2021 Controversial Issue Consensus in Breast Cancer

主編 台灣乳房醫學會

台灣乳房醫學會
Taiwan Breast Cancer Society

Preface

台灣乳房醫學會從 2018 年開始邀請相關領域的專家們，一同推動一系列乳癌治療共識、制定標準臨床處置流程等。秉持加強乳癌疾病之醫療、教學及研究之宗旨精神，特參照國際準則及國內臨床實況，制定全國性的治療共識，且依證據強度設定建議等級，給予乳癌領域相關醫師遵循參考。

但至今仍有許多常見議題文獻實證結論不一，尚無法下定論述。因此在 2021 年初學會邀請多位專家們組成 Controversial Issue 共識會議小組進行會議籌備，擬定目前在乳癌治療中較具爭議性的議題，本人衷心感謝工作小組的辛勞付出。

本會於 2021 年 11 月 21 日，假臺北榮總致德樓正式舉辦「2021 Controversial Issue Consensus in Breast Cancer」，與全國專家學者們共同討論，聆聽多方建議且異中求同，會後彙整專家建議，經台灣乳房醫學會第八屆理監事審議通過，期盼能藉由本次的共識會議，提供一套在乳癌治療上的重要參考指引給臨床醫師。鑑往知來，醫學與時俱進，共同促進醫學之進步發展為吾人終生努力職志，誠摯期待各界先進能不吝指教、提供新知，共同為台灣乳癌治療盡最大努力，讓國人乳癌防治止於至善。

台灣乳房醫學會 理事長

曾令民 于 2022 年 4 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、王惠暢、王甄、李國鼎、杜世興、沈士哲 、沈陳石銘、林季宏、侯明鋒、俞志誠、洪志強、洪朝明、洪進昇、張金堅、張振祥、張源清、張獻崑、張耀仁、莊捷翰、許居誠、許桓銘、郭文宏、郭玟伶、郭耀隆、陳守棟、陳芳銘、陳訓徽、陳達人、曾彥敦、黃其晟、黃俊升、黃品逸、葉大成、葉顯堂、廖國秀、趙大中、趙祖怡、劉良智、劉建良、劉峻宇、歐陽賦、蔡宜芳、蔡青樺、蔡宛蓁、鄭翠芬、盧彥伸、蕭君平、賴鴻文、戴明燊、鍾為邦、羅喬、饒坤銘等諸位醫師。

