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Official Publication of the Society of Gynecologic Oncologists of the Philippines

Volume 17 Number 1 August 2020

EDITORIAL

PRACTICE GUIDELINES

ORIGINAL PAPERS

CASE REPORTS

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EDITORIAL CORRESPONDENCE ADDRESS:
Editorial Office, Philippine Journal of Gynecologic Oncology
Society of Gynecologic Oncologists of the Philippines, Inc.
Unit 414, Manila Astral Towers, 1330 Taft Ave. corner Padre Faura St., Ermita, Manila, 1000 Phlippines
Telephone: 63-2-3531688; 63-932-7282864 • Email: phil.j.gyn.onco@gmail.com

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The Philippine Journal of Gynecologic Oncology (ISSN 2704-3045) is the peer-reviewed journal produced as a program of the Society of Gynecologic Oncologists of the Philippines (SGOP). It is published biannually by the SGOP with business and production offices at Unit 404, Manila Astral Towers, 1330 Taft Ave. cor. Padre Faura Sts., Ermita, Manila, Philippines.

Instruction for Authors

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The Philippine Journal of Gynecologic Oncology (PJGO) is the official publication of the Society of Gynecologic Oncologists of the Philippines, Inc. (SGOP). It is a peer-reviewed journal that covers all aspects in gynecologic oncology and features original research papers and case reports, as well as correspondences. The journal is published biannually and sent by courier mail to all SGOP members in good standing, all POGS-accredited training institutions and medical schools.

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MARIA LORA C. TUPAS, MD, FPOGS, FSGOP
Editor in-Chief
Philippine Journal of Gynecologic Oncology
Unit 414, Manila Astral Towers, 1330 Taft Ave.
corner Padre Faura St., Ermita, Manila
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BOOK

Cunningham FG, Gant NF, Leveno KJ, Gilstrap III LC, Hauth JC and Wenstrom KD (eds): Williams Obstetrics, 21st ed. USA: McGraw-Hiall, 2001.

CHAPTER IN BOOK

Mishell DR. Amenorrhea. In: Droegemuller W, Herst AL, Mishell DR, Stencheber MA (eds): Comprehensive Gynecology. St. Louis: CV Mosby Co., 1987: 15.

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Editorial

Upended by the Unexpected: the negative impact of the COVID-19 pandemic on Gynecologic Cancer Care

Maria Lora C. Tupas, MD, FPOGS, FSGOP

The COVID-19 pandemic has had a profound detrimental impact on delivery of cancer care across the globe. As early as May 2020, Eric Raymond & colleagues looked into the ramifications of the multistep crisis borne out of this pandemic. The authors discussed the direct impact of concurrent infection with SARS-Cov2 on cancer patients and their health care providers, drawing largely from papers published from China in the early months of 2020. They also described its indirect effect of disabling access to oncologic services as health systems divert resources to the COVID response, and its long-term impact as economies (both local and global) suffer recession once the pandemic is over.[1]

Two population-based studies published in June and August 2020, looked into the drop in incident cancer referrals during the first weeks of the COVID-19 pandemic and compared it with data gathered from 2019. Lai AG et al found a 45-66% decrease in chemotherapy admissions and a 70-89% drop in urgent early cancer diagnosis referrals. From mathematical modeling, the group estimated as many as 33,890 and 6,270 excess deaths at 1 year from cancer in the United States and England, respectively.[2] In a similar analysis, Kaufman et al did a cross-sectional study on cancer diagnostic testing from Jan 2018 to April 2020. They reported a 46.4% decrease in the number of new cancer patients (breast, colorectal, lung, pancreatic, gastric and esophageal cancers) identified weekly during the pandemic as compared to the weekly counts in 2019 and early 2020.[3] Such delays in diagnosis can translate to more extensive disease upon initiation of treatment and ultimately, poorer prognosis and treatment outcomes.

Most cancer-related organizations worldwide, such as the European Society of Medical Oncology and the American Society of Clinical Oncology, released and updated guidelines for continuing cancer treatment during the pandemic. From April 23 to June 1, 2020, the International Gynecologic Cancer Society (IGCS) conducted a survey among its members on the pandemic's impact on their cancer practice. The survey drew 270 respondents from around the world, with the Philippines tied in 2nd place with Chile for gathering the 2nd most number of respondents (17 oncologists or 6.37% of the respondents).[4] The survey revealed that 51% of the respondents noted a drop in new cancer case referrals in their institutions in the months since the pandemic began and 55% were unable to perform elective surgery for cancer cases. While 84% noted a drop in oncologic surgery cases due to the pandemic, 66% said that the pandemic affected their surgical approach towards the cases they managed as well.[4] All these data point toward varying degrees of the deleterious impact that the COVID-19 pandemic has had and continues to impose on delivery of cancer care globally.

Thus, it is only fitting that we feature the SGOP Recommendations on management approaches for gynecologic malignancies during the COVID-19 pandemic in our first issue for the year 2020. Synthesizing various recommended policies and practices from our own Department of Health, and numerous local and international specialty societies, the guidelines cover management of Cervical, Endometrial and Ovarian cancers using the three standard treatment modalities of surgery, radiotherapy and chemotherapy.[5] For low to medium priority clinic consultations, the use of telemedicine is highly encouraged in the guidelines. However, this may prove challenging or even impossible for certain patients who cannot access the Internet due to lack of resources or technical know-how, or due to their isolated geographical locations where Internet signals are either absent or patchy at best. The discerning reader may feel the need to adapt and change these guidelines depending on the transmission patterns of COVID-19 in their region and locality, as well as the availability of their resources. Armed with these guidelines, and determination and diligence, it is only by learning to work with our cancer patients and their families in the New Normal, that we can surmount these negative effects that this pandemic has wrought upon our practice of gynecologic oncology.

Department of Obstetrics & Gynecology, West Visayas State University Medical Center, Iloilo City

Corresponding author:
Maria Lora C. Tupas, MD; email: mlctupas@wvsu.edu.ph

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Society of Gynecologic Oncologists of the Philippines (Foundation), Inc. [SGOP] recommendations on the management of gynecologic malignancies in the time of the COVID-19 pandemic

Ana Victoria V. Dy Echo, MD, MHPEd, FPOGS, FSGOP[1], Jericho Thaddeus P. Luna, MD, FPOGS, FSGOP[1], Maria Julieta V. Germar, MD, FPOGS, FSGOP[1], Richard Ronald B. Cacho, MD, FPOGS, FSGOP[2], The Society of Gynecologic Oncologists of the Philippines, Inc (SGOP) Board of Trustees 2020

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of the Philippines-Manila, College of Medicine, Philippine General Hospital; [2]Ilocos Training and Regional Medical Center, San Fernando City, La Union

With the COVID-19 pandemic upon us, the general recommendation is to reduce hospital visits and admissions for non-COVID conditions to ensure safety of the patients and minimize the burden on the health care system. A specific concern, however, is addressing the needs of women with gynecologic cancers. It is recognized that while these immunocompromised women may be at higher risk for the severe effects of the COVID-19 infection when they continue treatment, disruption of treatment may result in tumor progression and poorer prognosis.

In response to the mandate of the Department of Health (DOH) for the different subspecialty societies to release clinical pathways at the time of the COVID-19 pandemic, the Society of Gynecologic Oncologists of the Philippines, Inc. (SGOP), through its Board of Trustees, came up with the following guidelines. These guidelines were developed after reviewing the different policies and practices adopted by international societies, taking into consideration local adaptability.

CERVICAL CANCER

Outpatient Visits

Face-to-face outpatient consultations should be limited to conditions classified as high priority. For conditions considered to be of medium and low priority, consultations using telemedicine should be maximized (Table 1).

