Breast Cancer

Cancer Centre of Southeastern Ontario
Standard Management Guidelines

Intended for use by Clinicians and Health Care Providers involved in the Management or Referral of adult patients with Breast Cancer. Management of Breast Cancer necessitates incorporation of Patient Values, and Physician Expertise and Recommendations. Guidelines may not be suitable for every patient, and the patient - physician relationship is paramount. If a physician is considering managing a patient in an alternative way to guidelines, discussion at a Multidisciplinary Case Conference is strongly encouraged. These guidelines are for the common variants of breast cancer - ductal and lobular carcinoma. Other histologies of epithelial breast cancer and breast sarcoma require different management strategies.

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Section	Activity	Activity Description	Details	Reference(s)
I	Presentation	Asymptomatic Screening	BiRads 4, 5 lesions refer to surgery or Breast Assessment Program BiRads 3 - followup/biopsy as per radiologist recommendations	
		Symptomatic Detection	Suspicious Palpable Breast Lump Palpable Axillary or Supraclavicular Lymph Node (s) Suspicious Cystic fluid Non-Clear Nipple Discharge Any of the above mandates a surgical or breast health referral, REGARDLESS of mammogram/imaging results.	
		Breast Erythema	Breast inflammatory changes in a non-breast feeding patient mandates urgent communication between initial physician and surgeon (i.e. telephone call)	
II	Initial Surgical Assessment		All patients should be staged clinically using History and Physical for distant and local disease, obvious contraindications to either surgery or radiation therapy.	
A	Diagnosis	i) Clinical Node negative, non-palpable	Image guided core biopsy of Breast recommended	
		ii) Clinical Node negative, palpable primary	Image guided core biopsy of Breast recommended Clinical biopsy an option if image guided core biopsy not feasible in reasonable time frame, and/or if breast conserving surgery is not considered an option. For patients in whom breast conserving surgery may be an option, image guided biopsies allow the biopsy of clinically undetected multifocal tumours	

Section	Activity	Activity Description	Details	Reference(s)
		iii) Clinical N1	Image guided core biopsy of Breast recommended Image guided biopsy of axillary lymph node recommended	
		iv) Clinically T3 or T4 Non-inflammatory	Core biopsy of breast recommended. U/S guided lymph node biopsy OR sentinel node procedure recommended if feasible.	
		v) Any T, Clinical N2 or N3	Core biopsy of breast recommended U/S guided biopsy or Clinically directed biopsy of Most accessible and distant node (i.e. if axillary and supraclavadenopathy, biopsingsupraclav reasonable). If internal mammary lymphadenopathy on imaging, biopsy likely not feasible	
		vi) T4d	Core biopsy of breast and skin biopsy recommended Sentinel Node biopsy not indicated (time delay AND questionable effectiveness) A clinically positive lymph node may be biopsied if treatment is not delayed. Caution in interpreting negative FNA results in the setting of clinically positive nodes in this setting must be exercised	
		vii) T any N any clinical M1	Core biopsy of breast recommended. Biopsy of distant site if feasible.	

Section	Activity		Activity Description	Details	Reference(s)
B	Pathology of Initial Diagnostic Specimen	i)	Non-Locally Advanced	Histologic type. Invasive or Non-invasive. *Note, ASCO-CAP and CCO guidelines differ on role of biomarkers.	ASCO-CAP Guideline
		ii)	Patients considered for neo-adjuvant systemic therapy (e.g. Locally-Advanced) or Metastatic	Histologic type. Invasive or Non-invasive. Estrogen, Progesterone, and HER2 status.	
	Pathology Requirements from Local Surgery	i)	Non-Invasive Breast Cancer	Primary tumour As per synoptic criteria for DCIS. Size, grade, margins status, histological subtype. Estrogen receptors only required if requested.	
		ii)	Invasive Early Stage Breast Cancer	Primary Tumour • As per synoptic criteria for invasive breast cancer • Sentinel lymph node/lymph nodes as per synoptic criteria. Amount of extracapsular extension required if present. Immunohistochemistry not routinely required. • Recurrence Score (OncotypeDx) requested if tumour greater than 1.0 cm, estrogen receptor positive, her 2 negative, lymph node negative, and patient less than 70 years of age. • For patients greater than 70, or tumours less than 1.0 cm, recurrence score may still be ordered by medical oncologist.	College of American Pathologists (CAP): Invasive Breast Cancer Pathology Protocol

