Original Article

Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancer

The Singapore Cancer Network (SCAN) Gynaecological Cancers Systemic Therapy Workgroup

Abstract

Introduction: The SCAN gynaecological cancers systemic therapy workgroup aimed to develop Singapore Cancer Network (SCAN) clinical practice guidelines for the systemic therapy of endometrial (uterine) cancer. Materials and Methods: The workgroup utilised a modified ADAPTE process to calibrate high quality international evidence-based clinical practice guidelines to our local setting. Results: Three international guidelines were evaluated—those developed by the National Cancer Comprehensive Network (2015), the European Society of Medical Oncology (2013) and the Cancer Council Australia (2011). Recommendations on the role of chemotherapy following surgery in women diagnosed with endometrial cancer, the chemotherapeutic options for women with advanced or recurrent endometrial cancers and the role of chemotherapy in women with uterine papillary serous carcinoma or clear cell carcinoma were developed. Conclusion: These adapted guidelines form the SCAN Guidelines 2015 for the systemic therapy of endometrial (uterine) cancer.

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Key words: ADAPTE, Chemotherapy, Evidence-based, Review

Introduction

Endometrial (uterine) cancer is the fourth most common cancer in women in Singapore and the most common cancer of the female genital tract. It accounts for 6.2% of all cancers in women.[1] The age standardised incidence rate for endometrial cancer has increased significantly over the last 40 years from 4.1 per 100,000 in 1973 to 1977 to 13.1 per 100,000 in 2008 to 2012.[1] Amongst the ethnic groups, the age standardised incidence rate was highest among the Indians.[1] The Singapore cancer registry estimates there will be 350 new cases this year.[1] Endometrial cancer which is usually diagnosed in early stage has a high curative rate. Despite the rising incidence, endometrial cancer is associated with a lower mortality, and is the eleventh most common cause of cancer death in females in Singapore. There were 203 deaths from endometrial cancer for the period 2008 to 2012.[1] The majority of cases diagnosed are in women under the age of 50 years. The peak age at diagnosis is 50 to 59 years of age. The majority of cases are stage I cancers.[1]

There are several histological types of endometrial cancer. Among the subtypes endometrioid endometrial cancers have a favourable prognosis and typically present at an early stage. Other histologic types (e.g. serous, clear cell) are associated with a poorer prognosis.

The management of endometrial cancer has traditionally consisted mainly of surgery and radiation therapy. However a recent randomised controlled trial showed improved outcomes from treatment with chemotherapy in patients with high risk disease.[2] Other studies on the role of chemotherapy with more diverse patient selection and treatment protocols showed more variable outcomes for chemotherapy. To reflect evolving standards of care and practice, there is a need to systematically review existing high quality expert guidelines and to formulate a set of clinical practice guidelines to best suit our patients and resources in Singapore.

The SCAN Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancer

The SCAN Guidelines are clinical practice guidelines for the management of endometrial cancer. The guideline applies to women with endometrial (uterine) cancer, including uterine carcinosarcoma. The guideline does not

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apply to uterine leiomyosarcoma and endometrial stromal sarcoma.

These first edition guidelines are intended to serve as treatment recommendations by members of this working group regarding their views on current existing international guidelines for the management of endometrial cancer. While it hopes to harmonise the management of this disease, it is not intended to serve as the standard of care or to replace good clinical judgment and the individualisation of treatments.

Target Users of the Guidelines

The guidelines will be of interest to oncologists, oncology nurse specialists, pharmacists, allied health workers and general practitioners involved in the management of women with endometrial (uterine) cancer.

Guideline Recommendations/Development

The SCAN gynaecological cancers workgroup comprises a panel of 8 medical oncologists and one oncology pharmacist with special interests in the management of endometrial cancer. Membership of the workgroup was based on invitation of relevant Singapore medical oncology subspecialists. The workgroup elected its own chairperson and decided on its own scope. Guideline selection was conducted through workgroup consensus. Potential conflicts of interest were declared by the International Committee of Medical Journal Editors (ICMJE) guidelines. Secretarial support for the overall guideline development effort was provided by Annals, Academy of Medicine Singapore. No other financial support was obtained. Guideline searching was conducted by all members of the group. The group met once in person, and completed guideline development through email communication.

