuvant ET Pre-menopausal patients with luminal A-like tumours ^a : offer trial of neoadjuvant ET + OFS
Adjuvant	No change to institutional standard	<u>Post-NACT</u> : ET <u>No NACT</u> Decision for adjuvant chemotherapy based on clinicopathologic factors and/or precision testing High risk of recurrence: can offer chemotherapy (q3w preferred to dose dense or weekly regimens) starting 4–6 weeks post-surgery, followed by ET Intermediate risk of recurrence: consider q3m OFS and tamoxifen or AI in lieu of chemotherapy in pre-menopausal women. ET alone in post-menopausal women. Low risk of recurrence: ET alone	<u>Post-NACT</u> : ET <u>No NACT</u> Decision for adjuvant chemotherapy based on clinicopathologic factors and/or precision testing (if available) High risk of recurrence: can offer q3w chemotherapy starting 6 weeks post-surgery, followed by ET Intermediate risk of recurrence: consider q3m OFS and tamoxifen or AI in lieu of chemotherapy in pre-menopausal women. ET alone in post-menopausal women. Low risk of recurrence: ET alone
Supportive care Fertility preservation	No change to institutional standard Oocyte harvesting or ovarian tissue cryopreservation is available	Option limited to OFS with GnRH agonist	Option limited to OFS with GnRH agonist (use q3m formulation)
Primary prophylactic GCSF	No change to institutional standard	Routine use for regimens, for example, AC, TC, docetaxel-based, dose dense paclitaxel, TCH(P)	
Cardiac function monitoring for anti-HER2/anthracycline	No change to institutional standard	Delay monitoring or increase interval from q3m to q4–5m as long as patient is asymptomatic for LVEF dysfunction and prior LVEF ≥50%	
OFS	No change to institutional standard	Consider q3m GnRH agonist for the short term	Use q3m GnRH agonist for the short term
Bone-modifying agents	No change to institutional standard	Choose oral anti-resorptive agent if treating osteoporosis	Avoid initiating new therapy Suspend ongoing i.v. therapy

^alow grade, strongly ER+, PR+, HER2–, low proliferative fraction.

AC, doxorubicin, cyclophosphamide; AI, aromatase inhibitor; CMF, cyclophosphamide, methotrexate, fluorouracil; ddT, dose dense (2-weekly) paclitaxel; DH(P), docetaxel, trastuzumab, pertuzumab; DORSCON, Disease Outbreak Response System Condition; ER, oestrogen receptor; ET, endocrine therapy; GCSF, granulocyte colony-stimulating factor; GnRH, gonadotrophin releasing hormone; HER2, human EGF receptor 2; H(P), trastuzumab, (pertuzumab); HR, hormone receptor; LVEF, left ventricular ejection fraction; NACT, neoadjuvant chemotherapy; N1mi, microinvasive disease in lymph nodes; OFS, ovarian function suppression; pCR, pathological complete response; PR, progesterone receptor; q3m, once 3-monthly; q3w, once 3-weekly; q4–5m, once in 4–5 months; SACT, systemic anti-cancer therapy; TC, docetaxel, cyclophosphamide; TC + H, docetaxel, cyclophosphamide + trastuzumab; TCH(P), docetaxel, carboplatin, trastuzumab, (pertuzumab); T-DM1, trastuzumab emtansine; TNBC, triple negative breast cancer; weekly T, weekly paclitaxel.

inadequately (i.e. non-pCR) after pre-operative anti-HER2-based SACT can consider risk-adapted adjuvant strategies that may improve disease-free survival, further elaborated in the next section. As such, neoadjuvant SACT should be strongly considered in patients with tumours larger than 1 cm ($\geq T1c$) or node positive disease (Gianni *et al.* 2014).

Compared with single-agent HER2 blockade, dual anti-HER2 therapy further increases the likelihood of achieving pCR (Schneeweiss *et al.* 2013, Gianni *et al.* 2016). Therefore, NACT plus dual anti-HER2 therapy can be considered, especially for patients with locally advanced HER2+ disease. In patients with good performance status, consideration of docetaxel, carboplatin, trastuzumab and pertuzumab (TCHP) for six cycles may potentially reduce total treatment duration and represents an anthracycline-sparing option to reduce the risk of cardiotoxicity (Schneeweiss *et al.* 2013). Should sequential anthracycline- and taxane-containing regimens be chosen as the chemotherapy backbone, use of docetaxel instead of paclitaxel can be considered to obviate the need for weekly infusions of the latter.

Adjuvant SACT We advocate the completion of a year's HER2 blockade wherever possible, due to robust evidence of improved treatment outcomes compared to no therapy. Nonetheless, in selected patients for whom cardiotoxicity is of concern or who have multiple comorbidities putting them at high risk of developing COVID-19, the option of HER2 blockade for total 6 months may be discussed after weighing the risk-benefit ratio (Earl *et al.* 2019). Truncating adjuvant anti-HER2 therapy may be considered in DORSCON Red, particularly if the risk of COVID-19 infection and resource limitation outweigh the benefits of completing a full year of treatment.