本共識手冊僅做為參考，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	曾令民 理事長 / 台灣乳房醫學會	
Local–regional management after neoadjuvant therapy: what are the controversial issues?		
Breast and axillary management after NAC	羅喬 醫師 / 臺大醫院	陳芳銘 秘書長 / 台灣乳房醫學會
Image–guide biopsies and localization for non–palpable breast lesion during NAC	蔡宛蓁 醫師 / 和信醫院	黃俊升 部長 / 臺大醫院
Radiotherapy management after NAC	黃品逸 醫師 / 臺北榮總	沈陳石銘 教授 / 北醫附醫
The role of minimally invasive surgery in early breast cancer	郭耀隆 醫師 / 成大醫院	陳達人 教授 / 彰化基督教醫院
Panel discussion	羅　喬 醫師 / 臺大醫院 蔡宛蓁 醫師 / 和信醫院 黃品逸 醫師 / 臺北榮總 郭耀隆 醫師 / 成大醫院 歐陽賦 醫師 / 高醫附醫 洪進昇 醫師 / 北醫附醫 賴鴻文 醫師 / 彰化基督教醫院 鄭翠芬 醫師 / 新光醫院 蔡宜芳 醫師 / 臺北榮總	王惠暢 顧問 / 中國附醫 杜世興 教授 / 北醫附醫
Controversial issues in medical management of early breast cancer		
The role of anthracyclines in adjuvant chemotherapy	郭文宏 醫師 / 臺大醫院	張獻崑 醫師 / 長庚醫院
The extended endocrine therapy; the duration of GnRh agonists used in adjuvant endocrine therapy in premenopausal patients	蕭君平 醫師 / 高醫附醫	侯明鋒 教授 / 高醫附醫
Controversial issues in medical management of advanced breast cancer		
Should the PIK3CA and/or gBRCA testing be at the timing of 1st line treatment of HR(+) mBC, or after failure of 1st line (such as CDK4/6i)?	黃其晟 醫師 / 臺北榮總	陳訓徽 教授 / 長庚醫院
Panel discussion	郭文宏 醫師 / 臺大醫院 蕭君平 醫師 / 高醫附醫 黃其晟 醫師 / 臺北榮總 張源清 醫師 / 馬偕醫院 鍾為邦 醫師 / 成大醫院 葉顯堂 醫師 / 羅東博愛醫院 李國鼎 醫師 / 成大醫院	張振祥 主任 / 新樓醫院 張耀仁 副院長 / 台北慈濟醫院
Miscellaneous controversial issues		
The role of cell therapy in advanced breast cancer	戴明燊 醫師 / 三軍總醫院	俞志誠 教授 / 三軍總醫院
The role of immune checkpoint inhibitors and PARPi in TNBC (neoadjuvant, advanced disease, and ….)	林季宏 醫師 / 臺大醫院	盧彥伸 教授 / 臺大醫院
Nutritional supplements for breast cancer patients (vitamin D, glutamine, etc…)	郭玟伶 醫師 / 長庚醫院	陳守棟 醫師 / 彰化基督教醫院
Panel discussion	戴明燊 醫師 / 三軍總醫院 林季宏 醫師 / 臺大醫院 郭玟伶 醫師 / 長庚醫院 趙大中 醫師 / 臺北榮總 劉峻宇 醫師 / 臺北榮總 劉良智 醫師 / 中國附醫 洪志強 醫師 / 臺中榮總 曾彥敦 醫師 / 高雄榮總	趙祖怡 副院長 / 台北癌症中心 饒坤銘 副院長 / 義大癌治療醫院
Wrap up and closing	張金堅 教授 / 臺大醫院	

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.

Breast and axillary management after NAC

—— 臺大醫院 / 羅喬 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Resection margin after NAC: no ink on tumor	II	A	1, 2
2. Upfront SLNB before NAC in cN0 patients	II	C	3, 4
3. Improvement of the false-negative rate of SLNB in cN(+) -> ycN0 patients			
• 3.1 : Targeted axillary dissection (TAD) (Clipped node and sentinel lymph node were dissected)	I	A	5, 6
• 3.2 : >= 3 sentinel nodes removed, dual-mapping technique and ypN0 (i-)	II	A	7, 8, 9
4. Omitting ALND in ypN(+) (macrometastasis) patients	II	D	10, 11
5. Omitting ALND in ypN1mic (SLN) patients	II	D	12, 13
6. Omitting ALND in ypN0(i+) (SLN) patients	II	D	12, 13

Reference

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Image-Guide Biopsies and Localization for Non-palpable Breast Lesion during NAC

—— 和信醫院 / 蔡宛蓁 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Marker clip placement should be performed in breast cancer tumor bed before NAC.	III	A	1–3
2. Image (US, mammography, MRI) guided biopsy (or fine needle aspiration) should be performed for any suspicious nonpalpable breast lesions before NAC	III	A	3,4
3. Image (US, mammography or breast MRI) guided localization of (nonpalpable) breast cancer tumor bed for residual tumor and suspicious lesions should be performed after NAC before surgery	III	A	2,3
4. Specimen mammography +/– sonography after breast conserving surgery should be performed to confirm safe margin	III	B	

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4. **Consensus–Guideline–on–Image–Guided–Percutaneous–Biopsy–of–Palpable–and–Nonpalpable–Breast–Lesions.** *Breast Surgeons* 2018:1–5.