The ADAPTE framework[3] was used as a pragmatic structure and guidance for calibration of international high quality guidelines to the Singapore context. The framework involves 3 phases: set-up, adaptation and finalisation. During the set-up phase, available resources were considered. During the adaptation phase, high quality guidelines were selected for evaluation and structured approaches developed for guideline evaluation and selection. This involved the extraction of data on source guideline development, the setting up of mechanisms for selecting recommendations and also recognising possible dissent amongst panel members. Calibration of guidelines to the local context based on available Singapore data was encouraged. The finalisation phase involved writing, external review, stakeholder feedback, and the setting up of a mechanism for regular updating. For each individual recommendation, agreement was established by a simple majority for established international recommendations and by a two-third majority for independent local recommendations. Dissenting workgroup members were invited to include comments for each recommendation. International measures of cost-effectiveness for each recommendation were obtained where available but not used to inform the recommendations.

The panel felt that the following questions regarding systemic treatment of endometrial cancer should be addressed in these guidelines given that they are commonly encountered scenarios for medical oncologists treating patients with these cancers in clinical practice. As such, these guidelines set out to answer the following questions pertaining to systemic therapy of endometrial (uterine) cancer (Table 1):

1. What is the role of chemotherapy following surgery in women diagnosed with endometrial cancer?
2. What are the chemotherapeutic options for women with advanced or recurrent endometrial cancers?
3. What is the role of chemotherapy in women with uterine papillary serous carcinoma or clear cell carcinoma?

Only guidelines that were updated in the last 2 years were reviewed. Three international guidelines were selected for review (Supplementary Table 1):

- "NCCN Clinical Practice Guidelines in Uterine Neoplasms" (version 2.2015) by the National Cancer Comprehensive Network (NCCN, USA)[4]
- "Endometrial Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up" by the European Society of Medical Oncology (ESMO) – 2013[5]
- "Clinical Practice Guidelines for the Treatment and Management of Endometrial Cancer" by Cancer Council Australia – 2014[6]

These guidelines will be reviewed or updated every 2 years. If there are significant new developments that impact the management of endometrial cancer, it will be reviewed earlier.

1. What is the Role of Chemotherapy Following Surgery in Women Diagnosed with Endometrial Cancer?

It was unanimously agreed by all members of the workgroup that the NCCN guidelines version 2.2015, regarding the use of adjuvant chemotherapy in endometrial (uterine) carcinoma (EC), were sufficiently comprehensive and evidence-based for it to be adopted in Singapore.

In the specific context of endometrioid EC, all members agreed that all FIGO (International Federation of Gynecology and Obstetrics) stage II (although rare), III and IV patients who have had their disease resected should be offered adjuvant chemotherapy. This is based on the results from the pooled analysis of 2 randomised clinical trials

Table 1. Singapore Cancer Network (SCAN) Guidelines for the Systemic Therapy of Endometrial (Uterine) Cancer

	Guideline Recommendations
What is the Role of Chemotherapy Following Surgery in Women Diagnosed with Endometrial Cancer?	NCCN Guidelines: It was unanimously agreed by all members of the workgroup that the NCCN guidelines version 2.2015, regarding the use of adjuvant chemotherapy in endometrial (uterine) carcinoma (EC), were sufficiently comprehensive and evidence-based for it to be adopted in Singapore. Adjuvant chemotherapy should be offered to patients with endometrial cancer stage III/IV. Chemotherapy could be offered to women with stage 1B or II, grade III, with adverse risk factors, due to higher risk of extrapelvic relapse and possible benefit.
What are the Chemotherapeutic Options for Women with Advanced or Recurrent Endometrial Cancers?	ESMO Guidelines: The group unanimously endorsed the ESMO guidelines 2013 on the treatment of advanced endometrial cancer as it was felt to be the most comprehensive among the 3 chosen guidelines. The use of taxane - platinum-based chemotherapy should be considered as standard of care (in comparison to platinum-non-taxane combination); while the use of hormones can be considered. There is data to support the role of mTOR inhibitors in patients with metastatic/recurrent endometrioid endometrial cancer following failure of first-line chemotherapy.
What is the Role of Chemotherapy in Women with Uterine Papillary Serous Carcinoma or Clear Cell Carcinoma?	NCCN Guidelines: The group unanimously endorsed the NCCN guidelines version 2.2015 on the treatment of uterine papillary serous carcinoma or clear cell carcinoma. All the members agree that chemotherapy should be recommended for all stages of UPSC/clear cell, including stage I disease. NCCN recommendations were considered to be the most comprehensive and to best represent the current evidence.