Following neoadjuvant SACT, the choice of adjuvant anti-HER2 therapy is largely guided by neoadjuvant response. Among patients with residual invasive disease, adjuvant trastuzumab emtansine (T-DM1) has been shown to improve invasive DFS over trastuzumab and can be considered (von Minckwitz *et al.* 2019).

For patients who underwent upfront surgery, adjuvant anti-HER2 therapy should be administered together with chemotherapy. In patients with node positive disease, the guiding principles for chemotherapy choice are consistent with those stated in the neoadjuvant setting. Adjuvant dual HER2 blockade has demonstrated benefit especially for higher stage disease and may be discussed with patients with node positive disease (von Minckwitz *et al.* 2017), although the resource availability to administer

pertuzumab may be limited under dire DORSCON Red conditions.

In patients with node negative or microscopic disease (pN0/N1mi) and small primary tumours (pT1b-2), we recommend 3-weekly docetaxel/cyclophosphamide with trastuzumab over weekly paclitaxel-trastuzumab to reduce outpatient visits (Jones *et al.* 2013). Adjuvant T-DM1 may be an alternative for stage I patients (Dietz *et al.* 2020) who may be at higher risk of developing chemotherapy toxicities or decline doublet/weekly chemotherapy, based on unpublished data from the phase II ATEMPT trial (ClinicalTrials.gov identifier NCT01853748). In an extreme DORSCON Red setting, omission of adjuvant multiagent chemotherapy may be considered for hormone receptor (HR) positive, HER2+ node negative tumours smaller than 8 mm on the basis of an observational cohort study suggesting that chemotherapy does not confer incremental OS benefit over ET for such cases (Cardoso *et al.* 2019, Ma *et al.* 2020).

HR+ HER2– breast cancer

Hormone receptor (HR) positive, HER2 negative breast cancers are heterogeneous, with luminal A tumours being more indolent and strongly endocrine sensitive whereas luminal B tumours being more aggressive (Cardoso *et al.* 2019).

Neoadjuvant and adjuvant chemotherapy The role of NACT in HR+ HER2– breast cancer is limited because pCR rates are lower compared to TNBC or HER2+ tumours and correlate weakly with long-term survival outcomes (Cortazar *et al.* 2014). NACT is typically indicated in HR+ HER2– primary breast cancers which are locally advanced or upfront inoperable. Primary surgery particularly for early stage breast cancer (cT1–2 N0–1) allows for precision testing, for example, Oncotype DX to inform post-operative treatments; the necessity for adjuvant chemotherapy and sequelae from immunosuppression may be eliminated in patients with good prognostic indices (Sparano *et al.* 2018). After primary surgery, if patients are determined to have high risk disease based on precision testing and/or clinicopathologic factors, adjuvant chemotherapy using the previously mentioned principles should be offered.

Neoadjuvant and adjuvant endocrine therapy Many patients with early stage HR+ HER2– breast cancer need not undergo chemotherapy, particularly in the modern era of precision testing. In a subset of patients with luminal A–like breast cancers (low grade, strongly ER+,

strongly progesterone receptor positive, HER2– and low proliferative fraction) who are otherwise well, neoadjuvant ET can serve as a bridge to reduce the need for surgery and chemotherapy for 6 to 8 months (Smith *et al.* 2005, Masuda *et al.* 2012), which will be a resource-friendly strategy in DORSCON Red. Pre-menopausal patients, particularly those with intermediate risk scores on Oncotype DX, can also consider the option of ovarian function suppression (OFS) in conjunction with ET in lieu of adjuvant chemotherapy (Francis *et al.* 2018). Follow-up consultations while on ET can be stretched up to 3- to 6-monthly intervals which are desirable in higher DORSCON alert levels.

(ii) Palliative treatments

The following are guiding principles in caring for patients with inoperable or metastatic breast cancer during the COVID-19 pandemic:

- Delay therapy when the expected efficacy is modest, maintenance therapies, and treatments for patients with low disease burden and slow progression. Consider treatment breaks if appropriate
- Delay non-urgent radiological scans including for response assessment
- Increase the duration of a treatment cycle, for example, from 3-weekly to 4-weekly, or choose alternative dose schedules, for example, biweekly eribulin
- When initiating a new SACT, an alternative oral agent or non-i.v. route of administration of the same drug is preferred to i.v. if their anticipated efficacy is similar
- Consider non-i.v. maintenance therapy, if appropriate, after sustained partial response or stable disease
- Refer patients on best supportive care (BSC) to home hospice service if appropriate

Our recommendations for palliative treatments are summarised in Table 3 and elaborated subsequently.

Triple negative breast cancer

In the setting of DORSCON Green/Yellow, we will still primarily consider TNBC patients for trial enrolment while clinical trials remain for recruitment. Several ongoing trials at academic cancer centres in Singapore are in late phases and evaluate combinations of chemotherapy, immunotherapy and/or targeted therapies.