When scheduling women for face-to-face outpatient consultation, pre-consultation screening for COVID-19 symptoms should be done via telemedicine and upon clinic check-in. Women suspected to have COVID-19 infection should be advised regarding protocols to address the symptoms; the face-to-face outpatient consultation should be deferred and rescheduled once there is certainty that the woman does not have the COVID-19 infection.

In discussing the therapeutic options for cervical cancer, women should be adequately informed of the risks and benefits of the interventions in the setting of the COVID-19 pandemic, with particular emphasis on the risk of potential exposure to COVID-19 infection.

Table 1. Outpatient Visit Priority in Cervical Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Potentially unstable conditions (acute abdominal symptoms, postoperative complications, complications during/ after pelvic radiation and/or chemotherapy, renal/bowel obstruction) • Symptomatic persistent bleeding • Anuria • Symptoms of deep vein thrombosis (DVT)/ pulmonary embolism • New histologically confirmed patient, no prior treatment, for staging workup	• Postoperative visit with no complications • Established patients with new problems or symptoms from treatment • Follow up visit after palliative treatment for advanced/persistent/ recurrent disease	• Follow up visit after radical treatment for early disease • Asymptomatic surveillance visits

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Cervical Cancer

Correspondence to:
Ana Victoria V. Dy Echo, MD, MHPEd; email: anadyecho@yahoo.com
Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of the Philippines-Manila, College of Medicine, Philippine General Hospital, Taft Avenue, Manila

It is ideal to perform RT-PCR SARS CoV2 testing prior to initiating any form of treatment. When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted

immediately. Management of the COVID-19 infection should be prioritized, and gynecologic cancer treatment should only be initiated, or resumed, after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Cervical Cancer Screening

Outpatient clinic visit for routine cervical cancer screening (i.e. Pap smear with or without co-testing with human papillomavirus [HPV] test, or visual inspection with acetic acid [VIA]) is not recommended during the COVID-19 pandemic. It should be postponed until after the pandemic has been completely controlled and provisions for safe outpatient clinic visits are in place.

Management of Abnormal Pap Smears

Diagnostic evaluation of women with Pap smear result of low grade squamous intraepithelial lesions (LSIL) may be postponed up to 6-12 months from the time of diagnosis. On the other hand, women with Pap smear result of high grade squamous intraepithelial lesions (HSIL) should be scheduled for diagnostic evaluation within 3 months from the time of diagnosis, and women with Pap smear result of suspected invasive cervical cancer should be scheduled for diagnostic evaluation within 2 weeks from the time of diagnosis.

When a woman with abnormal pap smear result is suspected or confirmed to have COVID-19 infection, diagnostic evaluation should be deferred. Management of the COVID-19 infection should be prioritized, and the diagnostic evaluation should only be performed after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before diagnostic evaluation).

Management of Premalignant Cervical Lesions

For women with high grade premalignant lesion without suspected invasive disease, the appropriate procedure may be delayed up to 3 months from the time of diagnosis. However, when invasive disease is suspected in a woman with high grade premalignant lesion, the appropriate procedure should be performed within 1 month from the time of diagnosis.

Surgery

When considering surgery for cervical cancer, the clinician should utilize a prioritization scheme (Table 2). Surgeries considered urgent or emergent should be scheduled immediately; surgeries considered semi-urgent may be delayed 1-4 weeks from the time of diagnosis; while surgeries considered non-urgent may be delayed 4-14 weeks from the time of diagnosis. In instances where surgeries are delayed, re-evaluation at 2-4 weeks interval is necessary.

As long as health care facilities allow, surgery may still be performed. Acceptable delay for performing radical trachelectomy or radical hysterectomy for early stage cervical cancer is 6-8 weeks. Enhanced recovery after surgery (ERAS) protocols should be followed to ensure shorter hospital stay and reduce postoperative complications. If surgery is still not feasible beyond this period, radiotherapy with or without concurrent chemotherapy should be first line treatment option.

For women at greater risk of serious illness from COVID-19 infection (i.e. > 65 years of age, immunocompromised and/or with co-morbidities such as uncontrolled diabetes, cardiovascular disease or chronic pulmonary disease), surgery should be considered only when a significant delay would result in a greater risk than benefit.

Clinicians should avoid performing surgeries on women suspected or confirmed to have COVID-19 infection, unless the case is classified as urgent/emergent.

Radiotherapy +/- Concurrent Chemotherapy

Radiotherapy with or without concurrent chemotherapy plays an important role in the management of cervical cancer. It is considered the first line treatment option for locally advanced disease, as well as those with early stage disease but are medically inoperable or refuse surgical intervention. When given as a primary treatment, it should not be delayed and should be scheduled immediately after diagnosis (high priority). When given as adjuvant therapy, it should be scheduled not later than 8 weeks from surgery (medium priority) (Table 3).

Hypofractionization (i.e. increasing the dose per day and decreasing the number of delivered fractions to the fewest number when possible), while respecting tolerance doses of nearby structures, should be considered to reduce the number

Table 2. Priorities for Surgery in Cervical Cancer

URGENT/EMERGENT (HIGH PRIORITY)	SEMI-URGENT (MEDIUM PRIORITY)	NON-URGENT (LOW PRIORITY)
• Radiologically confirmed bowel perforation, peritonitis • Complications during/ after radiotherapy (fistulization/bowel perforation) • Acute postoperative complications (perforation, ureteral dissection)	• RH +/- BSO, BLND, PALS for stage IA2, IB1-IIA1 • Trachelectomy/EH +/- BSO, BLND, PALS for stage IA1 • Cervical AIS or inadequate colposcopy and concern for invasive surgery	• Repair of asymptomatic fistula • HSIL/CIN 2/3 for conization • Resection of slowly growing central recurrence

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Cervical Cancer

Table 3. Priorities for Radiotherapy in Cervical Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Locally advanced stage IB3, IIB-IVA • Stage IB1-IIA1 who are medically inoperable or refuse surgical intervention • Spinal cord compression, brain metastasis, other critical metastatic lesions • Severe bleeding secondary to pelvic tumor	• Symptomatic localized recurrence • Adjuvant for post-surgery stage IA1-IB2 with risk factors	• Asymptomatic recurrence not amenable to surgery

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Cervical Cancer

of hospital visits.

When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and radiotherapy with or without chemotherapy should be initiated or resumed only after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Chemotherapy

For women requiring systemic chemotherapy (Table 4), regimens that may be administered in the outpatient setting, and that will avoid frequent visits are preferred. Colony stimulating factors (CSF) should be routinely given after every chemotherapy.

Hospital visits should be limited to the time of chemotherapy administration. Evaluation in between chemotherapy sessions should be done via telemedicine.

When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and chemotherapy should be initiated or resumed only after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Table 4. Priorities for Chemotherapy in Cervical Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Stage IB3, IIB-IVA for radiotherapy with concurrent chemotherapy • Stage IVB first line, first local recurrence after > 12 months from primary treatment	• Continuation of standard chemotherapy	• Second line `chemotherapy

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Cervical Cancer

ENDOMETRIAL CANCER

Outpatient Visits

Face-to-face outpatient consultations should be limited to conditions classified as high priority. For conditions considered to be of medium and low priority, consultations using telemedicine should be maximized (Table 5).

When scheduling women for face-to-face outpatient consultation, pre-consultation screening for COVID-19 symptoms should be done via telemedicine and upon clinic check-in. Women suspected to have COVID-19 infection should be advised regarding protocols to address the symptoms; the face-to-face outpatient consultation should be deferred and rescheduled once there is certainty that the woman does not have the COVID-19 infection.