Section	Activity	Activity Description	Details	Reference(s)
		iii) Locally-Advanced Breast Cancer treated with Neo-Adjuvant Chemotherapy	Primary tumour • As per synoptic criteria for invasive breast cancer, including y prefixes. Biomarkers (ER,PR, HER2) to be repeated if they were negative on initial core biopsy.	
C	Breast Imaging	i) Early Stage Breast Cancer (T1 or T2, N0 or N1)	• Bilateral mammogram. • MRI of breasts recommended if breast conservation therapy considered in following indications: • Known BRCA positive patients. • Age 35 or less. • Mass not assessable on mammogram. • Lobular breast cancer.	
		ii) Locally Advanced Breast Cancer	• MRI of breasts) • Marking clip in tumour (whether or not breast conservation is considered)	
D	Investigations for Staging	i) Early Stage Breast Cancer (Pathologic Stage 1)	No routine imaging. Imaging only as directed by clinical findings.	CCO PEBC: Baseline Staging Tests in Primary Breast Cancer
		ii) Pathologic Stage 2	Bone Scanning optional (CCO recommendation is for, ASCO recommendation is against). Abdominal and Chest imaging discretionary, depending on symptoms or other risk factors (i.e. 4+ nodes).	CCO PEBC: Baseline Staging Tests in Primary Breast Cancer

Section	Activity	Activity Description	Details	Reference(s)
		iii) Locally Advanced or Pathologic Stage 3	Bone Scan, abdominal and chest imaging (US/Cxr or CT depending on physician discretion and availability)	CCO PEBC: Baseline Staging Tests in Primary Breast Cancer
D1	Special Considerations	Fertility/Pregnancy	Fertility preservation options are more feasible if initiated early in process. Early consultation with medical oncology and fertility medicine is encouraged to coordinate care. Management during pregnancy depends on stage of pregnancy and disease. Early consultation and discussion at MCC's is encouraged.	
		Hereditary Breast Cancer Syndromes	Patients with possibility of hereditary breast cancer syndromes should have this possibility considered early, as it may affect local management decisions. Criteria for referral may be viewed at the OBSP high risk program.	
		Male Breast Cancer	Partial mastectomy is not routine in male breast cancer. The use of aromatase inhibitors should be discouraged. Tamoxifen and chemotherapy +/- trastuzumab remain the mainstays of systemic treatment.	
		Breast Reconstruction	For patients who require mastectomy, multiple reconstruction options may be considered. Timing of reconstruction in relation to primary surgery, radiation therapy, and chemotherapy can be complex and patient/resource specific. For patients considering early reconstruction, discussion at a multi-disciplinary case conference prior to surgery is recommended, to ensure	

Section	Activity	Activity Description	Details	Reference(s)
			radiation considerations are incorporated into care. Patients who initially don't wish reconstruction may change their mind after a year or more from surgery, and this should also be facilitated.	
E	Management: DCIS or LCIS/ADH/ALH	Surgical Therapy	DCIS: Partial mastectomy with clear margins. OR Simple Mastectomy with Sentinel lymph node biopsy, based on Patient Preference, high risk features not wishing radiation, or large size (i.e. greater than 5.0 cm). LCIS/ADH/ALH - Surgical excision of LCIS or other pre-cursors is not recommended, unless the surgeon/radiologist feel the sample was not-representative.	CCO PEBC: Management of Ductal Carcinoma in Situ of the Breast
		Radiation Therapy	DCIS: Radiation Oncology Assessment required, and radiation to be considered. There is NO risk group that does not appear to have reduced risk of local disease from radiation, except mastectomy with clear margins. LCIS/ADH/ALH – no role for radiation therapy	CCO PEBC: Management of Ductal Carcinoma in Situ of the Breast
		Systemic Therapy	DCIS: Tamoxifen (TMXF) in premenopausal or postmenopausal women may be considered. Anastrozole (ANAS) or Exemestane (EXEM) may also be considered in postmenopausal patients. *Adjuvant tamoxifen or aromatase inhibitors may be offered to women with DCIS, after consideration of known risk	CCO PEBC: Management of Ductal Carcinoma in Situ of the Breast