Cytotoxics remain the mainstay of standard SACT for TNBC. Taxanes, platinum salts, anthracyclines, eribulin

and capecitabine as single agents or as combination for heavy tumour burden are options for TNBC patients (Cortés *et al.* 2011, Tutt *et al.* 2018), with consideration for competing comorbidities and toxicities. Poly(ADP-ribose) polymerase inhibitors may be considered for the treatment of germline *BRCA* mutated breast cancers as well as preferentially over chemotherapy in treatment-naïve patients due to their convenient oral administration and lower myelosuppression (Robson *et al.* 2017).

The combination of atezolizumab and nab-paclitaxel as first-line therapy in TNBC (Schmid *et al.* 2018) is not approved or routinely accessible in Singapore. We note that immune checkpoint inhibition may elicit pneumological toxicities with features overlapping COVID-19 related interstitial pneumonia. Furthermore, a theoretical synergism between COVID-19 pathogenesis and immunotherapy may both promote immune hyperactivation (Mehta *et al.* 2020).

During DORSCON Orange/Red, trial recruitment shall halt. In patients with low tumour or symptom burden or declining i.v. chemotherapy, or if i.v. SACT resources are restricted during DORSCON Red, oral chemotherapy such as capecitabine is recommended. Otherwise, 3-weekly docetaxel or carboplatin are reasonable first-line i.v. agents (Tutt *et al.* 2018) and can be crossed over to the other drug in the second line upon disease progression. In patients who have had maximal response to i.v. chemotherapy, we consider switch to oral maintenance with capecitabine or metronomic cyclophosphamide/methotrexate (Fedele *et al.* 2012, Munzone & Colleoni 2015). In selected patients with low-volume, well-controlled disease, it is appropriate to offer a short chemotherapy holiday. Finally, we consider BSC after progression on third-line therapy where the anticipated therapeutic benefits are modest at best.

HER2+ breast cancer

In the first line during DORSCON Orange/Red, docetaxel once 3-weekly with primary prophylactic GCSF is preferred to weekly paclitaxel, as the chemotherapy partner to HER-directed therapies (Swain *et al.* 2020). T-DM1 is an acceptable alternative to frontline taxane plus trastuzumab because the former is non-inferior for efficacy and better tolerated (Perez *et al.* 2017). In patients with HR+ HER2+ tumours and low disease burden, especially those who decline i.v. therapy, first-line ET plus HER2 blockade is reasonable (Kaufman *et al.* 2009, Huober *et al.* 2012). T-DM1 or oral capecitabine/lapatinib are our recommended regimens in the second or third line

(Diéras *et al.* 2017, Krop *et al.* 2017). For HR+ HER2+ patients who have benefitted from induction i.v. chemotherapy, an early switch to maintenance ET plus anti-HER2 therapy can be considered (Cardoso *et al.* 2018).

Treatment benefit beyond the second or third line may be modest for some patients with HER2+ MBC; non-i.v. chemotherapy-based or chemotherapy-sparing regimens are suggested if initiated for this indication. During the COVID-19 pandemic, it is possible to increase the dosing interval of maintenance trastuzumab from 3-weekly to 4-weekly to reduce visits. We also recommend suspending or discontinuing maintenance trastuzumab for patients on extended therapy longer than 2 years (Dietz *et al.* 2020). Wherever possible, i.v. trastuzumab should be substituted with the s.c. formulation (Pivot *et al.* 2017) to reduce the length of time spent for drug administration.

HR+ HER2– breast cancer

Among patients with *de novo* metastatic HR+ HER2– breast cancer or who relapsed more than 12 months after adjuvant ET, those with bone-limited disease can receive first-line non-steroidal aromatase inhibitor (NSAI) monotherapy; NSAI plus cyclin dependent kinase 4/6 (CDK4/6) inhibitor is recommended for those with moderate to high visceral disease (not in crisis) or symptom burden (Spring *et al.* 2020). Otherwise, during DORSCON Orange/Red, it is possible to commence the aromatase inhibitor (AI) first for patients with low-volume visceral metastases and add the CDK4/6 inhibitor later when the COVID-19 pandemic eases. Our recommended first-line therapy for patients with early relapse during or within 12 months of adjuvant ET is fulvestrant, preferably with CDK4/6 inhibitor (Spring *et al.* 2020). The same guidance for a phased introduction of the CDK4/6 inhibitor where suitable as mentioned previously applies. Clinicians should consider toxicity profiles and monitoring parameters when choosing a CDK4/6 inhibitor during the pandemic.

First-line patients on a stable dose of CDK4/6 inhibitor therapy can be reviewed 2-monthly instead of monthly or considered for a treatment break with continuation of AI alone, when DORSCON is Orange/Red.

For the initiation of second-line therapy, we recommend single-agent ET. ET combinations with everolimus or alpelisib have not shown OS benefit (Piccart *et al.* 2014, André *et al.* 2019). A potential improvement in progression-free survival must be weighed against toxicities associated with these agents, for instance non-infective pneumonitis which is relevant during a respiratory infection outbreak.

Premenopausal women receiving AI or fulvestrant in any line should receive concurrent OFS.

We recommend oral capecitabine as the first cytotoxic chemotherapy to initiate for endocrine resistant patients after progression on prior endocrine-based therapies and not requiring rapid response.