In discussing the therapeutic options for endometrial cancer,

Table 5. Outpatient Visit Priority in Endometrial Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Potentially unstable (acute abdominal pain, postoperative complications, complications during/ after pelvic radiation and/or chemotherapy) • Symptomatic persistent bleeding • Anuria • Symptoms of DVT/ pulmonary embolism	• Investigations for postmenopausal bleeding • Postoperative patients with no complications requiring adjuvant treatment • Established patients with new problems or symptoms from treatment	• Fertility preserving therapy in premalignant and early stage clinical disease • Follow-up after primary treatment • Slowly growing asymptomatic vaginal/ central recurrence • Asymptomatic surveillance visits

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Endometrial Cancer

women should be adequately informed of the risks and benefits of the interventions in the setting of the COVID-19 pandemic, with particular emphasis on the risk of potential exposure to COVID-19 infection.

It is ideal to perform RT-PCR SARS CoV2 testing prior to initiating any form of treatment. When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and gynecologic cancer treatment should only be initiated, or resumed, after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Evaluation of Postmenopausal Bleeding

In the face of the COVID-19 pandemic, the recommended first line diagnostic test for women presenting with postmenopausal bleeding is immediate endometrial evaluation through endometrial biopsy using Pipelle at the first face-to-face outpatient consultation.

Hysteroscopy may be an option in certain situations (i.e. focal lesions, cannot tolerate outpatient biopsy) if resources are available, and preferably should be performed under regional anesthesia or intravenous sedation.

Management of Premalignant Lesions

For women diagnosed with hyperplasia with atypia / endometrial intraepithelial neoplasia (EIN), surgery may be delayed up to 8 weeks. Alternatively, nonsurgical options such as hormone therapy may be given until the COVID-19 pandemic is controlled.

Surgery

In determining optimal time (or acceptable delay) to perform surgery for endometrial cancer, the clinician should utilize a procedural scheme (Table 6). Surgeries considered urgent or emergent should be scheduled immediately; surgeries considered semi-urgent may be delayed 1-4 weeks from the time of diagnosis; while surgeries considered non-urgent may be delayed 4-14 weeks from the time of diagnosis. In instances where surgeries are delayed, re-evaluation at 2-4 weeks interval is necessary.

As long as health care facilities allow, women with newly diagnosed endometrial cancer should undergo definitive surgery. For women with high risk early stage endometrial cancer, it is particularly important for the surgery to be scheduled within 8 weeks from the time of diagnosis. Enhanced recovery after surgery (ERAS) protocols should be followed to ensure shorter hospital stay and reduce postoperative complications.

Table 6. Priorities for Surgery in Endometrial Cancer

URGENT/EMERGENT (HIGH PRIORITY)	SEMI-URGENT (MEDIUM PRIORITY)	NON-URGENT (LOW PRIORITY)
• Uterine/pelvic hemorrhage • Radiologically confirmed peritonitis • Complications during/after radiotherapy • Acute postoperative complications (perforation, ureteral dissection, bleeding)	• EHBSO, PFC +/- BLND, PALS in newly diagnosed endometrial cancer or known/ suspicious for uterine sarcoma	• Risk reducing surgery for genetic predisposition to endometrial cancer • Endometrial hyperplasia with atypia not controlled by hormonal therapy • Repair of asymptomatic fistula • Resection of slowly growing central recurrence

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Endometrial Cancer

When the hospital COVID-19 situation could not allow timely surgical intervention, alternative treatment strategies may be given. Women with low risk early stage endometrial cancer may be considered for hormonal therapy, women with high risk early stage endometrial cancer may be considered for radiotherapy, while women with advanced disease may be considered for systemic chemotherapy.

For women at greater risk of serious illness from COVID-19 infection (i.e. > 65 years of age, immunocompromised and/or with co-morbidities such as uncontrolled diabetes, cardiovascular disease or chronic pulmonary disease), surgery should be considered only when a significant delay would result in a greater risk than benefit. Alternative treatment strategies are preferred.

Clinicians should avoid performing surgeries on women suspected or confirmed to have COVID-19 infection, unless the case is classified as urgent/emergent.

Chemotherapy

Women requiring adjuvant chemotherapy should be scheduled for treatment not more than 8 weeks from surgery (Table 7). Regimens that may be administered in the outpatient setting, and that will avoid frequent visits are preferred. Colony stimulating factors (CSF) should be routinely given after every chemotherapy.

Hospital visits should be limited to the time of chemotherapy administration. Evaluation in between chemotherapy sessions

should be done via telemedicine.

When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and chemotherapy should be initiated or resumed only after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Table 7. Priorities for Chemotherapy in Endometrial Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Previously untreated symptomatic metastatic/recurrent disease not sensitive to hormone therapy • Adjuvant chemotherapy +/- radiotherapy in high risk patients	• Slowly growing metastatic/recurrent disease that is potentially hormone-sensitive	• Second line chemotherapy in patients not suitable for hormone therapy

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Endometrial Cancer

and chemotherapy should be initiated or resumed only after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Radiotherapy

Women requiring adjuvant radiotherapy should be scheduled not later than 8 weeks (Table 8).

Hypofractionization (i.e. increasing the dose per day and decreasing the number of delivered fractions to the fewest number when possible), while respecting tolerance doses of nearby structures, should be considered to reduce the number of hospital visits.

When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and radiotherapy with or without chemotherapy should be initiated, or resumed only after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Table 8. Priorities for Radiotherapy in Endometrial Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• EBRT as adjuvant therapy for high risk patients • Symptomatic unresectable primary tumor not suitable for surgery	• Brachytherapy as adjuvant therapy for intermediate high risk patients • Isolated vaginal relapse after surgery, with curative intent	• Asymptomatic vaginal/ pelvic recurrence

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Endometrial Cancer

OVARIAN CANCER

Outpatient Visits

Face-to-face outpatient consultations should be limited to conditions classified as high priority. This includes women who are symptomatic for a suspected ovarian cancer. For conditions considered to be of medium and low priority, consultations using telemedicine should be maximized (Table 9).

When scheduling women for face-to-face outpatient consultation, pre-consultation screening for COVID-19 symptoms should be done via telemedicine and upon clinic check-in. Women suspected to have COVID-19 infection should be advised regarding protocols to address the symptoms; the face-to-face outpatient consultation should be deferred and rescheduled once there is certainty that the woman does not

Table 9. Outpatient Visit Priority in Ovarian Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Potentially unstable (acute abdominal pain, bowel/urinary obstruction, postoperative complications) • Symptomatic new patient (symptomatic ascites or pleural effusion, bowel obstruction)	• Newly diagnosed asymptomatic patients, no prior surgery • Postoperative patients with no complications • Patients continuing on chemotherapy • Established patients with new problems or symptoms from treatment	• Follow up visit on maintenance medications after primary treatment • Asymptomatic surveillance visits

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Epithelial Ovarian Cancer

have the COVID-19 infection.

In discussing the therapeutic options for ovarian cancer, women should be adequately informed of the risks and benefits of the interventions in the setting of the COVID-19 pandemic, with particular emphasis on the risk of potential exposure to COVID-19 infection.

It is ideal to perform RT-PCR SARS CoV2 testing prior to initiating any form of treatment. When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and gynecologic cancer treatment should only be initiated, or resumed, after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Surgery

In determining optimal time (or acceptable delay) to perform surgery for ovarian cancer, the clinician should utilize a procedural scheme (Table 10). Surgeries considered urgent or emergent should be scheduled immediately; surgeries considered semi-urgent may be delayed 1-4 weeks from the time of diagnosis; while surgeries considered non-urgent may be delayed 4-14 weeks from the time of diagnosis. In instances where surgeries are delayed, re-evaluation at 2-4 weeks interval is necessary.

Although primary debulking surgery has its benefits, in this time of the COVID-19 pandemic, there is a trend towards favoring obtaining tissue biopsy followed by neoadjuvant chemotherapy. This is particularly true for women with presumed advanced stage ovarian cancer which would otherwise require extensive surgeries and subsequent intensive postoperative care.

For women at greater risk of serious illness from COVID-19 infection (i.e. > 65 years of age, immunocompromised and/or with co-morbidities such as uncontrolled diabetes, cardiovascular disease or chronic pulmonary disease), surgery should be considered only when a significant delay would result in a greater risk than benefit. Alternative treatment strategies are preferred.