Section	Activity	Activity Description	Details	Reference(s)
			factors: in particular age and margin status and whether or not radiation is given, and after confirmation of ER positivity. It should not be considered for women with bilateral mastectomies, with an increased risk of endometrial cancer or thromboembolic events (for tamoxifen), or for women with a life expectancy of <10 years or who have recently been on tamoxifen for prevention. The tamoxifen dose should be 20 mg/day for 5 years. LCIS/ADH/ALH: In premenopausal patients, tamoxifen (TMXF) may be indicated. In postmenopausal patients, raloxifene, tamoxifen (TMXF), exemestane (EXEM), or anastrozole (ANAS) are options.	
	Management: Early Invasive (cT1 or cT2, cN0)	Surgical Therapy	Partial mastectomy with Sentinel lymph node biopsy (if patient suitable/willing to have radiation) Simple mastectomy with sentinel lymph node biopsy, for multicentric disease. For select patients (i.e. over 80, extensive comorbidities), a SLN may not be required, presentation at tumour board is recommended)	
		Radiation Therapy	Adjuvant radiation therapy to the breast should be considered in all patients receiving partial mastectomy.	

Section	Activity	Activity Description	Details	Reference(s)
			Acceptable radiation alternatives include • Standard fractionation • Hypofractionation • Accelerated Breast Partial Irradiation in selected cases as per external guidelines. • Brachytherapy For patients who are definitely to receive chemotherapy, radiation should begin 4-6 weeks after the final dose of chemotherapy. For patients who are not receiving chemotherapy, radiation should begin within 8 weeks of the final surgical procedure For close or positive margins who are not suitable for further surgery (i.e. posterior margins), a boost to this area is considered. Margins will be considered negative if there is no cancer at inked margin.	
	Management: Early Invasive (pT1-T3, pN1/2) – sentinel lymph node positive	Surgical Therapy	Consideration of level 1 and 2 axillary dissection, in certain situations is reasonable, including patients with significant extranodal extension, greater than 3 Lymph Nodes positive. These patients should be discussed at multidisciplinary case conferences.	
		Radiation Therapy	For patients with sentinel lymph node positive disease treated with partial mastectomy, consideration may be given	

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			to including nodal areas in treatment fields. For patients with sentinel lymph node positive disease treated with simple mastectomy, consideration may be given to adjuvant post mastectomy radiation.	
	Management: Early invasive breast cancer – T1,T2 cN1 or pN1	Surgical Therapy	Partial or simple mastectomy. Level 1/2 axillary dissection if known node positive prior to surgery.	
		Radiation Therapy – pathologic node positive	For patients with partial mastectomy: post-operative nodal and breast radiation recommended. For patients with simple mastectomy: Adjuvant post-mastectomy chest wall radiation and nodal radiation recommended.	
	Management: Adjuvant Systemic Therapy for Early Breast cancer	Hormonal Therapy in Estrogen Receptor Positive or Progesterone Receptor positive breast cancer		
		Pre/Peri-menopausal	5 years of tamoxifen (TMXF) is considered most appropriate in most pre/peri menopausal patients. After 5 years, depending on menopausal status, aromatase inhibitors or additional tamoxifen MAY be considered (up to ten years at present).	