Radiotherapy management after NAC

—— 台北榮總 / 黃品逸 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
Reginal nodal irradiation			
◆ Clinical N0 → ypN0: observation	II	A	2, 4
◆ Clinical N+ → ypN+: regional nodal irradiation	II	A	1, 2, 5
◆ Clinical N2–3 → ypN0: regional nodal irradiation	II	A	2, 4, 5
◆ Clinical N1 → ypN0: • Regional nodal irradiation (cT3, cT4) • Observation: clinical small tumoe volume, ypT0, ypT1 Luminal A, older age	III	B	2, 5
Chest wall irradiation after mastectomy			
◆ Clinical T > 5 cm: chest wall irradiation	II	A	2, 4, 5

* ypN0: by SLNB or ALND

Reference

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The role of minimally invasive surgery in early breast cancer

成大醫院 / 郭耀隆 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Nipple–skin or skin sparing mastectomy	I	B	1–10
2. Endoscopic nipple–skin or skin sparing mastectomy	II	B	11–15
3. Robotic nipple–skin or skin sparing mastectomy	III	D	16–22
4. Minimally invasive procedure for omission of Surgery	III	D	23–27

Reference

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The role of anthracyclines in adjuvant chemotherapy

—— 臺大醫院 / 郭文宏 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. In luminal breast cancer, standard or dose dense anthracycline/cyclophosphamide/taxane combination would be recommended in luminal disease with higher stage or higher tumour burden.	I	A	1, 2
2. The non-anthracycline 'TC' regimen may be an effective substitute for anthracycline/cyclophosphamide/taxane combination , particularly in women with ER positive, HER2 negative cancers and lower risk TNBC such as secretory or adenoid cystic carcinomas or very early (T1aN0) tumours	II	A	3, 4 5, 6, 9
3. For Her-2 positive breast cancer, non-anthracycline regimen with targeted therapy could be considered. In neoadjuvant setting, post-surgical treatment could be tuned according to the condition of residual disease. In adjuvant setting, the use of anthracycline depends on tumor burden and severity of axillary lymph node involvement.	II	A	1, 7, 8
4. Sequential anthracycline/taxane-based regimen is the standard for the majority of TNBC patients who should receive chemotherapy.	II	A	1, 3, 9
5. In the neoadjuvant setting, there is high- to low-certainty evidence of equivalent outcomes for the sequence in which taxanes are delivered. Both sequence of anthracyclines and taxanes could be considered, especially in neoadjuvant setting.	III	B	10

Reference

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The Extended GnRH agonist in still premenopausal patients after initial 5-years of adjuvant endocrine therapy

—— 高醫附設中和紀念醫院 / 蕭君平 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Premenopausal women at diagnosis who become amenorrheic during adjuvant treatment with or without chemotherapy may have continued estrogen production from ovaries without menses. Panel suggests serial assessment of circulating LH, FSH, and estradiol to assure the true postmenopausal status if women are considered for extended endocrine therapy.	I	A	1, 2
2. Anti–mullerian hormone (AMH) could be used for checking ovary function status during or after initial 5–years of adjuvant endocrine therapy with/without ovarian function suppression. Baseline AMH level could be obtained before initiating either chemotherapy or endocrine therapy for future comparison.	III	B	3
3. For women who are premenopausal during diagnosis but became postmenopausal after initial 5 years of adjuvant endocrine therapy, Panel recommends considering extended endocrine therapy with either aromatase inhibitor or tamoxifen for additional 5 years.	I	A	4, 5
4. For women who are still premenopausal after initial 5 years of adjuvant endocrine therapy plus OFS, Panel recommends continuing tamoxifen alone (category 1). Additional 2~5 years. additional 2~5 GnRH agonist plus either tamoxifen or aromatase inhibitor may provide clinical benefit in high risk group, such as age <40, multiple axillary lymph node metastasis, high Ki–67, HER2 positive, intermediate or higher–risk genomic signature.	III	C	6, 7, 8, 9

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Should the PIK3CA and/or gBRCA testing be at the timing of 1st line treatment of HR(+) mBC, or after failure of 1st line (such as CDK4/6i)?