Clinicians should avoid performing surgeries on women suspected or confirmed to have COVID-19 infection, unless the case is classified as urgent/emergent.

Table 10. Priorities for Surgery in Ovarian Cancer

URGENT/EMERGENT (HIGH PRIORITY)	SEMI-URGENT (MEDIUM PRIORITY)	NON-URGENT (LOW PRIORITY)
• Radiologically confirmed intestinal obstruction, bowel perforation, peritonitis • Acute postoperative complications (perforation, anastomotic leak) • Pelvic mass with torsion or causing urinary or intestinal obstruction	• Establishment of cancer diagnosis when high suspicion exists • Primary cytoreductive surgery • Interval debulking surgery • Patients with recurrent disease without nonsurgical options • Symptomatic patients with inoperable primary or recurrent cancer requiring palliative cancer procedures	• Risk reducing surgery for genetic predisposition to gynecological cancer • Completion surgery for early stage ovarian cancer • Recurrent cancer requiring palliative resection • Oligometastatic first relapse where complete resection is feasible

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Epithelial Ovarian Cancer

Chemotherapy

Women with advanced or high grade tumors and malignant germ cell tumors should be prioritized for chemotherapy (Table 11). Regimens that may be administered in the outpatient setting, and that will avoid frequent visits are preferred. Colony stimulating factors (CSF) should be routinely given after every chemotherapy. Should there be significant delay in instituting chemotherapy for advanced and high grade cancers, re-evaluation should be done at 2-4 weeks interval.

Women with apparent advanced stage ovarian cancer should be considered for neoadjuvant chemotherapy. The number of cycles of the neoadjuvant chemotherapy may be extended to up to 6 cycles, rather than 3, before considering interval debulking surgery.

When maintenance therapy is considered after upfront adjuvant chemotherapy, the oral therapy (PARPi) should be preferred over intravenous therapy (Bevacizumab) to lessen the need for frequent hospital visits.

Hospital visits should be limited to the time of chemotherapy administration. Evaluation in between chemotherapy sessions should be done via telemedicine.

When a woman is suspected or confirmed to have COVID-19 infection, treatment should not be initiated, or if already ongoing treatment, should be interrupted immediately. Management of the COVID-19 infection should be prioritized, and chemotherapy should be initiated or resumed only after the woman is determined to be no longer infectious (i.e. minimum of 14 days from symptom onset or from a positive RT-PCR SARS CoV2 test, symptom-free for a minimum of 3 days before treatment).

Table 11. Priorities for Chemotherapy in Ovarian Cancer

HIGH PRIORITY	MEDIUM PRIORITY	LOW PRIORITY
• Adjuvant chemotherapy in high grade serous/ endometrioid tumors and malignant germ cell tumors • Neoadjuvant chemotherapy in symptomatic patients	• Adjuvant chemotherapy in stage IC-IIA infiltrative mucinous tumors • Adjuvant chemotherapy in advanced stage clear cell or mucinous tumors • High grade serous/ endometrioid symptomatic platinum sensitive recurrent patients	• Adjuvant chemotherapy in stage IC-IIA low grade serous/endometrioid/ clear cell/ expansile mucinous tumors • High grade serous/ endometrioid platinum resistant recurrent patients • Symptomatic slowly growing recurrent disease • Recurrent low grade serous tumors

Adapted from: ESMO Management and Treatment Adapted Recommendations in the COVID-19 Era: Epithelial Ovarian Cancer

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Development of a quality-of-life assessment tool for patients diagnosed with gynecologic malignancies receiving radiation and/or chemotherapy in a tertiary hospital

Hannah Faye A. Magdoboy, MD and Concepcion D. Rayel, MD, MAHA, FPOGS, FSGOP

ABSTRACT

Background: Gynecologic malignancies affect a significant portion of the population in the Philippines and globally. The diagnosis of malignancy can tremendously impact one's life. Hence, maximizing a cancer patient's living condition is equally important as preventing progression of the disease. Today, there is still a paucity of assessment tools that focus on the Quality-of-Life (QoL) of gynecologic cancer patients.

Objective: This study aims to develop a QoL questionnaire specific for gynecologic cancer patients undergoing radiation and/or chemotherapy in a tertiary hospital.

Materials and Methods: Different domains affecting QoL and factors that affect each domain were identified after thematic analysis of output from focus group discussion and key informant interviews. Questions were formulated and pilot tested to 30 gynecologic cancer patients undergoing different treatment modalities to establish internal consistency and factor analysis. A Test-Retest method followed and was analysed.

Results: Testing for psychometric property of internal reliability revealed that the formulated questions were internally reliable (Cronbach's alpha score of 0.782). The final domains that emerged were Physical, Psychological and Social. Factor analyses were done to determine structure construction suitability which was confirmed by Bartlett's Test of sphericity - 0.05. Component analyses of each domain identified 3 sub-dimensions for Physical domain with cumulative eigenvalue of 70%, 4 sub-dimensions for Psychological domain with cumulative eigenvalue of 79% and 3 sub-dimensions for Social aspect with 77% cumulative eigenvalue. All domains revealed p-values higher than the level of significance after Wilcoxon Signed Rank Test affirming that questions pertaining to each dimension are not time dependent and hence can be used to produce equally reliable results.

Conclusion: A QoL assessment tool designed specifically for gynecologic cancer patients undergoing treatment and subjected to rigorous validity and reliability testing was created in this study. Factors affecting the different dimensions of the patients' QoL were explored.

Keywords: *gynecologic malignancy, physical domain, psychological domain, quality of life questionnaire, social domain*

INTRODUCTION

In 2018, gynecological cancers accounted for 17% of 7.8 million total estimated new cancers in women and 16% of 3.8 million deaths from all cancers.[1] In the Philippines, the values rise to 24% and 21%, respectively.[2]

Early cancer detection has improved patient survival. Coupled with this advantage are different treatment-associated toxicities that have been shown to affect quality-of-life (QoL) negatively.[3] Needless to say, the toxicity and tolerability of a treatment is as crucial as its efficacy. Better QoL increases patients' desire to complete her therapy and overcome symptoms.[4] Understanding QoL is vital to the family members and health care providers as they are to the patients. In spite of the need, QoL is rarely reported.

QoL is defined as a personal sense of well-being that encompasses physical, psychological, social, and spiritual dimensions.[4] Morris et al. looked into how QoL is viewed in clinical practice. He ran a survey on 260 senior oncologists where almost all (80%) of the questionnaire responders believe that QoL should be assessed. Limitations in time and resources may preclude compliance. In another study, patients appreciate that their doctors know them better and seem to show greater understanding about their status. They end up being more satisfied with their clinic visits.[5]

Physical well-being pertains to the control of symptoms and the maintenance of function. Typically distressing to the patients are alopecia, mucositis, tingling sensation, nausea and vomiting, dietary changes and bone marrow depression which are common acute side effects of cancer treatment. Fatigue and pain are common late physical effects known to negatively affect QoL.[4]

Psychological well-being is determined by a patient's effort to maintain a sense of control among major life changes in the face of life-threatening illness. This includes anxiety, uncertainty of the future, fear of recurrence, metastatic disease and trauma over recall of the initial cancer treatment.[6]

Social well-being is the attempt to deal with the impact of cancer on individuals, their roles, and relationships. Sexual and marital problems as well as adjustment of children name pertinent family issues. At work, special concerns include discrimination, cancer disclosure, stigma, reentry into the

From the Department of Obstetrics and Gynecology, Davao Doctors Hospital

Corresponding authors:
Hannah Faye A. Magdoboy, MD; email: mhannahfaye@yahoo.com
Concepcion D. Rayel, MD, Department of Obstetrics & Gynecology, Davao Doctors Hospital;
email: cdrayel@yahoo.com

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workplace, changes in work priorities, financial stability and health insurance.[4]

Spiritual well-being is the ability to maintain hope and find meaning from the cancer experience. Religiosity and spiritual support have been correlated with recovery from cancer. Other important aspects affecting spiritual health are hopefulness and discovering a purpose in life.[4]

Treatment of most gynecologic malignancies generally include surgical intervention and systemic treatment. Issues pertinent to affected women may include infertility, sexual dysfunction, urinary and bowel symptoms as well as sudden appearance of menopausal complaints on top of the common adverse effects of radiotherapy and chemotherapy. These negative implications of treatment may significantly affect other aspects of a patients' life.[7]

From our literature review, there is still lack of tools that focus on the assessment of gynecologic cancer patients' QoL. The bulk of the previous studies use general questionnaires which may not be accurate in covering issues relevant to this study population. Newer studies supplement modular (disease-specific) tools to core/general questionnaires to enhance sensitivity to the target population.[8] Reviews of existing modules report incomplete coverage of the four dimensions affecting QoL described earlier.[9,10] These limitations are the basis of this study.