Section	Activity	Activity Description	Details	Reference(s)
		Post-Menopausal	Menopause Definition Patients must: Have had surgical documentation of a bilateral oophorectomy OR Age greater than 60 OR Amenorrheic for 12 months in women with intact uterus prior to chemotherapy OR Ovarian Radiation with No menses for 3 months OR FSH and estradiol in postmenopausal range prior to chemotherapy, in patients with hysterectomy No adjuvant hormones: May be reasonable in patient with limited life expectancy, small T1 grade 1 tumours. Otherwise, 5 to 10 years of adjuvant hormonal therapy, including tamoxifen (TMXF) and/or aromatase inhibitors are reasonable options for patients	CCO PEBC: Adjuvant Taxane Therapy for Women with Early-Stage, Invasive Breast Cancer
		Systemic Chemotherapy and antibody therapy in Early Breast cancer		
		General Chemotherapy principles and assessment – adjuvant/Neo-Adjuvant	If Patient is to have anthracyclines or long term treatment, may consider venous Access (PICC or PORT) If patient is to have anthracyclines, and has any cardiac risk or age over 50, order pre-chemotherapy MUGA scan or echocardiogram.	
		Invasive Breast Cancer Post-Surgical – indications for treatment with chemotherapy	Indications for Adjuvant Chemotherapy in suitable patients High Risk: Any ONE of the following should be considered	CCO PEBC: Adjuvant Taxane

Section	Activity	Activity Description	Details	Reference(s)
			high risk in patients with T1c disease or above • Lymph node positive disease (N1 or higher) OR Lymph node negative and ONE of the following • "Triple-Negative" Breast Cancer • HER2 positive breast cancer • Oncotype Recurrence Score greater than 25 (node negative) • T3 or T4 pathologic Intermediate Risk (may consider based on other factors, such as Oncotype score, or combinations of factors) • HER2 Positive T1a or T1b • "Triple-negative" – T1a or T1b • Grade 2 or 3 • Lymphovascular Invasion • Young Age (35 or under) • Oncotype intermediate score • Tumours over 2.0 cm *The use of online predictive and prognostic tools such as Adjuvant! Online and PredictPlus is recommended for personalized care.*	Therapy for Women with Early-Stage, Invasive Breast Cancer
		Adjuvant Chemotherapy and Trastuzumab Regimens	For high risk patients with no comorbidities or contraindications: • Anthracycline and Taxane Recommended: FEC-D or ddAC-T (AC-PACL(DD))	Cancer Care Ontario Adjuvant/ Curative/

Section	Activity	Activity Description	Details	Reference(s)
			For intermediate risk patients (including node-negative patients): • Consider high risk regimen (AC-PACL(DD) or FEC(D)) OR 4 cycles of Docetaxel Cyclophosphamide (CYCLDOSE) Acceptable if wish for shorter chemo or to avoid anthracyclines For patients with contraindications to anthracyclines and/or taxanes: • Consider Docetaxel Cyclophosphamide (CYCLDOSE) for 4 cycles OR oral CMF (CMF(PO))for 6 months may be appropriate. • CEF may be appropriate or FEC (FEC100) x6 if taxane contraindicated. For HER2 positive patients Tumours greater than or equal to 1.0 cm • FEC-DH (FEC-D) or ddAC-TH (AC-PACL(DD)+TRAS) (recommended if cardiac function is adequate). • If patients' cardiac status borderline or anthracycline not preferred, Docetaxel Carboplatin and Trastuzumab (CRBPDOCETRAS) for 6 cycles recommended; Docetaxel/Cyclophosphamide and Trastuzumab (CYCLDOCE+TRAS) is an alternative.	Neo-Adjuvant Intent Systemic Therapy

Section	Activity	Activity Description	Details	Reference(s)
			• Cardiac status is ideally to be assessed prior to initiation of any chemotherapy and again prior to initiation of trastuzumab. MUGA or ECHO are acceptable imaging modalities. • Cardiac status (ejection fraction) should be measured at baseline and every 3 months while on trastuzumab and follow recommended algorithm for dose delays. • Cardiology consults recommended if cardiac status precludes treatment or during treatment if cardiac dysfunction. • Consider following patient's cardiac status after completion of adjuvant trastuzumab, if there were significant ejection fraction drops during treatment. <u>Tumours < 1.0 cm</u> • Consider chemotherapy as part of evidence-building program (as per high-risk category)	