(iii) Supportive care

During DORSCON Orange/Red, we recommend against initiating bone-modifying agents in the curative or palliative settings unless treating severe hypercalcaemia. Subcutaneous denosumab can be considered as a substitute for i.v. bisphosphonate as adjunctive treatment of bone metastases. Dosing intervals for ongoing supportive care interventions can also be increased, for instance zoledronate (van Poznak *et al.* 2017) or gonadotropin-releasing hormone analogue for OFS from monthly to 3-monthly. Likewise, elective on-treatment cardiac function monitoring can be delayed during DORSCON Orange/Red as long as patients do not exhibit cardiac symptoms and have preserved ejection fractions on previous measurements.

(iv) Clinical trials

COVID-19 impacts the conduct of clinical trials. Considerations include travel restrictions both internationally and locally, quarantine of patients, site closure, interruptions to supply chain of investigational products, reassignment of study staff to COVID-19 related work, challenges in on-site monitoring visits and infection risk of site personnel and trial subjects. The Health Sciences Authority of Singapore issued guidance on trial conduct during the outbreak to aid sponsors and investigators in ensuring the safety of trial subjects while complying with trial regulations and Good Clinical Practice, thereby minimising risk to trial integrity. During DORSCON Yellow, clinical trials within academic medical centres are reviewed and classified as (1) essential studies providing what is considered equivalent to standard of care; (2) intermediate priority such as studies fulfilling unmet clinical needs; or (3) low priority studies. The categorisation criteria are:

- The investigational product, safety, efficacy and extent of clinical experience
- The ability to manage adverse events and to implement dose modifications or delays as necessary in a timely fashion

Table 3 Recommendations for SACT and supportive care of inoperable and metastatic breast cancer according to DORSCON status.

Clinical situation	DORSCON Green and Yellow	DORSCON Orange	DORSCON Red
TNBC	No change to institutional standard	<p>1L: clinical trial^a, docetaxel^b or carboplatin Consider combination chemotherapy only for high tumour burden whereby rapid response is desired</p> <p>2L: clinical trial^a, switch from docetaxel to carboplatin or <i>vice versa</i>, capecitabine, eribulin^b</p> <p>Consider PARP inhibitor for known germline <i>BRCA</i> mutation carriers, especially in earlier lines</p> <p>Consider switch to oral maintenance (capecitabine or metronomic cyclophosphamide/methotrexate) upon maximal response</p> <p>Consider short chemotherapy breaks</p> <p>Consider increasing chemotherapy cycles from 3-weekly to 4-weekly or alternative dose schedules</p> <p>Consider BSC after progression on 3L therapy where anticipated therapeutic benefits are modest</p>	<p>1L: docetaxel^b or carboplatin. Capecitabine is recommended if i.v. SACT resources are limited.</p> <p>Avoid combination chemotherapy unless absolutely indicated (e.g. visceral crisis)</p> <p>2L: capecitabine, oral vinorelbine, switch from docetaxel to carboplatin or <i>vice versa</i>, eribulin^b</p>
HER2+	No change to institutional standard	<p>1L: DH(P)^b preferred to TH(P); ET + anti-HER2 is possible for selected HR+ patients</p> <p>2L-3L: T-DM1 or capecitabine/lapatinib</p> <p>HR+: switch to maintenance ET + anti-HER2 if possible</p> <p>Increase dosing interval of maintenance trastuzumab (q4w)</p> <p>Suspend or discontinue maintenance trastuzumab for patients on extended therapy (> 2 years)</p> <p>Substitute i.v. trastuzumab with s.c. formulation</p> <p>Therapy beyond 2L-3L: consider capecitabine/lapatinib, capecitabine/trastuzumab, lapatinib/trastuzumab</p> <p>Delay cardiac function monitoring (if done) as long as patient is asymptomatic and prior LVEF ≥ 50%</p>	<p>1L: DH(P)^b or T-DM1; consider ET + anti-HER2 for HR+ patients with low-volume disease</p> <p>2L-3L: capecitabine/lapatinib preferred to T-DM1</p>
HR+ HER2–	No change to institutional standard	<p>1L: NSAI (bone-limited, <i>de novo</i> MBC or late relapse^c); NSAI ± CDK4/6i (visceral metastases or symptomatic, <i>de novo</i> MBC or late relapse^c); fulvestrant ± CDK4/6i (early relapse^d)</p> <p>2L: ET monotherapy (fulvestrant, alternative AI, tamoxifen)</p> <p>Stable CDK4/6i dose: convert to q2m reviews or consider break (continue ET alone)</p> <p>OFS for pre-menopausal patients: convert GnRH agonist to q3m formulation</p> <p>Endocrine-resistant patients: capecitabine is the preferred first cytotoxic chemotherapy</p>	
Bone-modifying agents	No change to institutional standard	<p>–</p> <p>Avoid initiating new therapy (unless treating severe hypercalcaemia)</p> <p>Consider s.c. denosumab instead of i.v. bisphosphonate</p> <p>Increase dosing intervals, for example, i.v. zoledronate q3m</p>	<p>Suspend therapy, especially if patient is on oral SACT only</p>

^aapplicable to patients already enrolled in clinical trials. Trial screening and recruitment shall be suspended during DORSCON Orange/Red; ^bwith primary prophylactic GCSF; ^cLate relapse refers to cancer recurrence greater than 12 months after adjuvant ET; ^dEarly relapse refers to cancer recurrence during or within 12 months of adjuvant ET.