The objective of this project is to develop a self-administered questionnaire that will assess the QoL of gynecologic cancer patients undergoing radiation and/or chemotherapy in a tertiary hospital. Specifically, the authors aim to identify the different domains of the QoL of these patients, determine the factors that affect each identified domain, establish the validity of the questionnaire by determining the construct and content validity and establish the reliability of the questionnaire by determining the internal consistency and test-retest analysis.

METHODOLOGY

This is a Mixed (Qualitative-Quantitative) Study Design in which the researchers explored the domains that significantly affect the patients and the factors under each dimension. A questionnaire was formulated which was pilot tested and underwent the process of rigorous validation and reliability testing.

The study subjects included women aged 18-65 years old diagnosed with either Cervical, Endometrial, Ovarian or Breast Cancer undergoing chemotherapy, radiation or chemoradiation as primary or adjunct therapy given at least one cycle/fraction. They must be able to read, write and comprehend English language as baseline tool. Excluded from the study are women diagnosed with other malignancies aside from Gynecologic Cancers, those who have signs of altered levels of consciousness (psychiatric disorders, delirium, dementia) and those with recurrent disease after initial treatment with radiotherapy, chemotherapy or chemoradiation. Those with Stage IV diseases were also not included in the study as end-of-life concerns might affect assessment. These criteria apply to both the focus group discussion and pilot testing.

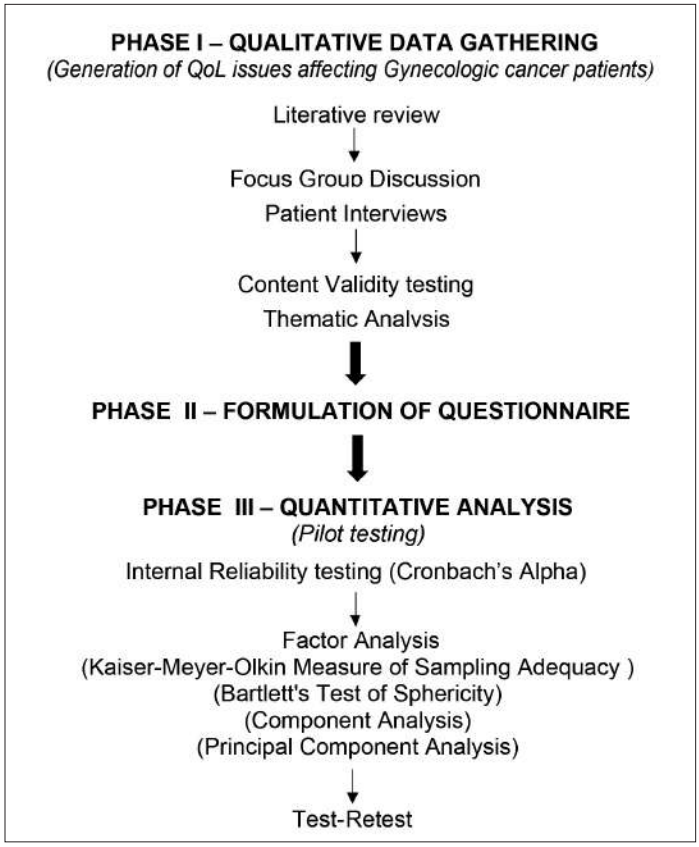

Figure 1. Overview of questionnaire developments

The development of this questionnaire entailed three phases (Figure 1). Upon the approval of Ethics and Review Board of the institution, the research process began with qualitative data gathering in the form of focus group discussion (FGD) and interviews. This was attended by the researchers, a gynecologic oncologist, a radiation and chemotherapy nurse, a psychologist, a transcriber and the patients. Participants were given time to read and sign an informed consent prior to any involvement in the study. The output of these discussions was analyzed by a qualified psychologist. Collaizzi's method was employed as a framework of analysis. Once saturation and consistency of data was established, the questionnaire was now formulated (Phase II) based on the results by listing down the identified domains and the questions comprising each dimension.

Quantitative data analysis began with pilot testing of the formulated questionnaire to 30 gynecologic cancer patients different from the subjects in Phase 1 but with the same inclusion and exclusion criteria (Phase III). Item analysis was done and Cronbach's alpha statistic was identified to establish internal consistency and reliability. Two analyses were performed to determine the suitability of data for factor analysis through Kaiser-Meyer-Olkins Measure of Sampling Adequacy and relatibility of question items through Barlett's Test of Sphericity. A component analysis was also done to determine how many subdimensions can be generated out of the list of questions under each thematic dimension of the assessment tool. To confirm the presence of factors and or undercover other domains in the study, Principal component analysis was employed with varimax as its rotation method. Test-Retest Method followed, where the

same set of patients were asked to answer the same test after two (2) weeks to measure the consistency of their answers as a result of time difference. This was analyzed using Wilcoxon Sign Ranked test to determine significant difference between scores pre and post evaluation.

RESULTS

Phase I

There were a total of 8 patients interviewed in the initial part of the study (5 from FGD supplemented by 3 interviews) with ages ranging from 26-61 years old. Two of them were Cervical cancer patients (Stage 2A and Stage 2B both on chemoradiation), another two were ovarian cancer patients (Stage 1C and Stage 2A, both on chemotherapy), two had endometrial cancer (Stage II on radiotherapy and Stage IIIB on chemoradiation), and also two were breast cancer patients (Stage II on chemotherapy and Stage III on chemoradiation). A semi-structured in-depth qualitative interview guided by findings from available assessment tools was done. Content validity was ascertained by a gynecologic oncologist and a psychologist. The following themes emerged after thematic analysis of the data: Physical, Psychological, Spiritual and Social.

Phase II

A provisional list of factors affecting each dimension were listed down for testing in Phase 3. Factors were chosen and included in the list based on its presence in all the participants regardless of the diagnosis. There were a total of 38 issues identified (10 for physical, 10 for psychological, 8 for social and 10 for spiritual domain). The factors were mostly converted to a question form with corresponding Likert scale responses.

Phase III

30 patients participated in this phase of the study aged 21-65 years old. 11 of these are cervical cancer patients (3 on radiotherapy, 8 on chemoradiation), 8 patients had endometrial cancer (4 on radiotherapy and 4 on chemoradiation), 6 patients were ovarian cancers patients all on chemotherapy and 5 were breast cancer patients (3 on chemotherapy and 2 on chemoradiation).

Internal Reliability Testing

Table 1 reveals that the computed Cronbach's alpha of 0.782 is greater than 0.70 indicating that the questions reliably measure the overall quality of life. However, item analysis suggests the removal of Spiritual aspect to improve the internal reliability score of the questionnaire.