ESMO: European Society of Medical Oncology; NCCN: National Cancer Comprehensive Network; UPSC: Uterine papillary serous carcinoma

(NSGOEC-9501/EORTC-55991 and MaNGO ILIADE-III) that were undertaken to clarify if sequential combination of chemotherapy and radiotherapy improves progression-free survival (PFS) in high risk endometrial cancer.[7] In the NSGO/EORTC study, combined modality treatment was associated with a 36% reduction in the risk for relapse or death (HR = 0.64; 95% CI, 0.41 to 0.99; *P* = 0.04). The result from the MaNGO-study pointed in the same direction (HR = 0.61), but was not significant. In combined analysis, the estimate of risk for relapse or death was similar but with narrower confidence limits (HR = 0.63; CI, 0.44 to 0.89; *P* = 0.009). Neither study showed significant differences in overall survival (OS). However, in combined analysis, OS approached statistical significance (HR = 0.69; CI, 0.46 to 1.03; *P* = 0.07) and cancer-specific survival was significant (HR = 0.55; CI, 0.35 to 0.88; *P* = 0.01). The results of these 2 studies suggest that addition of adjuvant chemotherapy to radiation improves PFS in endometrial cancer patients following surgical resection with no residual tumour and a high risk profile. However, it remains unclear if the addition of radiotherapy to chemotherapy improves the results.

There was, however, initially a difference in opinion regarding the role of adjuvant chemotherapy for patients with stage IA and IB fully staged uterine endometrioid cancer with grade III disease. Three workgroup members were not in favour of routinely offering chemotherapy to patients with stage IA/IB grade III endometrioid uterine carcinoma while 3 other members were of the opinion that these patients (especially those who are younger and/or who have additional risk factors for distant and/or vaginal recurrence e.g. lymphovascular and myometrial invasion) should be offered adjuvant chemotherapy together with a detailed discussion on the lack of high quality clinical data regarding its risks and potential benefit or lack thereof for PFS and OS in this context. One member had no comments on the issue and 2 members were absent from the discussion. Two members quoted the results of a retrospective data analysis of patient outcomes with endometrioid uterine cancer from KK Women's and Children's Hospital (KKWCH) showing that patients with IC (i.e. new FIGO 2009 stage IB) grade III uterine cancers without adjuvant chemotherapy had a 5-year OS of 89% (unpublished data), hence suggesting that there is likely to be minimal OS benefit for the addition of chemotherapy. One member proffered the opinion that the KKWCH data was not a randomised controlled study of adjuvant chemotherapy in early stage uterine cancer and it would therefore be inappropriate to infer too much from this single retrospective unpublished study of a small number of patients as a basis to define guidelines for practice in Singapore. Furthermore, 64% of patients in the NSGOEC-9501/EORTC-55991 and MaNGO ILIADE-III pooled analysis who showed benefit for adjuvant chemotherapy had stage I disease (IC n = 190 [36%], IB n = 109 [20%], IA n = 44 [8.2%]),[7] which would support the use of adjuvant chemotherapy in this subgroup of patients. Additionally, while the local data from KKWCH would suggest that OS outcomes for local patients with stage IB grade III are generally very good even without adjuvant chemotherapy, published data from other groups have also demonstrated improved disease-free survival and OS outcomes following adjuvant chemotherapy in early stage high risk endometrial cancer

(i.e. grade II-III, stage IB or II cancers with more than 50% myometrial invasion).[8] In view of published data suggesting that the addition of chemotherapy may improve outcomes for women considered to be at the highest risk of distant and/or vaginal recurrence (i.e. outer one-third myometrial invasion, grade II-III, and the presence of lymphovascular invasion LVSI), one member felt cautious about adopting the practice of not offering chemotherapy to stage IB uterine cancers as a standard of care on the basis of this single retrospective study. In reply, a member mentioned further data collection would be performed to update this series and to further delineate the effect of adjuvant treatment in patients with stage IB uterine cancer in Singapore. Until then, the group endorses the NCCN version 2.2015 guidelines in its entirety, including the use of adjuvant chemotherapy in combination with radiotherapy in patients with stage IB disease with high risk features, which have been defined in the NCCN guidelines as age, positive lymphovascular invasion, tumour size, and lower uterine segment or surface cervical glandular involvement. For patients with high risk stage IA disease, 3 members were not in favour of routinely offering chemotherapy to patients with high risk features, while 4 were of the opinion that these patients (especially those who are younger and/or who have additional risk factors for distant and/or vaginal recurrence e.g. lymphovascular and myometrial invasion) should be offered adjuvant chemotherapy together with a detailed discussion on the lack of high quality clinical data regarding its risks and potential benefit or lack thereof for PFS and OS in this context.