1L, first line; 2L, second line; 3L, third line; AI, aromatase inhibitor; BSC, best supportive care; CDK4/6i, cyclin D kinase 4/6 inhibitor; DH(P), docetaxel, trastuzumab and pertuzumab; DORSCON, Disease Outbreak Response System Condition; ET, endocrine therapy; GCSF, granulocyte colony-stimulating factor; GnRH, gonadotrophin releasing hormone; HER2, human EGF receptor 2; HR, hormone receptor; LVEF, left ventricular ejection fraction; NSAI, non-steroidal aromatase inhibitor; OFS, ovarian function suppression; PARP, poly(ADP-ribose) polymerase; q2m, once 2-monthly; q3m, once 3-monthly; q4w, once 4-weekly; SACT, systemic anti-cancer therapy; T-DM1, trastuzumab emtansine; TH(P), paclitaxel, trastuzumab and pertuzumab; TNBC, triple negative breast cancer.

- The disease under study
- The ability to comply with study related procedures and alternative methods for safety monitoring of trial participants without impacting data credibility

Trials considered essential or of intermediate priority may continue without amendment, but low-priority trials are temporarily halted. During DORSCON Orange/Red, to support national efforts in COVID-19 containment and to conserve hospital resources, trial screening and recruitment shall be suspended. Where permissible on protocol, i.v. study drug administration and study-related visits are delayed. Investigators exercise clinical discretion in ensuring that essential safety assessments are completed. Where feasible, remote study visits are considered and oral investigational products are delivered to trial participants.

Radiotherapy

Prioritisation of radiotherapy (RT) is based on treatment indication as per the conceptual framework in Fig. 1. The highest priority is accorded to treatments for function-threatening cases (e.g. acute cord compression with paralysis, proptosis from retroorbital metastases, intractable tumoral bleeding), followed by treatments associated with OS benefit, then those with locoregional DFS benefit only and, lastly, other palliative treatments. We highlight situations in which RT can be reasonably abbreviated or omitted during this pandemic. Our recommendations in Table 4 are tiered and situational; for instance, use of the most hypofractionated regimen for invasive breast cancer and omission of RT for DCIS during DORSCON Red.

(i) Adjuvant RT

DCIS

In low-risk cases (i.e. age 50 years or older with no necrosis, low grade, small tumour size, at least 2 mm margins), omission of RT is to be strongly considered. The UK/ANZ trial showed that adjuvant RT reduced ipsilateral breast tumour recurrence (IBTR) rate but with no survival benefit (Cuzick *et al.* 2011). For higher-risk cases, treatment should be abbreviated to use large dose-per-fraction hypofractionation regimen.

DCIS comprised about 25% of the NSABP-B39 trial cohort. This study demonstrated no statistically significant difference in 10-year cumulative incidence of IBTR between whole breast irradiation (WBI) and accelerated

partial breast irradiation (APBI). Despite NSABP-B39 not fulfilling equivalence criteria of APBI (38.5 Grays (Gy) in ten fractions delivered twice a day over 5–8 days) to WBI, there was only a marginal 1% absolute difference in 10-year cumulative incidence of IBTR (Vicini *et al.* 2019). In contrast, RAPID trial demonstrated that APBI delivered in similar fashion was non-inferior to WBI in preventing IBTR (Whelan *et al.* 2019) due to its stricter eligibility criteria. Nonetheless, during an active pandemic, once-daily treatment is preferred for ease of logistics and safe distancing considerations. Therefore, the RT regimen using 40 Gy in ten daily fractions is preferred (Braunstein *et al.* 2019). Should WBI be indicated, we recommend the shorter fractionation of FAST FORWARD regimen (26 Gy in five daily fractions) as a pragmatic solution (FAST Trialists Group 2011). During DORSCON Red, we recommend omission of RT for DCIS cases.

Invasive breast cancers

Node negative breast cancer Before surgery, patients with clinically node negative disease should be screened for eligibility for intraoperative radiotherapy according to TARGIT trial (Vaidya *et al.* 2014). Post-operatively, patients aged 65 years and above with HR+ tumours shall be considered for potential omission of RT which only modestly reduces IBTR compared to ET alone (Kunkler *et al.* 2015).

For low-risk patients aged 40–64 years (maximum tumour size 3 cm, ER+ and receiving adequate systemic treatment), APBI, partial breast irradiation (Coles *et al.* 2017) and WBI are applicable. Livi *et al.* showed no significant differences in IBTR or OS between APBI and WBI. Additionally, patients in the APBI arm experienced better cosmetic outcomes and fewer toxicities. Therefore, 30 Gy in five fractions daily using intensity-modulated radiotherapy technique (Livi *et al.* 2015) or 40 Gy in ten fractions daily using 3D conformal RT (Braunstein *et al.* 2019) may be employed, if the APBI method is selected. Where WBI is indicated, standard hypofractionation regimen of 40 Gy in 15 fractions (Haviland *et al.* 2013) shall be used. The FAST FORWARD regimen is an alternative (FAST Trialists Group 2011). During DORSCON Red, options are restricted to APBI using 30 Gy in five fractions or WBI using 26 Gy in five fractions.