Factor Analysis

The KMO value for all the dimensions is less than 0.6 suggesting that the data used were not significantly suited for factor analysis (Table 2). However, Barlett's test showed that the p-values of all the dimensions were less than 0.05 (P=<0.01) suggesting that the question items were related, and therefore, still suited for structure identification.

A. Physical Dimension

Table 3 shows 3 major subdimensions with initial eigenvalues cumulative sum of 70.4% and this is graphically shown using the Scree Plot in Figure 2. This means that there were 3 sub-dimensions within Physical aspect explaining 70% of the variations.

Table 1. Cronbach's Alpha

Dimension	Cronbach's Alpha
Physical Dimension	0.777
Psychological Dimension	0.741
Social Dimension	0.700
Spiritual Dimension	0.008
Overall Cronbach's Alpha	0.782

Extraction of the subdimensions or clusters was done using Principal Component analysis (Table 4). The result showed that statements 4, 6, 9 and 10 converged to a single cluster which stresses on Eating and Appetite, statements 1, 7 and 8 also converged in another cluster concerned on Fatigue and Pain either in the body or as a result of having sexual intercourse and statement 2 and 3 clustered on the third sub-dimension pointing on Sleeping patterns.

B. Psychological Dimension

4 major sub-dimensions were identified under psychological dimension (Table 3) also illustrated in Figure 2. These four explain 79% of the variations. Other sub-dimensions detected in the analysis had low eigenvalues, and as such did not contribute much to the improvement in a separation of a new cluster or component.

The first cluster in Table 4 identified Anxiety as a component of the Psychological dimension. The second cluster concerned Self-care. Roles in the family was the focus of the third cluster. The last subdimension dealt with one's acceptance.

C. Social Dimension

In this dimension, 3 major sub-dimensions explaining majority or 77% of the variations were identified which were

Table 2. Kaiser-Meyer-Olkin Measure of Sampling Adequacy and Bartlett's Test of Sphericity

DIMENSION		PHYSICAL	PSYCHOLOGICAL	SOCIAL
KMO value		0.466	0.291	0.45
Bartlett's Test of Sphericity	Approx. Chi-Square	90.949	127.431	104.869
	df	45	45	45
	Sig.	0.000	0.000	0.000

Table 3. Component analysis

DIMENSION	Component	Initial Eigenvalues			Extraction Sums of Squared Loadings			Rotation Sums of Squared Loadings		
		Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
PHYSICAL	3	1.492	14.915	70.74	1.492	14.915	70.74	2.03	20.297	70.74
PSYCHOLOGICAL	4	1.149	11.495	79.424	1.149	11.495	79.424	1.496	14.963	79.424
SOCIAL	3	1.078	13.477	76.289	1.078	13.477	76.289	1.769	22.111	76.289

Table 4. Principal Component Analysis

	COMPONENT			
	1	2	3	4
PHYSICAL				
1. I easily get tired after the treatment.	0.279	**0.728**	-0.144	
2. I have difficulty in sleeping.	0.197	-0.127	**0.933**	
3. I have a difficult time staying asleep.	0.095	-0.004	**0.910**	
4. I eat less now.	**0.902**	-0.025	0.056	
5. I experience numbness after the treatment.	0.175	0.682	-0.249	
6. Food tastes different since I started treatment.	**0.718**	0.142	0.185	
7. I often have pain in my body.	0.266	**0.797**	0.114	
8. Sexual intercourse has become uncomfortable/painful.	-0.291	**0.578**	0.394	
9. I lost weight since I started treatment.	**0.744**	0.264	0.173	
10. I feel nauseous after the treatment.	**0.827**	0.306	-0.116	
PSYCHOLOGICAL				
1. I think too much about my illness	**0.820**	-0.071	0.044	0.124
2. I have gotten closer to my family since I was diagnosed with cancer	0.253	-0.110	**0.702**	0.34
3. My libido has decreased.	0.155	-0.147	**0.881**	0.071
4. Sexual intercourse has become unpleasurable for me.	-0.281	-0.122	**0.733**	0.446
5. I am more concerned about my health issues now.	0.007	**0.984**	0.029	-0.009
6. I pay more attention to what my body is telling me now.	0.093	**0.942**	-0.130	0.102
7. Did you believe your doctor when you were first told about your illness?	0.065	0.063	0.072	**0.894**
8. Did you think about how your life would be if you didn't get the diagnosis?	**0.754**	0.283	-0.237	-0.185
9. Did you feel sad and gloomy after you were diagnosed?	**0.836**	0.056	-0.058	0.163
10. Are you more willing to go through the treatments so you can get better?	0.405	0.499	-0.162	**0.540**
SOCIAL				
1. I continue to do my usual chores at home.	0.058	**-0.765**	0.265	
2. I exert effort now to have better relationship with my family.	**0.838**	0.292	0.050	
3. I exert effort now to have better relationship with my friends.	**0.865**	-0.161	0.230	
4. I reach out to the people I used to dislike before.	**0.781**	-0.038	0.289	
5. I am now more open with my feelings and thoughts to my family.	0.234	0.212	**0.829**	
6. I am now more open with my feelings and thoughts to my friend.	0.296	-0.281	**0.836**	
7. My work has been affected since I was diagnosed with cancer.	-0.069	**0.803**	0.417	
8. I am able to settle my financial obligations that arise from my treatments.	0.150	**0.797**	-0.008	

also shown in the scree plot in Figure 2.

Questions 2, 3 and 4 talked about exerting effort with family, friends and people the patient used to dislike. Taking on responsibility was also identified as a subdimension. The third subdimension of social dimension was being more open to family and friends.

TEST-RETEST ANALYSIS

Table 5 made use of Wilcoxon Signed Rank test (a paired t-test equivalent) for comparing two related data. Due to the non-normality of the data, a non-parametric analysis was used instead to compare the difference between pre and post values. In this case, all dimensions showed p-values higher than the level of significance a=0.05. This suggests that the questions pertaining to their respective dimension do not get affected through time.

An analysis was also done to determine significant relationship between the pre and post test scores of patients among the different dimensions. Table 6 shows that Physical dimension showed a correlation coefficient of r=0.831 and Social dimension with r=0.903 suggesting a moderate to a very strong relationship, respectively. The relationship was significant indicating that the dimension was not easily affected by the time factor. However, for the Psychological dimension, a r=0.238 was not significant and denoted a small relationship. However, overall analysis of the QoL scores revealed a r=0.775 which was significant, suggesting that overall the questionnaire was of good quality. Hence, results were more stable over time for physical, social and overall quality of life. However, the psychological aspect may be lower because as treatment progresses, it was possible that psychological states can change.

DISCUSSION

Two of the most widely used QoL assessment questionnaires include the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Functional Assessment of Cancer Therapy-General (FACT-G). The development of both questionnaires was not restricted to a specific type of cancer but included a wide variety of diagnoses. They are both "core/general" questionnaires which needed to be supplemented with disease-specific modules to enhance sensitivity to a certain set of patients.[8] The primary advantage of our study is that the questions were formulated from and tested

Table 6. Testing of Significant Relationship Between Pre and Post Test Scores

	Posttest	
Pretest	**Correlation Coefficient**	**P-value**
Physical	0.831**	0.000
Psychological	0.238	0.205
Social	0.903	0.000
Overall QoL	0.775	0.000