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	Management: Locally Advanced Breast Cancer (N2 or N3 OR T3 or T4)	Surgical Treatment: Locally Advanced Breast Cancer previously treated with Neo-Adjuvant therapy	<u>Breast Surgery should include a Partial Mastectomy or Mastectomy.</u> An option for a partial mastectomy may be considered if the following conditions are met: T3 or lower tumour pre-chemotherapy Patient willing to have radiation therapy to breast. Patient not a known BRCA carrier/high risk (relative contraindication <u>Lymph Node Management</u> If any of the following conditions are met, a lymph node dissection level 1/2 is required: 1. Positive sentinel OR U/S biopsy of Lymph node prior to chemotherapy. 2. T4d prior to chemotherapy. 3. Palpable lymph nodes unevaluated pathologically prior to chemotherapy. 4. Progressing primary tumour, regardless of lymph node status. Note: In the case of clinically apparent node positive disease, and a negative biopsy pre-chemotherapy, the consideration of a false negative result must be considered.	

Section	Activity	Activity Description	Details	Reference(s)
			Candidates for sentinel lymph node after Neo-Adjuvant chemotherapy: Patients with clinical T3/T4 N0 who have good response to Neo-Adjuvant chemotherapy, and had no sentinel node procedure prior to chemotherapy may be considered.	
		Radiation Therapy	Neo-adjuvant radiation may be considered in patients not suitable or not responding to systemic therapy. For patients responding to systemic therapy, radiation should be based on the pre-treatment stage of cancer, and include chest wall and nodal irradiation.	
		Endocrine Therapy	In patients not suitable for Neo-Adjuvant chemotherapy, consider Neo-Adjuvant hormones (aromatase inhibitor such as letrozole (LETR)) for 6 months or until best response, followed by mastectomy. Agent is to continue after surgery for a minimum of 5 years. In patients who received Neo-Adjuvant chemotherapy and are hormone receptor positive prior to or after chemotherapy, a minimum of 5 years of adjuvant hormonal therapy is recommended regardless of response to chemotherapy.	Cancer Care Ontario Adjuvant/ Curative/ Neo-Adjuvant Intent Systemic Therapy
		Chemotherapy and Antibody Therapy	Acceptable neo-adjuvant chemotherapy regimens in non-HER2 amplified patients with no contraindications. Manage as per high-risk (Adjuvant)	Cancer Care Ontario Adjuvant/ Curative/ Neo-Adjuvant

Section	Activity	Activity Description	Details	Reference(s)
			IF PATIENT IS STABLE OR RESPONDING, TREATMENT SHOULD CONTINUE AS PLANNED AT THE BEGINNING (i.e. don't avoid taxane just because patient responding well to FEC). For HER2 positive patients: Acceptable chemotherapy regimens in patients with HER2 amplified disease, and good cardiac function include the same regimens as in the adjuvant setting. If patient has borderline cardiac function or contraindication to anthracyclines: Docetaxel carboplatin Trastuzumab (CRBPDOCETRAS), OR Docetaxel Cyclophosphamide Trastuzumab (CYCLDOCE+TRAS) Cardiology Assessment to optimize function Post-operative adjuvant chemotherapy: For patients who have received a full regimen of pre-operative chemotherapy, postoperative adjuvant therapy is not recommended. An exception may be patients who have not had a full course of chemotherapy preoperatively. Patients should continue with their targeted and endocrine therapies.	Intent Systemic Therapy

Section	Activity	Activity Description	Details	Reference(s)
	Management: Metastatic Breast Cancer	Surgical Treatment (of breast)	PRIMARY BREAST SURGERY IN METASTATIC DISEASE: Hygienic Mastectomy if indicated for Local Control. Lymph node dissection only if nodes are grossly enlarged. Surgical treatment of other sites of metastatic disease, including resection of solitary CNS metastases, spinal surgery, orthopaedic stabilization, and resection of solitary lesions elsewhere (i.e. lung, liver) is beyond the scope of this guideline	
		Radiation Therapy	Radiation may be used for palliative purposes in metastatic breast cancer, including palliation of the primary tumour. Bony metastases may be radiated both for pain control and prevention of fracture in individual patients. Central nervous system (Brain, Spinal Cord, Leptomeningeal Disease) metastases may also benefit from palliative radiation therapy, for both symptomatic relief and prevention of complications. Symptomatic metastases elsewhere (i.e. lung, skin, axilla, neck, etc.) also often benefit from radiation therapy. Metastases to other sites, such as liver, adrenal gland, ovary etc. may also benefit from radiation therapy, and clinical trials are addressing the benefit of radiation therapy in some of these circumstances.	