In all other patients (age 40 years or younger; or high-risk, age above 40 years; or tumours larger than 3 cm, of high grade, ER-, HER2+ or involved margin), WBI (or post-mastectomy RT [PMRT] for tumours larger than 5 cm or

positive margin) with either standard hypofractionation 40 Gy in 15 fractions or the FAST FORWARD regimen shall be employed. If boost is indicated, it shall be given either simultaneously using 48 Gy in 15 fractions as per RTOG 1005 (ClinicalTrials.gov identifier NCT01349322) or sequentially as 10.5 Gy in three fractions. During DORSCON Red, WBI or PMRT using 26 Gy in five fractions (FAST Trialists Group 2011) shall be used.

Node positive breast cancer Patients with N1 disease shall either be given either adjuvant RT to the breast/chest wall and ipsilateral supraclavicular fossa (and axilla, as indicated) using standard hypofractionation 40 Gy in 15 fractions (Haviland *et al.* 2013) or 26 Gy in five fractions (FAST Trialists Group 2011).

Adjuvant RT to the internal mammary nodal chain for patients with N2 disease shall be delivered using standard hypofractionation 40 Gy in 15 fractions (Haviland *et al.* 2013).

When indicated, boost shall be given either simultaneously using 48 Gy in 15 fractions or sequentially 10.5 Gy in three fractions.

During DORSCON Red, we recommend adjuvant RT using 26 Gy in five fractions (FAST Trialists Group 2011). Strict compliance to the organ-at-risk constraint should be observed (Brunt *et al.* 2020) and treatment should be delivered using free breath hold, with daily image guidance and using conformal techniques, for example, helical therapy for cardiac sparing.

(ii) Palliative RT

For patients with cord compression or bony metastases, we recommend RT using either 20 Gy in five fractions or single-fraction 8 or 10 Gy (Hoskin *et al.* 2019). In addition, for breast palliation, RT should be given weekly 6 Gy fractions for 5 to 6 weeks.

In patients with brain metastases, stereotactic radiosurgery shall be given following standard indications. Otherwise, whole brain RT shall be given using 20 Gy in five fractions or 12 Gy in two fractions daily.

During DORSCON Red, palliative RT should be administered over the least number of fractions possible.

Palliative and supportive care

Breast cancer patients encounter many adversities and have unmet needs. Besides having to cope with treatment side effects such as fatigue, nausea and pain, these

patients have psychological and informational needs that often remain unmet (Fiszer *et al.* 2014). This struggle is exacerbated by the COVID-19 pandemic. Many patients report the COVID-19 pandemic as a major stressor, fuelling worries about the future and fears of getting infected during cancer treatment. Those who receive in-person emotional and information support from supportive care clinics find themselves bereft of such resources due to decreased non-essential clinic visits. To continue meeting supportive care needs within a pandemic situation, telemedicine solutions may be a possible avenue to enable continual care delivery yet maintain restrictive safety measures. Medications can be supplied via courier systems and titration done via symptom diaries and phone follow-up. Providing additional communication channels such as phone lines or emails manned by trained supportive care nurses are also viable options.

The untimely decision to hold or discontinue palliative SACT in the midst of a pandemic can be devastating to a patient with terminal breast cancer, misconstrued as 'giving up' or even fracture rapport and trust between the oncologist and the patient. Thus, discussions about goals of care between oncologists and patients are imperative (Ueda *et al.* 2020). Focusing future care plans on 'what matters most' for the individual patient against the background of the COVID-19 pandemic can help facilitate decision-making during this period of uncertainty.

The COVID-19 pandemic also poses difficulties to the care of cancer patients in the community. As cancer centres start reducing non-essential clinic visits and admissions, patients who no longer benefit from active oncological treatment will be referred to home hospice services to continue care within the community. These are also the frailer patients at higher risk of contracting and dying from COVID-19. A likely surge in referrals can easily overwhelm most hospice services that are already functioning at capacity. Moreover, as community spread of SARS-CoV-2 intensifies, the safety of home hospice personnel needs to be addressed, for instance when called to attend to terminally ill patients with fevers and/or chest infections at home. Home hospice services require adequate PPE and manpower to function at the frontline of continuing cancer care within the community.

The outbreak's impact is amplified at the end of life. Stringent hospital visitor policies aggravate the isolation of hospitalised cancer patients at their most vulnerable, while quarantine orders and social distancing policies can end up preventing loved ones from visiting even in the last weeks or days of life. Such isolation can lead to a sense of powerlessness, helplessness and frustration,

Table 4 Recommendations for radiotherapy of breast cancers according to DORSCON status.