In terms of the choice of adjuvant chemotherapy regimen, the working group would suggest 4 to 6 cycles of 3-weekly carboplatin and paclitaxel to be used as the regimen of choice in this setting. Our preference for carboplatin plus paclitaxel in the adjuvant setting is based on the results of GOG 209 (currently unpublished), which was presented at the 2012 Society of Gynecologic Oncology Annual Meeting.[9] This trial compared carboplatin plus paclitaxel to the 3-drug regimen of paclitaxel, doxorubcin and cisplatin (TAP) in 1300 women with chemotherapy-naïve advanced uterine cancer, including women with stage III disease, and demonstrated that carboplatin and paclitaxel results in an equivalent overall response rate and similar PFS, but is also less toxic.[9]

There are currently no cost-benefit/cost-effectiveness analyses available with regard to the NCCN guidelines/ recommendations on adjuvant chemotherapy of uterine cancer.

2. What are the Chemotherapeutic and Hormonal Therapy Options for Women with Advanced or Recurrent Endometrial Cancer?

The group unanimously endorsed the ESMO guidelines 2013[5] on the treatment of advanced endometrial cancer as it was felt to be the most comprehensive among the 3 chosen guidelines.

Paclitaxel and platinum-based combination chemotherapy (carboplatin/paclitaxel) is the preferred first-line chemotherapy regimen for patients with advanced or recurrent endometrial cancer. In non-randomised trials, paclitaxel with carboplatin/cisplatin demonstrated a response rate of more than 60% and prolonged survival compared with historical non-paclitaxel based combination therapy. The results of GOG 2099 showed that the carboplatin and paclitaxel combination is non-inferior to the triple drug regimen in response rate and PFS, and is also less toxic.

The use of hormonal therapy can also be considered in certain circumstances. Hormonal therapy, mainly progestins, and less commonly tamoxifen or aromatase inhibitors, are recommended for endometrioid-type histology only. The predictors of response include well differentiated tumours, a long disease-free interval and site of disease (pulmonary metastases). The overall response rate to progestin is about 25%.

Endometrial cancer recurring after first-line chemotherapy is usually chemo-resistant. Various agents have been tested in small phase II trials. The PI3K/Akt/mTOR pathway is frequently upregulated in endometrial cancer because of the loss of the tumour suppression gene *PTEN*. There is emerging phase II data to support the role of mTOR inhibitors in patients with metastatic or recurrent endometrioid endometrial cancer following failure of first-line chemotherapy.[10] The mTOR inhibitor temsirolimus has been reported to have a 24% response rate in chemotherapy-naive patients. In previously treated patients, the response rate to temsirolimus is 4% with 46% disease stabilisation.[10] Predictive factors of response to mTOR inhibitors have not yet been identified.

Our recommendation is to first treat with hormonal therapy for patients with endometrioid-type histology who are asymptomatic with low volume disease. Symptomatic disease or high-grade/large volume disease should be treated with platinum and taxane combination chemotherapy.

3. What is the Role of Chemotherapy in Women with Uterine Papillary Serous Carcinoma or Clear Cell Carcinoma?

The group unanimously endorsed the NCCN guidelines 2015 on the treatment of uterine papillary serous carcinoma (UPSC) or clear cell carcinoma. All the members agree that chemotherapy should be recommended for all stages of UPSC/clear cell, including stage I disease.

