2023 Systemic Adjuvant Therapy for

ER-Positive / HER2-Negative Early Breast Cancer Consensus

主編 台灣乳房醫學會

TBCS

台灣乳房醫學會

Taiwan Breast Cancer Society

Preface

早期乳癌的治療策略對於提高病人的存活率和生活品質至關重要，隨著不斷演進的醫學知識和技術，理應能夠提供更有效的方法和更全面的照護，然而卻也因為臨床醫事人員能夠使用的工具更多，以及多元化的病人需求與背景，讓選擇出最適合的治療方式這件事情變得更為複雜。

因此我們希望能夠藉由這本指引整合更多關於荷爾蒙受體陽性的早期乳癌治療的參考資訊，從生物標記、高危險復發因素及性腺激素釋放素促進劑 (GnRHa)，再到細胞週期素激酶抑制劑 (CDK4/6 Inhibitor)、PARP inhibitor 的新方法。我們將盡力將每個主題的最新研究成果和臨床應用整合到文章中，以提供全面且有用的資訊。

在編寫指引的過程中，我們的編輯團隊經過了三次會議，包括線上和實體會議型式的討論，仔細審查了最新的醫學文獻和相關研究，並與多位領域專家進行了廣泛的討論，這些討論和修正的過程是關鍵，確保這本指引的可靠性與實用性。因此，我們希望這份指引能夠提供臨床醫事人員更多的參考資訊，幫助他們做出更明智和符合病人需求的治療決策。

最後，我代表台灣乳房醫學會感謝編輯團隊各位醫師的參與和支持，他們的專業知識、經驗和奉獻精神使得這份指引得以完成，同時也期待這份共識能夠為病人和乳房疾病治療帶來更多的福祉和價值。

台灣乳房醫學會 理事長

陳守棟 于 2023 年 6 月

特別感謝以下專家提供寶貴建議（依姓氏筆畫排列、職稱省略概以醫師稱謂）

于承平、王明暘、李國鼎、沈士哲、沈陳石銘、周旭桓、林季宏、林金瑤、侯明鋒、俞志誠、施昇良、洪志杰、洪志強、洪朝明、洪進昇、張金堅、張振祥、張源清、張献崑、張端瑩、張耀仁、莊捷翰、許桓銘、郭文宏、郭玟伶、郭耀隆、陳守棟、陳芳銘、陳訓徹、陳偉武、陳達人、曾令民、黃其晟、黃俊升、葉顯堂、廖國秀、趙大中、趙祖怡、劉良智、劉峻宇、歐陽賦、蔡青樺、鄭翠芬、盧彥伸、賴峻毅、賴鴻文、戴明燊、鍾為邦、饒坤銘等諸位醫師。

本治療共識僅做為參考，因每人狀況不同，而由各醫師選擇最適當之處置方式，不作為醫療訴訟用。

Agenda

Topic	Speaker	Moderator
Opening	陳守棟 理事長 / 台灣乳房醫學會	
Revision of ER(+) HER2(–)MBC statement (based on update finding from SABCS 2022)	盧彥伸 教授 / 臺大醫院	張金堅 教授 / 臺大醫院
諮詢顧問：侯明鋒 教授 (高醫附醫)		
Clinical Risk Stratification for ER (+)/HER2(–) EBC and the Role of Neoadjuvant Endocrine Therapy	周旭桓 醫師 / 長庚醫院	戴明燊 主任 / 三軍總醫院
Biomarkers for Adjuvant Endocrine and Chemotherapy in Early–Stage Breast Cancer	陳偉武 醫師 / 臺大醫院	郭文宏 醫師 / 臺大醫院
Principles of Adjuvant Chemotherapy and When to Consider Neoadjuvant Chemotherapy	林金瑤 主任 / 台中慈濟	鄭翠芬 主任 / 新光醫院
諮詢顧問：俞志誠 教授 (三軍總醫院)		
PARP Inhibitor for ER(+)HER2(–) Early Breast Cancer	張端瑩 醫師 / 臺大醫院	趙祖怡 副院長 / 台北癌症中心
Other Choices of Adjuvant Chemotherapies or Adjuvantives	莊捷翰 醫師 / 高醫附醫	陳芳銘 副院長 / 大同醫院
CDK4/6 Inhibitors for ER(+)/HER2(–) Early Breast Cancer	鍾為邦 醫師 / 成大醫院	張振祥 主任 / 新樓醫院
諮詢顧問：沈陳石銘 教授 (北醫附醫)		
Adjuvant Endocrine Therapy for Post–Menopausal Patients	賴峻毅 醫師 / 臺北榮總	趙大中 醫師 / 臺北榮總
Adjuvant Endocrine Therapy for Pre–Menopausal Patients	黃其晟 秘書長 / 台灣乳房醫學會	洪朝明 院長 / 義大癌醫
Update on immunotherapy for early TNBC	郭玟伶 主任 / 長庚醫院	葉顯堂 副院長 / 羅東博愛
Panel Discussion	Working Group	黃俊升 教授 / 臺大醫院
Wrap up & Closing	陳守棟 理事長 / 台灣乳房醫學會	