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			For any of these issues, consultation with a Radiation Oncologist is recommended.	
		Systemic Therapy in Metastatic Breast Cancer		
		Endocrine Therapy	Aromatase inhibitors are first line therapy in patients with estrogen receptor or progesterone receptor positive, HER2 neu negative disease, who meet the following criteria: • No impending visceral crisis • Not currently on adjuvant aromatase inhibitor • Clearly postmenopausal. Considerations for initiating hormonal therapy include: Visceral vs. non-visceral disease and extent; estrogen receptor positivity of primary and metastatic tumour; long disease free interval. Factors may include length of time on previous hormone, impending tumour problems (i.e. visceral crisis, spinal cord etc.), and patient preference. For patients who have relapsed while on an aromatase inhibitor, or progressed while on, the following options may be considered. There is no evidence for sequencing of these various agents.	Cancer Care Ontario Adjuvant/ Curative/ Neo-Adjuvant Intent Systemic Therapy

Section	Activity	Activity Description	Details	Reference(s)
			For second AND above lines of hormonal therapy in postmenopausal patients sensitive/predicted to be sensitive to hormone therapy, options include: • Fulvestrant 500 mg dosing (Q28d) • Everolimus 10 mg daily plus exemestane 25 mg daily • Tamoxifen 20 mg/day (TMXF) • Other aromatase inhibitors (exemestane 25 mg daily (EXEM), anastrozole (ANAS) 1mg daily, letrozole (LETR) 2.5 mg daily) • Megesterol Acetate 160mg daily • Estradiol 6 mg daily	
		General Principles of Chemotherapy in Metastatic disease	1. Venous access using Port usually indicated in metastatic setting. 2. Prophylactic growth factors NOT warranted (dose reductions are). 3. For patients on oral chemotherapy, blister packing medications, and counselling recommended. 4. Chemotherapy is to extend and enjoy life. Treatment interruptions for life events (i.e. travel, etc.) are warranted. 5. Chemotherapy should not be given concurrently with a hormonal treatment. 6. There is no indication that one form of sequencing is preferred over another in most cases. Options may	

Section	Activity	Activity Description	Details	Reference(s)
			depend on patient circumstances, toxicities, drug reimbursement costs etc. 7. Assessments of progression should follow general palliative principles, with patient outcome outweighing imaging, outweighing tumour markers. Bone scans (in general) should not be repeated more than once per year. Screening for asymptomatic disease in the brain at regular intervals is not currently recommended, regardless of the risk of brain metastases. Patients with good responses to chemotherapy may have several lines of chemotherapy with effect.	
		Metastatic Breast Cancer (Estrogen receptor positive)	First line chemotherapy may include an anthracycline, if not received previously or long Disease free interval (i.e. FEC50, FAC, AC, single agent adriamycin). There is no evidence that one anthracycline is superior or less toxic than another (doxorubicin or epirubicin). High dose epirubicin (i.e. 100 mg/m2) or dose-dense therapy are not recommended in palliative setting). First line chemotherapy may include docetaxel (DOCE) Q3 wks (75-100 mg/m2), growth factors not recommended. Paclitaxel (PACL) 80mg/m2 weekly, vinorelbine (VINO) 30 mg/m2 weekly, nab-Paclitaxel (NPAC) 100 mg/m2 weekly, or capecitabine (CAPE) 1250 mg/m2 BID PO 14 days are all	Cancer Care Ontario Palliative Intent Systemic Therapy