In comparison with endometrioid adenocarcinomas, uterine serous and clear cell carcinomas are more aggressive histologic types and are considered high risk endometrial cancers. There is a paucity of data to help inform treatment recommendations for this group of patients, and they should be encouraged to participate in clinical trials. Most of the data on chemotherapy in these subtypes are largely retrospective or derived from randomised trials that included patients with all histologies. Treatment options include radiation therapy, adjuvant chemotherapy or a combined approach (chemotherapy plus radiation therapy). There is considerable evidence from retrospective series that platinum-based adjuvant chemotherapy for early (stage I and II) disease improves PFS and OS.[11,12] Platinum-based chemotherapy is recommended in patients with stage III or IV. The same chemotherapy regimens usually employed for epithelial ovarian cancer can be considered in women with advanced or recurrent serous or clear cell uterine cancer. Historically, serous endometrial carcinomas have not been considered to be hormone responsive.

Conflicts of Interest

Dr Chia reports receiving advisory board fees from GSK, Astra Zeneca and Bayer; Dr Lim, receiving travel support from Roche; Dr See, receiving accommodation and travel grants from GSK, conference support from GSK and Sirtex and advisory fees from Roche; Ms Foo, Dr Lim, Dr Lim, Dr Ngo, Dr Soh and Dr Tan have nothing to disclose.

Workgroup Members

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Reviewers

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Supplementary Table 1. International Guidelines for the Treatment of Endometrial Cancer

Guideline Title	**Endometrial Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up**	**Clinical Practice Guidelines for the Treatment and Management of Endometrial Cancer**	**NCCN Clinical Practice Guidelines in Uterine Neoplasms (Version 2.2015)**
Date Released	2013	2014	2015
Guideline Developer	European Society for Medical Oncology (ESMO)	Cancer Council Australia	National Cancer Comprehensive Network (NCCN), United States
Description of Method of Guideline Validation	Recommendations developed from discussion at consensus conferences (CCs). Group decision-making that seeks the consensus of experts and the fulfilment of objectives.	Working party develops clinical questions, searches literature, formulates recommendations and writes guideline chapters. Content is uploaded to Guidelines Wiki and undergoes public consultation prior to update. Annual working party meeting to review changes made by authors.	Statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Validation method not specified.
Target Population	Endometrial cancer	Endometrial cancer	Endometrial cancer
1. What is the Role of Chemotherapy Following Surgery in Women Diagnosed with Endometrial Cancer?	Could be considered for: - Stage IA, grade III with high risk features or stage IB with high risk features (age >65 years, lymphovascular positive, high tumour volume, cervical glandular involvement) (2B)* - Stage II with high risk features (2B)* - Stage III, stage IV	Should be considered for: - Stage I-III, completely resected high risk disease, particularly if high risk disease, and to encourage participation in trial using chemotherapy (level B)* - Stage III with residual disease - Stage IV	Could be considered for: - Stage IB, grade III, with adverse risk factor (2B)* - Stage II, grade III (2B)* - Stage IIIA – with or without chemotherapy, radiation therapy or both (stage IIIA is heterogeneous disease) - Stage IIIB, IIIC, IV (Based on updated staging FIGO/AJCC 2010)
Member Votes			All
2. What are the Chemotherapeutic Options for Women with Advanced or Recurrent Endometrial Cancers?	Carboplatin/paclitaxel preferred as first-line cytotoxics Hormonal therapy (mainly progestin therapy; tamoxifen or aromatase inhibitors can be considered) for endometroid histologies only	Sequential adjuvant chemotherapy either before or after radiotherapy, or given as part of a sandwich regimen (C)* Acceptable chemotherapy regimens include cisplatin and doxorubicin, or carboplatin and paclitaxel	Chemotherapy can be used for all carcinoma histologies Multi-agent chemotherapy regimens preferred Platinum-based chemotherapy preferred Hormonal therapy can be considered for endometrioid histologies only with low-grade or asymptomatic or ER/PR positive
Member Votes	All		
3. What is the Role of Chemotherapy in Women with Uterine Papillary Serous Carcinoma or Clear Cell Carcinoma?	Platinum-based chemotherapy for: - Stage I, II (3B)* - Stage III and IV (1A)*	Counselled that there is only very low evidence that adjuvant chemotherapy may have any impact on survival (level D)*	Considered for: - Stage IA without myometrial invasion (observe or chemotherapy) - Stage IA with myometrial invasion - Stage IB-4 Multi-agent platinum-based chemotherapy, if tolerated
Member Votes			All

ER/PR: Estrogen receptor/progesterone receptor

*( ) denotes level of evidence and strength of recommendation as predetermined by the guidelines.