Contents

Strength of the Recommendation and Quality of Evidence

Strength	Recommendation
A	Strong recommendation for use
B	Moderate recommendation for use
C	Marginal recommendation for use
D	Recommendation against use

Quality	Evidence
I	Evidence from at least 1 properly designed randomized, controlled trial
II	Evidence from at least 1 well–designed clinical trial, without randomization; from cohort or case–controlled analytic studies (preferably from > 1 center); from multiple time series; or from dramatic results of uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive case studies

1. AGREE Next Steps Consortium. AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ 2012; 182: E839—E842
2. Grading quality of evidence and strength of recommendations in clinical practice guidelines part 3 of 3. The GRADE approach to developing recommendations. Allergy 2011; 66:8
3. Annals of Hematology (2018) 97:1271—1282

The Principle of Voting for Strength of Recommendation

Strength	Recommendation
A	Strong recommendation for use
B	Moderate recommendation for use
C	Marginal recommendation for use
D	Recommendation against use

For the "Strength of Recommendation A and B", a majority panel vote of at least 85% is required.

For the "Strength of Recommendation C", a panel vote of at least 50% (but less than 85%) is required.

For recommendations where there is strong panel disagreement regardless of the quality of the evidence, "Strength of Recommendation D" requires a panel vote of at least 25%.

1. NCCN giudelines. Development and Update of Guidelines.

Clinical Risk Stratification for ER (+)/HER2(-) EBC and the Role of Neoadjuvant Endocrine Therapy

—— 長庚醫院 / 周旭桓 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Clinical and pathological parameters for risk stratification of ER(+)/HER2(–) early breast cancer should include the patient's age, tumor size, node status, tumor grade, ER expression level, Ki–67 and response to neoadjuvant chemotherapy to individualize the personalized adjuvant treatment.	I	A	1,2,3
2. If a patient has stage I–II breast cancer, the clinician may use Ki–67 expression in conjunction with other clinical and pathologic parameters to guide decisions on adjuvant endocrine and chemotherapy when multigene assays are not available.	II	B	4,5,6
3. Ki–67 expression levels are most informative for prognosis when the level is < 5% (low proliferation) or > 30% (high proliferation) because the technical reliability of distinguishing values within this range is limited. The measuring Ki–67 level method needs to be standardized because the median Ki–67 level varied widely in different individual institutions.	II	B	4,5,6
4. A patient with 1–3 positive nodes ER+/HER2– breast cancer with a Ki–67 score of ≥ 20% may be offered 2 years of abemaciclib plus endocrine therapy, but KI–67 baseline with cut–off of 20% is prognostic not predictive for abemaciclib benefit.	I	B	3,7