—— 臺北榮總 / 黃其晟 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Clinicians should use either next–generation sequencing or qPCR in tumor tissue or cell–free DNA in plasma to detect PIK3CA mutations. If no mutation is found in cell–free DNA, testing in tumor tissue, if available, should be considered as this will detect a small number of additional patients with PIK3CA mutations when alpelisib is indicated.	II	A	4
2. Although PIK3CA mutations can be found throughout all stages of breast cancer, mutations can be acquired during treatment in the metastatic setting. Therefore, test should be conducted for the most recent tumor tissue sample, and if no sample is available, cf–DNA testing may be an alternative.	II	B	1, 2
3. Testing for PIK3CA mutations in SOLAR–1 focused on specific activating mutations in PIK3CA, including exons 9 and 20 (mutation subtypes E542K, E545X, and H1047X). These mutations are the basis for the regulatory approval of the combination therapy.	II	A	7
4. Patients with PIK3CA mutations which are not part of the therascreen panel, or hotspot and non–hotspot PIK3CA mutations identified using sequencing–based assays with higher sensitivities than therascreen, might benefit from alpelisib.	III	C	5
5. Mutation N345K represented 5.5% of all PIK3CA mutations which was the fourth most frequent PIK3CA mutation in the BC dataset. Moreover, N345K confers a gain of function, and it has shown to increase sensitivity to PI3K inhibitors in preclinical models. However, N345K isn't included in the therascreen panel.	III	C	6
6. Mutation E726K (the sixth most frequently observed PIK3CA mutation) has been shown that as a single mutation it is weakly activating but as a double mutation (with E545K or H1047R) it is synergistically activating.	III	C	6
7. Assess for germline *BRCA1/2* mutations in all patients with ABC/MBC to identify candidates for PARP inhibitor therapy. The NCCN panel recommends assessing for germline *BRCA1/2* mutations in all subtypes.	II	B	4
8. *BRCA1/2* pathogenic/likely pathogenic mutations revealed from tumor only sequencing such as multi–gene panel should elicit reflux germline testing and indicate potential benefits from synthetic lethality. If no *BRCA1/2* variants revealed from tumor–only sequencing, it is less likely to identify additional germline mutations.	II	B	1, 2
9. Testing for the HRD phenotype rather than the discrete, causal genomic aberrations of *BRCA1/2* may identify additional patients likely to benefit from platinum and/or PARP inhibitor based therapy.	II	C	8

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The role of cell therapy in advanced breast cancer

—— 三軍總醫院 / 戴明燊 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Adoptive Cell therapy in advanced/metastatic breast cancer	II	C	1, 2, 3, 7, 8
2. Adoptive Cell therapy with chemotherapy in advanced/ metastatic breast cancer	III	NA	1, 8
3. Adoptive Cell therapy with immunotherapy (ICIs) in advanced/metastatic breast cancer	III	NA	6

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The role of immune checkpoint inhibitors and PARPi in TNBC (neoadjuvant, advanced disease, and ….)

—— 臺大醫院 / 林季宏 醫師

▶ Current Guideline:

- Pembrolizumab plus paclitaxel, docetaxel, is a preferred treatment for first–line therapy for PD–L1–positive (CPS ≥ 10) triple–negative ABC, either de novo or at least 6 months since completed (neo)adjuvant chemotherapy.[1]
- For patients with a gBRCA mutation, single agent PARPi (olaparib or talazoparib) is a preferred treatment option for those with triple–negative ABC.[2.3]

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. Atezolizumab plus nab–paclitaxel is an option for first–line therapy for PD–L1–positive (IC ≥ 1%) triple–negative ABC, either de novo or at least 12 months since completed (neo)adjuvant chemotherapy.	I	B	4
2. Pembrolizumab monotherapy in later lines for triple–negative ABC is an option for CPS ≥ 20.	I	B	5
3. Anti–PD1/PDL1 plus chemotherapy in later lines for triple–negative ABC is an option.	II	C	6, 7
4. PARP inhibitor for chemotherapy pretreated triple–negative ABC patients with germline PALB2 mutation or somatic BRCA1/2 mutation is an option.	II	A (gPALB2), B (*sBRCA1/2*)	8, 9

▶ Current Guideline:

- For stage II or III TNBC, neoadjuvant pembrolizumab + carboplatin + paclitaxel, followed by pembrolizumab + AC or EC, followed by adjuvant pembrolizumab is a preferred treatment.[10,11]
- For high–risk early TNBC and gBRCA1/2 mutation, adjuvant olaparib after completion of local treatment and neoadjuvant or adjuvant chemotherapy is a preferred treatment.[12]