Section	Activity	Activity Description	Details	Reference(s)
			options for first line therapy and above. Combination treatments (doce/cap (DOCECAP) or pacl/gem (DOCEGEMC) should be only used if rapid cytoreduction necessary. Beyond First line treatments additionally include: eribulin (ERIB), gemcitabine combinations (DOCEGEMC, CRBPGEMC, CISPGEMC), CMF (CMF(PO)), and metronomic chemotherapy (daily oral cyclophosphamide (CM(PO)), etc.)	
		Metastatic Breast Cancer "Triple negative"	The same chemotherapy options as for ER positive disease are reasonable in triple-negative disease. Carboplatin and Gemcitabine (CRBPGEMC), or Carboplatin or cisplatin alone or in combination are also treatment options.	Cancer Care Ontario Adjuvant/ Curative/ Neo-Adjuvant Intent Systemic Therapy Cancer Care Ontario Palliative Intent Systemic Therapy

Section	Activity	Activity Description	Details	Reference(s)
		HER2 targeted therapy	General Principles: 1. Trastuzumab (TRAS) (or Trastuzumab/pertuzumab (PERT+TRAS)) should be continued until extra-cranial disease progression. 2. Brain metastases should be treated aggressively if they are the only site of metastases. Brain metastases do NOT constitute progression on their own, and systemic treatment should be unchanged. 3. Cardiac status should be assessed at baseline. Subsequent cardiac assessments are driven mainly by symptoms, and possibly periodic evaluations with MUGA/echocardiogram. Routine cardiac assessment Q3 months for patients with metastatic disease under good control is not indicated. **Regimens:** First line treatments include: • Trastuzumab, docetaxel/paclitaxel or nab-paclitaxel, and pertuzumab (as first line only) – preferred option • Trastuzumab and either: docetaxel (DOSE+TRAS), weekly paclitaxel (NPAC(W)+TRAS), or docetaxel and carboplatin, or nab-paclitaxel (NPAC+TRAS). Trastuzumab and vinorelbine (VINO+TRAS) is also an option.	Cancer Care Ontario Palliative Intent Systemic Therapy

Section	Activity	Activity Description	Details	Reference(s)
			Second line options include: • Trastuzumab-emtansine (KADC), if failed single agent trastuzumab, or early relapse on adjuvant trastuzumab-preferred option. • Trastuzumab/capecitabine (CAPE+TRAS) is an option for second line or above treatment (or continuation of trastuzumab with a different chemotherapy backbone) • Capecitabine plus Lapatinib (CAPELAPA) (only as second or above line of therapy) • Anthracycline based chemotherapy (DOXO, DOXO(W), EPIR(W)) (for patients not on trastuzumab). Consider use after HER2 based lines of therapy are expired. • Trastuzumab (TRAS) and hormonal therapy (aromatase inhibitor or tamoxifen) for low volume metastatic disease ER positive, or after chemotherapy. (NOT FUNDED IF CHEMO NOT RECEIVED)	
		Bone targeted therapy (bisphosphonates and denosumab)	In the presence of bone metastases, • Clodronate 1600 mg PO daily • Pamidronate (PMDR) 90 mg IV Q4 wks or 60 mg Q3wks • Zoledronic acid (ZOLE) 4 mg IV Q4 wks • Denosumab (DENO) 120mg SQ Q4wks Patients should have oral examination regularly while on bisphosphonates, and ideally prior to beginning therapy. Bone agents should be held prior to invasive dental procedures.	Cancer Care Ontario Adjuvant/ Curative/ Neo-Adjuvant Intent Systemic Therapy Cancer Care

Section	Activity	Activity Description	Details	Reference(s)
			If patients progress while on a bisphosphonate, a switch to denosumab or zoledronic acid may be attempted, although evidence is weak. In patients with stable metastases (over 24 months), work is underway examining lower frequency of administration. It is reasonable to consider de-escalation of bisphosphonate therapy after two years.	Ontario Palliative Intent Systemic Therapy
F	Follow-up with No Evidence of Disease	Follow-up with No Evidence of Disease	Follow-up for patients with no evidence of disease should include mammographic screening for new breast cancers or loco-regional recurrences, and assessment/education for distant metastases. For patients on hormonal therapy, assessment also includes assessment of toxicities, medication adherence, and concomitant medications. Patients should continue with other screening and prevention recommendations for malignancy, such as colon and cervical cancer screening and smoking cessation. Patients should also be asked periodically regarding new breast or ovarian cancers in the family, as this may affect eligibility for genetic testing. Follow-up should be performed by the patient's family physician in most cases. Separate guidelines are available.	CCO PEBC: Models of Care for Cancer Survivorship
		i) Determination of Metastatic Disease	No routine tests are recommended in asymptomatic patients with a history of breast cancer to screen for metastatic disease.	