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
5. If a patient is postmenopausal and had invasive breast cancer and is recurrence–free after 5 years of adjuvant endocrine therapy, the clinical treatment score post–5 years (CTS5) web tool may be used to calculate the estimated risk of late recurrence (recurrence between years 5–10), which could assist in decisions about extended endocrine therapy.	II	B	8,9
6. The CPS + EG staging system in ER+/HER2– patients receiving neoadjuvant chemotherapy may be used for the clinical risk stratification, which could adjust in decisions about adjuvant therapy.	II	B	10,11
7. If neoadjuvant chemotherapy is contraindicated or not available, neoadjuvant endocrine treatment in ER+/HER2– EBC patients is a rational alternative treatment option with lower toxicities compared with neoadjuvant chemotherapy which is still the standard treatment.	III	B	12,13,14
8. If a patient is postmenopausal and has breast cancer, there is insufficient evidence to use baseline Ki–67 expression or Ki–67 level after 2 weeks or PEPI score of neoadjuvant aromatase inhibitor (AI) therapy to guide decisions on adjuvant endocrine and chemotherapy.	III	B	12,13,14,15

◎ Reference

1. Hongchao Pan, Richard Gray, Jeremy Braybrooke, Christina Davies, Carolyn Taylor, Paul McGale, Richard Peto, Kathleen I Pritchard, Jonas Bergh, Mitch Dowsett, Daniel F Hayes, EBCTCG. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. N Engl J Med. 2017 Nov 9;377(19):1836-1846. doi: 10.1056/NEJMoa1701830.
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Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer

—— 臺大醫院 / 陳偉武 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Multigene expression signature could be applied to ER+/HER2– node–negative or node–positive with 1–3 positive nodes early–stage breast cancer to provide additional prognostic insights that could facilitate the discussion of adjuvant chemotherapy and endocrine therapy.	I	A	1
2. When multigene expression signature test result is not available, Immunohistochemistry 4 (IHC4) could be used for patients LN–negative or LN positive with 1–3 LNs to guided selection of chemotherapy and endocrine therapy. The interpretation of IHC results is recommended to perform by experienced breast pathologists.	I	B	1,2
3. Ki–67 is a prognostic marker and should not be used as the only biomarker for adjuvant chemotherapy or endocrine therapy. When the Ki–67 report is in doubt, clinicians could consult an experienced breast pathologist to validate or confirm the interpretation of Ki–67 level.	I	A	1,3
4. The recommendation regarding Oncotype Dx is shown in table 1:	I	A	4–6

» table 1

	Age	
Risk score	≤ 50	> 50
	N0	
0–15	recommend endocrine therapy	
16–25	consider chemoendocrine therapy*	recommend endocrine therapy
≥ 26	recommend chemoendocrine therap	
	N1 (LN1-3+)	
0–25	Insufficient evidence to use Oncotype Dx RS to guide treatment decision	recommend endocrine therapy
≥ 26		recommend chemoendocrine therapy
	N2-3 (LN ≥4)	
	Insufficient data to use Oncotype Dx RS to guide treatment decision	

* In a subgroup (n = 671, 23% of age <50; 7% of TAILORx) of Age ≤ 50, RS 16–20, low clinical risk, EndoCT treatment improved IDFS (recurrence, second primary, or death) but not distant recurrence risk (Sparano et al. NEJM 2019)

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
5. The recommendation regarding MammaPrint use is shown in Table 2:	I	A	7,8

» table 2

		Age	
		≤ 50	> 50
Clinical risk based on modified version of adjuvant online & LN 0–3	low–risk	Insufficient data to support MammaPrint test to guide adjuvant endocrine and chemotherapy	
	high–risk	Insufficient data to support MammaPrint test to guide decision for adjuvant endocrine and chemotherapy	May use MammaPrint test to guide decisions for adjuvant endocrine and chemotherapy

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
6. EndoPredict and Prosigna (PAM50) tests are prognostic and could be considered to assist in discussion of adjuvant chemotherapy and endocrine therapy in postmenopausal women with node–negative or node–positive with 1–3 positive nodes patients. There is insufficient data to support routine use of EPClin and Prosigna in premenopausal patients.	I	B	9, 10
7. If a patient has node–negative or node–positive with 1–3 positive nodes breast cancer and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer BCI test to guide decisions about extended endocrine therapy. There is insufficient data to use BCI for patients with 4 or higher LN involvement or premenopausal patients to guide extended endocrine therapy.	I	B	11,12