Clinical situation	DORSCON Green & Yellow	DORSCON Orange	DORSCON Red
Non-invasive cancer, for example, DCIS, pleomorphic LCIS			
High risk: ≤ 50 years old or grade 3/necrosis or positive margins	≤ 40 years old: WBI (40 Gy/15#) 40–50 years old: consider APBI (40 Gy/10# daily, 38.5 Gy/10# BD) Consider omitting RT	APBI (30 Gy/5# IMRT) or WBI (26 Gy/5#)	No RT
Low risk		No RT	No RT
Node negative invasive cancer			
>50 years old and ER+ PR+, T ≤ 3 cm, cN0, no LVI/EIC <u>preoperatively</u>	IORT	IORT	IORT
≥ 65 years old, ER+, T ≤ 3 cm N0 and willing for appropriate systemic therapy	No RT or APBI (30 Gy/5# daily IMRT, 40 Gy/10# daily, 38.5 Gy/10# BD, 40 Gy/15#) or WBI (26 Gy/5# daily, 40 Gy/15#)	No RT	No RT
Low risk 40–64 years old: ER+, T ≤ 3 cm, N0 and willing for appropriate systemic therapy	APBI (30 Gy/5# daily/EOD IMRT, 40 Gy/10# daily, 38.5 Gy/10# BD, 40 Gy/15#) or WBI (26 Gy/5# daily, 40 Gy/15#)	APBI (30 Gy/5# daily IMRT) or WBI 26 Gy/5# daily (most cases), 40 Gy/15# if cardiac dose is a concern	APBI (30 Gy/5# daily IMRT) or WBI (26 Gy/5#)
All others (≤ 40 years old, high risk >40 years old with N0): for example, T >3 cm, or grade 3, or ER-, or HER2+ or positive margin	<u>Post-BCS</u> : 40 Gy/15# + Boost 10.5 Gy/3#, 10 Gy/5#, 16 Gy/8#, SIB 48 Gy/15# <u>PMRT</u> : pT3–4: 40 Gy/15# pT3 only: 26 Gy/5# (to consider for ≥ 65 years old)	<u>Post-BCS/PMRT</u> : 26 Gy/5# daily (most cases) or 40 Gy/15# if cardiac dose is a concern	<u>Post-BCS + PMRT</u> : 26 Gy/5#
Node positive invasive cancer			
N1 $\rightarrow$ 3F/4F RT	<u>Post-BCS</u> : 40 Gy/15# + Boost 10.5 Gy/3#, 10 Gy/5#, 16 Gy/8#, SIB 48 Gy/15# <u>PMRT</u> : pT3–4: 40 Gy/15# pT3 only: 26 Gy/5# (to consider for ≥ 65 years old)	<u>Post-BCS/PMRT</u> : 26 Gy/5# daily (most cases) or 40 Gy/15# if cardiac dose is a concern	<u>Post-BCS + PMRT</u> : 26 Gy/5#
N2 $\rightarrow$ IMN RT	<u>Post-BCS</u> : 40 Gy/15# + Boost 10.5 Gy/3#, 10 Gy/5#, 16 Gy/8#, SIB 48 Gy/15# <u>PMRT</u> : pT3–4: 40 Gy/15#	<u>Post-BCS/PMRT</u> : 26 Gy/5# daily (most cases) or 40 Gy/15# if cardiac dose is a concern	<u>Post-BCS/PMRT</u> : 26 Gy/5# (note OAR guidelines)
Palliative indications			
Bony metastases or cord compression	Good prognosis 30 Gy/10# All others: 20 Gy/5# or 8–10 Gy/1# Supportive therapy alone, if appropriate	8–10 Gy/1# or 20 Gy/5# or supportive therapy alone, if appropriate	8–10 Gy/1# or supportive therapy alone, if appropriate
Brain metastases	Where appropriate: SRS All others: 20 Gy/5# or 12 Gy/2# (daily) Supportive therapy alone may be appropriate	Where appropriate: SRS All others: 12 Gy/2# (daily) or 20 Gy/5# Supportive therapy alone may be appropriate	Supportive therapy alone or 12 Gy/2# (daily)

#, fraction; 3F, three-field RT (breast/chest wall, supraclavicular fossa); 4F, four-field RT (breast/chest wall, supraclavicular fossa, axilla); APBI, accelerated partial breast irradiation; BCS, breast conserving surgery; BD, twice daily; DCIS, ductal carcinoma in situ; DORSCON, Disease Outbreak Response System Condition; EIC, extensive intraductal component; EOD, every other day; ER, oestrogen receptor; Gy, Grays; HER2, human EGF receptor 2; IMN, internal mammary nodal chain; IMRT, intensity-modulated RT; IORT, intraoperative radiotherapy; LCIS, lobular carcinoma in situ; LVI, lymphovascular invasion; OAR, organ at risk; PMRT, post-mastectomy RT; PR, progesterone receptor; RT, radiotherapy; SIB, simultaneous integrated boost; SRS, stereotactic radiosurgery; T, tumour size; WBI, whole breast irradiation.

with disruption of connectedness to self and also to family (Leong *et al.* 2004). Moreover, current rules to limit gatherings and truncate traditional death rituals can also disrupt bereavement by the family. Palliative care professionals should be cognisant of such issues and work proactively to mitigate them within the constraints of pandemic control. For instance, patients and their families can be encouraged to connect with one another via video phone calls or letter writing. Psychosocial and spiritual support for patients and families can be established using telehealth interventions, while patients can be taught to engage in meditation, mindfulness or yoga at home as coping mechanisms.