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
1. For stage II or III TNBC, neoadjuvant atezolizumab + nab–paclitaxel, followed by atezolizumab + AC, followed by adjuvant atezolizumab is an option.	I	C	13
2. For stage II/III TNBC, adjuvant immune checkpoint inhibitor with chemotherapy for non–CR to neoadjuvant chemotherapy is an option.	III	C	14, 15
3. For stage II or III TNBC, adjuvant pembrolizumab plus chemotherapy is an option.	III	C	10, 11, 16
4. Considering immune checkpoint inhibitor use, low (1%–10%) ER–positive (and/or PgR–positive), HER2–negative ABC can be considered as TNBC.	II	B	17, 18, 19

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Nutritional supplements for breast cancer patients (vitamin D, glutamine, etc…)

—— 長庚醫院 / 郭玟伶 醫師

2021 Consensus Statement	Quality of Evidence	Strength of Recommendation	Key Reference
營養素彼此間並非獨立互無關連，某一種營養素的攝取，同時也代表某種飲食或生活習慣的暴露，相關性不代表直接因果關係，解讀應用不宜過度衍申。建議程度 (Strength of Recommendation) 為針對各項粗體字部分而非整句描述。	Common scientific concept	A	No need
1. **習慣性酒精飲用**與乳癌發生率強烈正向相關 。	II	D	1, 2, 3
2. **維他命 B 群**服用與乳癌發生率在低或無酒精飲用族群，呈現反向關連。	II	B	1, 2, 8
3. **非澱粉類高纖蔬果、類胡蘿蔔素(花青素、葉黃素、番茄紅素等)和鈣**的攝取，與乳癌發生率呈現反向相關。	II	B	3
4. **全黃豆類食品每日 30 公克**（約含 10–20mg 大豆異黃酮）對乳癌患者可能有益，但萃取的黃豆蛋白或大豆異黃酮補充則應該避免	II	B	3
5. **綠茶或綠茶多酚**食用安全性高但對乳癌治療的幫助尚未具充足證據支持	I	C	8
6. 化療前與化療中使用**維他命 B12** 與較差之乳癌無病存活率有關。	II	C	8
7. **維他命 D** 濃度與乳癌發生率呈現反向相關，與乳癌總體存活率呈現正向相關，特別是停經前乳癌 。但維他命 D 的口服攝取量與與乳癌發生率並無關連。**日曬為最佳維他命 D 補充法則 (每天 10 分鐘)** 。	II	B /A	4, 5, 6, 7
8. 維他命 D 為類固醇類荷爾蒙，**檢測血液 25OH–vitamin D 濃度**數值可知，但其濃度一般荷爾蒙一樣正常狀態下時有波動變化，高低濃度的界定值目前並無一致標準，也不需特別界定。	III	D	4, 6, 7
9. **高劑量維他命 D** 合併鈣補充（2000 IU~7100 IU/day），於服用乳癌藥物芳香環酶抑制劑患者，與較低之關節疼痛和骨骼流失有關連性。然而腸胃道吸收效果及相對應血液濃度與上述指標之關連性則缺乏。	II	C	3
10. 乳癌患者**刻意補充維他命 A,E,C, Coenzyme Q10, 及類胡蘿蔔素**在化療前和化療中使用，與較差之無病存活率和死亡率有關。	I	D	8
11. **麩醯胺酸 (glutamine)** 預防化療、標靶治療及放療引起之口腔、食道及皮膚上皮缺損以及預防噁心嘔吐症狀未獲許多治療指引推薦（建議冷療法） 。而其加速口腔粘膜損傷修復之證據缺少一致性的結論。	II	C	9, 10, 11, 12, 17
12. **ω–3 多元不飽和脂肪酸 (EPA, DHA)** 對於化療引起的周邊神經與血液毒性等可能改善，並減少芳香環酶抑制劑治療引起的關節疼痛和骨質鬆化。	II	C	3

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Note

台灣乳房醫學會
TAIWAN BREAST CANCER SOCIETY

2021
Controversial Issue Consensus
in Breast Cancer