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
8. If a patient has node–negative breast cancer and has had 5 years of endocrine therapy without evidence of recurrence, there is insufficient evidence to use Oncotype DX, EndoPredict, Prosigna, Ki–67, or IHC4 tests to guide decisions about extended endocrine therapy.	II	B	1, 10

◎ Reference

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Principles of Adjuvant Chemotherapy and When to Consider Neoadjuvant Chemotherapy

—— 台中慈濟 / 林金瑤 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. In ER(+)/HER2(–) node–negative breast cancer, all tumors ≤ 0.5 cm (T1a) and most cases ≤ 1 cm (T1b), prognosis is good with endocrine therapy alone and adjuvant chemotherapy is usually not needed.	II	A	1–3
2. In patients with T1c–3N0–1 ER(+)/HER2(–) breast cancer, some clinicopathologic factors may consider adjuvant chemotherapy: younger age, histologic high grade, high Ki–67 and low ER expression.	II	A	2–8
3. Adjuvant chemotherapy is indicated in patients with T1–3, N2–3, or T4 ER(+)/HER2(–) breast cancer who have not received neoadjuvant chemotherapy.	II	A	10, 11
4. Neoadjuvant chemotherapy is indicated for inflammatory breast cancer and can be consider for ER(+)/HER2(–) breast cancer patients with clinical N2–3 nodal disease and T3–4 tumors.	II	A	12,13
5. Neoadjuvant chemotherapy can be considered for down–staging the tumor to achieve BCT and/or limited ALND in patients with ER(+)/HER2(–) breast cancer.	II	A	13–17
6. Adjuvant chemotherapy options range from anthracycline– containing regimens, or combined with taxane–containing regimens, or anthracycline–sparing (such as TC) regimens.	I	A	18–22
7. Adjuvant chemotherapy with anthracycline and taxane–containing regimens or TC regimens is recommeded for ER(+)/HER2(–) high–risk patients.	I	A	22–25

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PARP Inhibitor for ER(+)HER2(-) Early Breast Cancer

—— 臺大醫院 / 張端瑩 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Considered for those with gBRCA1/2m, and either LN ≥ 4 or CPS+EG ≥ 3 after NACT	I	A	1–2
2. For those who are gBRCA1/2m (+), and are both candidates for adjuvant olaparib or abemacilib, there are insufficient evidence to suggest which one is preferred.			3–6

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Other Choices of Adjuvant Chemotherapies or Adjuvantives

—— 高醫小港 / 莊捷翰 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Adjuvant bisphosphonate therapy (i.v. zoledronate or daily oral clodronate or ibandronate) should be discussed with all postmenopausal patients with primary breast cancer, irrespective of hormone receptor status and human epidermal growth factor receptor 2 status, who are candidates to receive adjuvant systemic therapy. Adjuvant bisphosphonates, if used, are not substitutes for standard anticancer modalities.*	I	B	1,2
2. Denosumab is not recommended for the prevention of metastasis.	I	B	1,2
3. Antiresorptive therapy is recommended for women receiving either an aromatase inhibitor (AI) or ovarian function suppression (OFS) for more than six months and having either a bone mineral density (BMD) T score of less than –2 or more than one risk factor for fracture.	I	A	1
4. Denosumab 60 mg every 6 months could be considered to prevent fractures in postmenopausal women with early breast cancer.	I	B	1

* Starting bisphosphonate therapy early, within 3 months of definitive surgery or within 2 months of completion of adjuvant chemotherapy.

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
5. The addition of 1 year S–1 to endocrine therapy in adjuvant setting significantly improves iDFS in HR+/ HER2– early breast cancer patients with risk factors which defines by prior treatment status: 1) When adjuvant chemotherapy is applied or patients received no prior adjuvant treatment: a) Positive axillary lymph node or lympho–vascular invasion b) Negative axillary lymph node with at least one of the following: i. Tumor size ≥ 3 cm ii. Grade 3 disease iii. Tumor size ≥ 2 to <3 cm and Grade 2 disease iv. Tumor size ≥ 2 to <3 cm or Grade 2 disease with Ki–67 ≥ 30% 2) When neoadjuvant chemotherapy is applied: a) Positive axillary lymph node before neoadjuvant chemotherapy b) Residual tumor after neoadjuvant chemotherapy	I	B	3