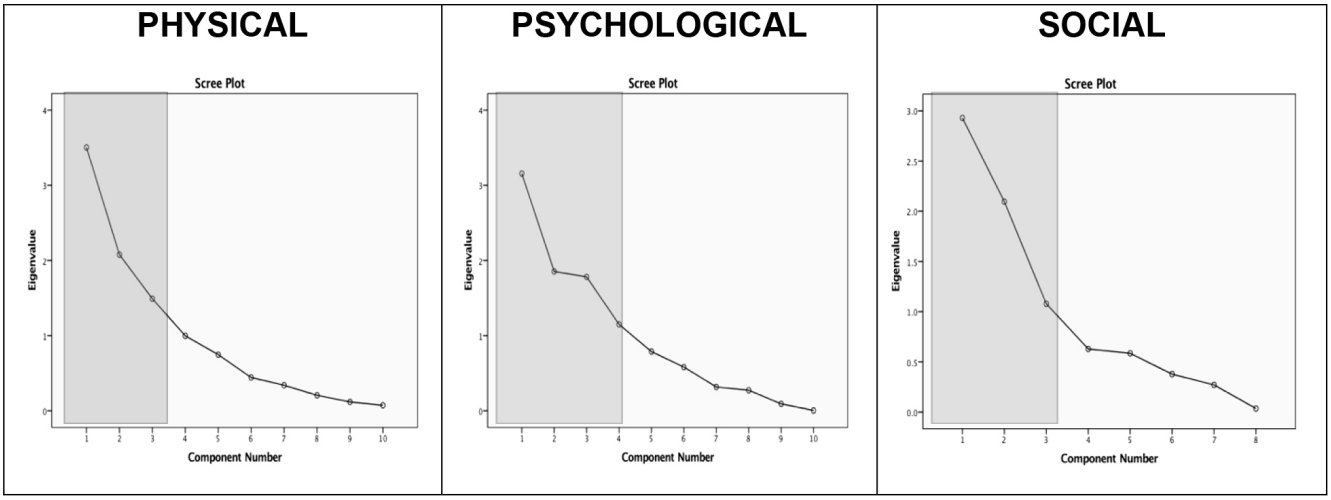

Figure 2. Scree Plot of all dimensions

Table 5. Comparative Analysis between Pre and Post Test Scores

DIMENSION		MEDIAN	MEAN	STD DEV	P-VALUE
Physical	PRE	3.15	3.26	0.78	0.885
	POST	3.25	3.27	0.73	
Psychological	PRE	3.89	3.96	0.35	0.274
	POST	3.83	3.86	0.41	
Social	PRE	3.94	3.87	0.55	0.194
	POST	3.88	3.80	0.62	

on gynecologic cancer patients themselves making it relevant and specific to the target population. If applied in cancer clinical research, patients will only need to answer one questionnaire bypassing the core plus module assessment. This is the first QoL assessment study for gynecologic malignancies done in the Philippines.

The themes/domains that emerged from our qualitative data gathering were consistent with Ferrell's model of QoL in cancer survivorship emphasizing the complexity of QoL and the need for an interdisciplinary approach.[4] EORTC QLQ-C30 reportedly did not cover all important domains of QoL, specifically the spiritual dimension which this study tried to explore. The questions were grouped to functional and symptomatic scales giving the tendency to become redundant.[9] On the other hand, FACT questionnaires may have categorized questions into their respective scales but lacked assessment of psychological and spiritual domains.[10]

The removal of the spiritual dimension was necessary to improve the reliability of our questionnaire. The questions under spiritual dimension may not have accurately defined spiritual well-being given that our country is culturally diverse, specially the Davao region. Tharin supports this idea and concluded that favorable family relationships, nature appreciation and adequate social support is correlated with better spiritual well-being.[11] It may also arise from quality care provided by the health care team.[12] Different cultural practices in the form of vows, sacrifices, drinking holy water or treatment from local herbalists did not affect the QoL according to another study. These actions, however, played a role on how Black Americans' dealt with anxiety which is a factor concerning psychological well-being rather than spirtual.[3]

A. Physical Dimension

Eating and Appetite is the subject of the first subdimension. A negative correlation between physical domain and nutritional risk had been significantly noted. Malnourished patients unfortunately describe poor QoL.[23] Dietary preferences can sorely change from the disease itself or as a result of treatment. Distorted taste and unusual sensitivity to smell eventually leads to weight loss.[13] Educating patients about these changes has been shown to reduce morbidity and improve functional performance.[14]

The second cluster has to do with fatigue and pain either in the body or as a result of having sexual intercourse. Fatigue was identified as the most severe symptom experienced by ovarian cancer survivors while on treatment.[9] It can be so severe that it may reduce tolerance for normal daily activities eventually leading to low levels of QoL specifically impairing sexual function and even bowel and urinary functions. The study of Iwase et al suggests that fatigue is as problematic as pain for cancer patients hospitalized in acute care hospitals.[15]

The third subdimension is about sleeping patterns. Fortner highlighted in his study that people who fail to achieve good sleep are usually accompanied with limitations in their ability to perform their functions.[16] In another study, poor sleep at night resulting to longer naps in the day were correlated with poorer physical QoL.[17]

B. Psychological Dimension

Anxiety, as a component of psychological well-being, was identified as more troublesome for gynecological cancer patients compared to depression.[6] A significant source of this anxiety are the inevitable changes in one's life from the diagnosis and the necessary interventions. Changes in routine and roles, for example, might be undesirable and may eventually lead to a poor perception of her QoL.[18]

The second cluster concerns the patient's Self-Care which may be blunted by a sense of emptiness, profound sadness, a perception of worthlessness and futility. However, educating these patients on self-care is protective since they will know better how to protect themselves and also educate others on how to prevent acquiring the disease and control their life plans according to their disease indicating acceptance of their condition.[19]

Roles in the family is the focus of the third cluster. This includes sexual functionality of the patient to her husband and her responsibility as a mother. Sexuality is a primary concern susceptible to distress in a previously sexually active gynecological cancer patient. The physical and emotional trauma from the disease and its treatment may start limiting sexual activities which may have a 'ripple effect' with patients' doubting their self-confidence and sexual esteem. This may be regarded as the most negative consequence of gynecological cancer. This may also cascade to negative perceptions of themselves as women including their desire to function as a good mother.[20]

The fourth cluster deals with one's acceptance. Denial is a normal initial reaction to the imminent threat of cancer that gradually diminishes over time. Many individuals blunt this protective mechanism and slowly adapt to the news when they start studying the illness, consider treatment options, and interview other patients and even when they consult their doctors. This allows patients to remain more focused on the decision making.[21]

C. Social Dimension

Questions 2, 3 and 4 talked about exerting effort with family, friends and people the patient used to dislike. Perception of good social support will do cancer patients good. Emotional fullness from significant others is positively correlated with better QoL as this satisfies the basic social requirements of love, affection and the feeling of belongingness.[21]

Taking on responsibility is also identified as a subdimension of the social dimension. When patients and their families treat cancer as a challenge, they are able to live normal lives by keeping themselves busy and maintaining flexibility in roles. With this, the demands brought on by the treatment can be minimized. The patient's and her family's ability to return to usual patterns of activities is a way to put the cancer behind them.[22]

The third subdimension of social dimension is being more open to family and friends. Going through the diagnosis and treatment of cancer is not bad at all. There are also obstacles that survivors are able to conquer. A study reported that patients express increased appreciation and acknowledgment to their families and friends.[22]

CONCLUSIONS

The questionnaire developed in this study is a self-administered assessment tool developed from patient-reported data for the measurement of QoL in gynecologic cancer patients undergoing treatment. It went through extensive reliability and validity testing. Dimensions and subdimensions identified were: PRINCIPAL DIMENSION- Eating and Appetite, Fatigue and Pain, Sleeping Patterns; PSYCHOLOGICAL DIMENSION- Anxiety, Self-care, Roles, Acceptance; SOCIAL DIMENSION- Relationships, Taking on responsibility and Openness to family and friends.

LIMITATIONS

This study was done in one institution with a convenient purposive sampling method. There were a total of 30 respondents who answered the same test within a 2-week period.

RECOMMENDATIONS

The researchers recommend to apply the questionnaire to a larger population size for standardization of the instrument as this would help strengthen the validity and reliability of the questionnaire and consider multicenter testing to improve sampling adequacy and suitability of questions. Other researchers may come up with a more culturally precise definition of the spiritual dimension.