The COVID-19 outbreak is truly a threat to the field of palliative care. However, innovative solutions coupled with a mindset to never stop advocating for the patient, while paying heed to the need to protect society at large, will allow us to surmount this crisis.

The Singapore experience compared to the rest of the world

How breast cancer management in each country or healthcare system adapts to the COVID-19 pandemic depends on the local epidemiological situation and implemented outbreak response measures as well as the availability and organisation of resources and specialist manpower. While specific strategies may differ, common themes revolve around patient triage and care prioritisation, minimising hospital visits and adopting telemedicine, and modifying treatment plans to acceptable alternatives (Çakmak & Özmen 2020, Dietz *et al.* 2020, Ismaili & El Majjaoui 2020, Liu *et al.* 2020). The European approach is similar to ours in that recommendations for practice adaptation are layered upon the epidemiological phases of the outbreak which are coincidentally also classified as four tiers (Curigliano *et al.* 2020). Singapore is a small city-state with cancer centres being embedded within general hospitals or a wider hospital campus, augmenting the complexities of segregating cancer patients from suspected or confirmed cases of SARS-CoV-2 infection. Solutions such as designating 'COVID-19 free' oncological hubs can be useful in the European epicentre of the outbreak but are not applicable to Singapore (Viale *et al.* 2020).

Conclusions

In the throes of the COVID-19 pandemic, health systems are under immense strain and standard clinical practice

has been disrupted globally. We depicted how elevating levels of epidemic response efforts in Singapore have affected the surgical, systemic and radiation treatments as well as palliative and support care of breast cancers. We also recommended prioritisation by clinical indication and practice modifications so as to marshal restricted resources for patient-centric care delivery without compromise to oncological outcomes. As the pandemic rapidly evolves, we recognise that our recommendations may need to be revised based on situational requirements. We strongly encourage clinicians to discuss the management of challenging or 'outlier' cases at tumour boards, especially if the prevailing circumstances dictate a deviation from standard practice or a prolonged delay to intended treatments.

The comprehensive, collaborative and multidisciplinary scope of our guidance can serve as a template for adaptations to clinical management in other tumour types during this pandemic or as a resource for breast oncology in future contingencies. The local contextualisation of the specific recommendations limits their generalisability to more resource-challenged healthcare settings during the COVID-19 epidemic. Nevertheless, the overarching principles underpinning our suggested conceptual framework are universally relevant and may be applied to pandemic planning guideline development in other parts of the world.

We anticipate a backlog of deferred cases and surge in new case referrals to breast oncologists when the pandemic eases. Just as our practices have become more focused with worsening outbreak severity, the transition back to conventional norms can be phased according to de-escalating DORSCON levels, applying the same standards of clinical priority but also considering the latest clinical status and the deferment period of diagnostic or therapeutic procedure in every patient.

Lastly, we recommend that breast cancer patients whose oncological care was modified from conventional standards during the COVID-19 outbreak be followed up for long-term outcomes. Doing so as part of clinical audits or observational studies will reveal the true impact of this pandemic on our patients and better prepare the breast oncology community to adapt our practice in response to another global health crisis

Declaration of interest

Jack Junjie Chan – Honoraria: Pfizer, Merck Sharp & Dohme, Eisai, AstraZeneca, Novartis; Consulting or Advisory Role: Pfizer; Research Funding: OncoQuest, Bristol-Myers Squibb; Travel, Accommodations, Expenses: AstraZeneca, Pfizer, Celgene. Joline Si Jing Lim – Honoraria: Pfizer, Novartis; Research Funding: Synthon; Travel, Accommodations,

Expenses: Novartis, Pfizer, AstraZeneca. Tira Jing Ying Tan – Consulting or Advisory Role: Roche, Novartis, Eli Lilly; Research Funding: AstraZeneca; Travel, Accommodations, Expenses: AstraZeneca, Eisai. The other authors have nothing to disclose.

Funding

This work was not supported by any specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Author contribution statement

Jack Junjie Chan and Jing Ying Tan performed conception and design, selection of notable articles for review, critical review of the literature, composition of the manuscript and final approval. Sim Yirong, Samuel Guan Wei Ow, Joline Si Jing Lim, Grace Kusumawidjaja, Qingyuan Zhuang, Ru Xin Wong, and Fuh Yong Wong performed selection of notable articles for review, critical review of the literature, composition of the manuscript and final approval. Veronique Kiak Mien Tan performed selection of notable articles for review, composition of the manuscript and final approval.

Acknowledgements

The authors acknowledge all medical and nursing staff who provided care for the patients at National Cancer Centre Singapore, National University Cancer Institute, Singapore, and Singapore General Hospital and colleagues in their respective departments who contributed to the drawing up of institutional practice guidelines during the COVID-19 outbreak.

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Received in final form 8 June 2020

Accepted 15 June 2020

Accepted Manuscript published online 16 June 2020