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CDK4/6 Inhibitors for ER(+)/HER2(-) Early Breast Cancer

—— 成大醫院 / 鍾為邦 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. A two–year addition of abemaciclib to endocrine therapy in the adjuvant setting significantly improved invasive disease–free survival in patients with high–risk early breast cancer, which has been defined as pN2 and pN3 or pN1 with at least one of the following: tumor size ≧ 5 cm, histologic grade 3, or Ki–67 ≧ 20%.	I	A	1, 2, 3

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Adjuvant Endocrine Therapy for Postmenopausal Patients

—— 臺北榮總 / 賴峻毅 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. For hormone receptor (HR)+ early breast cancers (EBC) who are postmenopausal at diagnosis, adjuvant endocrine therapy (ET) with aromatase inhibitors (AI) or tamoxifen may be given if not contraindicated.	I	A	1
2. For HR+ postmenopausal EBC patients, standard adjuvant ET include 5 years of AI, 2–3 years of AI followed by tamoxifen to complete 5 years, 2–3 years of tamoxifen followed by AI to complete 5 years, and tamoxifen 4.5–6 years.	I	A	2
3. For HR+ postmenopausal EBC patients who received tamoxifen 4.5–6 years, additional 5 years of tamoxifen or AI may be recommended.*	I	A	3,4,5
4. After being treated by AI for 5 years, extended ET for 2–5 years may be given to HR+ postmenopausal EBC patients with positive lymph nodes or tumors larger than 2 cm in size.*	II	B	6–9
5. Adjuvant AI for 10 years has not shown significant overall survival benefit over 7 years, and currently, the optimal length of extended AI is still unclear.	II	B	6–9

* Studies have demonstrated increased incidence of adverse effects (including but not limited to osteoarthritis, myalgia in AI, thromboembolic disease in tamoxifen) in patients receiving additional AI or tamoxifen

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Adjuvant Endocrine Therapy for Premenopausal* Patients

—— 臺北榮總 / 黃其晟 醫師

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. For hormone receptor (HR)+ early breast cancers (EBC) who are premenopausal at diagnosis, tamoxifen ± OFS or AI + OFS should be given if not contraindicated.	I	A	1,2,3
2. For HR+ EBC who are still premenopausal after 5 years of endocrine therapy, continue additional 5 years of tamoxifen if not contraindicated or no further therapy if the sufficiently low risk is impressed.	I	A	1,2
3. For HR+ EBC who are premenopausal at diagnosis and becomes post–menopausal after 5 years of endocrine therapy, continue additional 2 to 5 years of AI or tamoxifen may be given if not contraindicated or no further treatment is needed if the sufficiently low risk is impressed.	I	A	1,2, 5,6
4. For HR+ EBC who are premenopausal at diagnosis, OFS should be considered for those with a high risk of recurrence, including patients indicated for chemotherapy, and patients who do not achieve upfront ovarian function suppression or who later resume ovarian function within 24 months after chemotherapy–induced amenorrhea.	II	A	7,8
5. ASTRRA study: the addition of 2 years of OFS to tamoxifen improved disease–free survival (DFS) and overall survival (OS) in patients who remained premenopausal or resumed ovarian function after chemotherapy.	I	B	10

Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
6. Distant recurrence rate cutoffs of <5%, 5% to 15%, and > 15%, calculated by the Regan score, can be used to define low, intermediate, and high risk.	II	B	8,9
7. SOFT/TEXT data provided evidence of a benefit of AI over tamoxifen in DFS although not in OS. Meta-analysis of EBCTCG also indicates that using AI rather than tamoxifen with OFS can lower breast recurrence, distant recurrence but not breast cancer and overall survival.	I	B	9

* premenopausal: NCCN defines menopause as no menses for 1 year in the absence of prior chemotherapy or tamoxifen use, or no menses after surgical removal of all ovarian tissue. For chemotherapy-induced amorrhea, periodic menopause testing is warranted.

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2023 Systemic Adjuvant Therapy for

ER-Positive / HER2-Negative Early Breast Cancer Consensus

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