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			If patients have signs or symptoms suggestive of metastatic disease (bone pain, back pain, weakness, abdominal pain, weight loss, breathing difficulties, persistent cough etc.), then investigations to confirm metastatic disease are recommended. If possible, a biopsy of the metastatic site is recommended to confirm malignancy and receptor status.	
G	Controversies	Early Stage (T1, T2, N0, N1, N2)	The use of MRI scans of both breasts in patients undergoing breast conserving surgery is unclear in terms of which patients require it.	
		i) Early Stage – evaluation of lymph node status in patients who received Neo-Adjuvant Therapy	Significant interest in Canada and worldwide has been in the use of neo-adjuvant chemotherapy in the non-locally advanced population, largely to understand biology of disease and utility of systemic therapies. This is not currently the practice in Kingston. One area of controversy is in the proper lymph node assessment of these patients, and whether it is suitable to perform sentinel node biopsy only after neo-adjuvant chemotherapy.	
		ii) Adjuvant	The duration of adjuvant hormonal therapy is controversial, especially for those who received an aromatase inhibitor during their first five years of adjuvant hormones. MA17R and NSABP B-42 will be addressing these questions. The use of pertuzumab in the neo-adjuvant setting in HER2	

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				positive disease is controversial, as is the use of platinum compounds in the neo-adjuvant setting in "triple-negative" disease. The management and timing of chemotherapy and re-resection in patients who require re-resection for positive margins is unclear.	
		iii)	Bone-Targeted Agents	Adjuvant bisphosphonate trials have been equivocal, although a meta-analysis showed some benefit in the post-menopausal estrogen receptor positive patients, it has not yet been published. Adjuvant denosumab trials are pending. In the absence of the publication of new evidence, adjuvant and neo-adjuvant bone targeted agents are not indicated.	
H	Clinical Trials	i)	Radiation Trials	Current clinical trials in radiation include the LUMINA study, examining whether adjuvant radiation can be omitted for some patients after partial mastectomy for patients over the age of 60, with completely excised tumours and on hormonal therapy. Future trials may include the optimal use of radiation in patients with sentinel lymph node positive breast cancer.	Cancer Centre of Southeastern Ontario Clinical Trials
		ii)	Surgical Trials	There are no current surgical trials in Breast Cancer open in Kingston.	Cancer Centre of Southeastern Ontario Clinical Trials

Section	Activity	Activity Description	Details	Reference(s)
		iii) Systemic Therapy Trials	Current clinical trials in systemic therapy include a study in patients with metastatic breast cancer using a novel virus based therapy – Reolysin, in combination with chemotherapy. A second trial is looking at HER2 positive, node positive patients in the adjuvant setting, using trastuzumab-emtansine or pertuzumab-trastuzumab. Future clinical trial directions may involve adjuvant trials in estrogen receptor positive breast cancer and triple negative breast cancer.	Cancer Centre of Southeastern Ontario Clinical Trials

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Revisions

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- 2014/07/14: Edits to text and reference links; added in table of contents and section links
- 2014/08/07: Edits to text by clinical lead (A. Robinson)
- 2014/08/13: Finalization of edits by clinical lead (A. Robinson). Addition of reference links
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- 2014/10/04: Edits and feedback from Breast Disease Site Group Retreat (held October 4th 2014)
- 2014/10/16: Discussion for approval at Disease Site Group Chairs Council (held October 16th 2014)
- 2014/10/20: Edits after feedback from Disease Site Group Chairs Council (held October 16th 2014)
- 2014/12/03: Edits by clinical lead (A. Robinson), addition of QBP regimen links

Glossary

[Insert glossary of terms here]