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Clinical characteristics predictive of optimal primary cytoreduction in epithelial ovarian malignancy: A five-year retrospective study in a tertiary government hospital

Jehada-Inn U. Misuari-Alihuddin, MD, FPOGS, DSGOP, DPSCPC and Jericho Thaddeus P. Luna, MD, FPOGS, FSGOP

ABSTRACT

Objective: To determine the clinical characteristics predictive of optimal cytoreduction among women with epithelial ovarian malignancy who underwent primary cytoreductive surgery in a tertiary government hospital.

Methodology: This retrospective cohort study identified 218 patients with epithelial ovarian cancer who underwent primary cytoreductive surgery in a tertiary government hospital between January 2013 to December 2017. Demographic characteristics, imaging results, CA-125 levels, and surgico-pathologic findings were collected. Outcome measures included incidence of optimal cytoreduction and factors related to its attainment. Descriptive and inferential analysis were done to estimate odds ratio with 95% confidence interval and p-values. Univariate and multivariate logistic regression analysis were done to determine independent variables predictive of optimal cytoreduction.

Results: A total of 145 patients had optimal cytoreduction while 73 had sub-optimal cytoreduction. A simple logistic regression analysis showed that low pre-operative (I-Low), low and mid intra-operative extent of disease (DS-Low and DS-Mid), absence of ascites, CA-125 < 500 U/ml, size of tumor, stage I – II, and mucinous histologic types were independent predictors of optimal cytoreduction. Upon multiple logistic regression analysis, mid preoperative extent of disease (I-Mid), and low or mid intra-operative extent of disease (DS- Low, DS-Mid) were associated with more than 900 and 100 times increased odds of optimal cytoreduction (p-values < 0.001).

Conclusion: Pre-operative mid extent of disease (I-mid) and intraoperative low or mid extent of disease (DS-low and DS-mid) were statistically significant predictors of optimal cytoreduction.

Keywords: *ovarian cancer, optimal cytoreduction, prediction, residual disease, CA-125*

INTRODUCTION

Ovarian cancer is a lethal gynecologic malignancy. In 2012, the estimated age-standardized national incidence rate was 5.9 per 100, 000 in the Philippines with an estimated national standardized mortality rate of 3.9 per 100, 000.[1] At least two-thirds of women who are diagnosed with ovarian cancer have advanced disease at the time of diagnosis.

Based on data from two institutions with gynecologic oncology training programs in the Philippines, there were 1292 new cases of ovarian cancer diagnosed in the last 5 years, and almost 50% had advance disease. Consistent with international statistics, epithelial ovarian carcinoma (EOC) (89%) was the most common histologic type occurring most commonly in women 41-50 years old.[2]

From the Department of Obstetrics and Gynecology, Section of Gynecologic Oncology, Philippine General Hospital, NationsTaft Avenue, Manila, Philippines

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Corresponding authors:
Jehada-Inn U. Misuari-Alihuddin, MD; jum_alihuddin@yahoo.com
Mailing Address: NHA-047-A Baliwasan Grande, Zamboanga City

Jericho Thaddeus P. Luna, MD; email: rickluna2001@yahoo.com
Department of Obstetrics and Gynecology, Section of Gynecologic Oncology, Philippine General Hospital, NationsTaft Avenue, Manila, Philippines

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Cytoreductive surgery with maximal tumor debulking followed by platinum-based systemic chemotherapy is a key component of ovarian cancer treatment. Many experts now claim that complete resection, defined as absence of gross residual tumor, should be the goal of optimal cytoreductive surgery in ovarian cancer.[3-5] Cumulative data showed that debulking to microscopic disease, called R0 for gynecologic purposes, is associated with improved prognosis and should be the goal of surgical management. However, despite all efforts for maximal cytoreductive surgery, optimal cytoreduction is not always possible in patients with late stage disease.[6]

EOC is usually managed with exploratory laparotomy, total hysterectomy with bilateral salpingo-oophorectomy, complete surgical staging and/or tumor debulking. Primary surgery is done to achieve optimal cytoreduction and the amount of residual tumor is one of the most important prognostic factors affecting survival of EOC.[3-5] Many gynecologic oncologists administer neoadjuvant chemotherapy (NAC) in patients with advanced EOC when optimal primary cytoreductive surgery is not be feasible.[7,8] The timing of interval debulking remains to be controversial. Proponents of NAC cite the need for less complex surgery leading to fewer postoperative complications and patients' morbidity. Several international studies were conducted to predict the possibility of optimal cytoreduction utilizing imaging results, laparoscopic findings, clinical characteristic and Cancer Antigen-125 (CA-125) levels.[9-11] There are, however, no local studies conducted regarding the feasibility of predicting optimal cytoreduction

using these factors.

This study's main objective was to determine the clinical characteristics that are predictive of maximal cytoreduction. As such, it may help tailor subsequent patients' treatment according to the predicted resectability. Considering that patients who undergo suboptimal debulking will have minimal benefit from such surgery, this study will help stratify patients preoperatively and offer them an alternate approach to the current standard of care.

OBJECTIVES

The main objective of this study was to determine clinical characteristics of patients diagnosed with EOC that are predictive of optimal cytoreductive surgery in a tertiary government hospital from January 1, 2013 to December 31, 2017.

Specific Objectives were as follows:

1. To describe the clinical characteristics of patients diagnosed with EOC who underwent primary cytoreduction in terms of the following variables:
   a. Age
   b. Obstetric Score
   c. Body Mass Index (BMI)
   d. Education
   e. Occupation
   f. Eastern Cooperative Oncology Group (ECOG) status
   g. Co-morbidities (such as hypertension, diabetes or other cancers, family history of cancers)
   h. Preoperative extent of disease (as described by Horowitz et al. in 2017[12]) - Initial site of disease identified on ultrasound imaging
      - I-low (Imaging-low): with pelvic and retroperitoneal spread
      - I-mid: with additional spread to the abdomen but sparing the upper abdomen
      - I-high: with the presence of upper abdominal disease affecting the diaphragm, liver, spleen, or pancreas
   i. Ascites
   j. Pre-operative Cancer Antigen (CA) – 125 value
   k. Intraoperative extent of disease (as described by Horowitz et al. in 2017[12])
      - DS – low: with pelvic and retroperitoneal spread
      - DS-mod: with additional spread to the abdomen but sparing the upper abdomen
      - DS-high: with the presence of upper abdominal disease affecting the diaphragm, liver, spleen, or pancreas.
   l. Stage
   m. Histology

2. To estimate the odds of having optimal cytoreduction using clinical characteristics as predictors of optimal cytoreduction

MATERIAL AND METHODS

Study Setting

This retrospective cohort study utilized data and patient records from Outpatient Department (OPD) at a tertiary government hospital. A list of patients for review was generated using the OPD weekly census of the Section of Gynecologic Oncology from January 1, 2013 to December 31, 2017. Patients with histologically confirmed frankly malignant EOC who underwent primary surgery with a gynecologic oncologist being part of the surgical team were included in the study. Patients with incomplete or absent medical records (i.e. lack of information regarding preoperative evaluation of the extent of disease, preoperative CA-125, surgical procedure performed, intraoperative findings, residual disease description, and incomplete pathologic report), patients with non-epithelial histologic diagnosis and those with synchronous malignancies were excluded.

Patient population and Medical Record Abstraction

We identified 263 patients with histologically confirmed epithelial ovarian cancer who underwent primary cytoreductive surgery in a tertiary government hospital between January 1, 2013 to December 31, 2017. We excluded 5 patients with synchronous malignancies and an additional 40 patients who did not meet the inclusion criteria (incomplete medical records). After all exclusions, 218 cases were available for analysis.

A data collection form prepared by the investigator was used to obtain the following data: Patient demographics (age at diagnosis, ECOG status, gravidity and parity, BMI, co-morbidities), preoperative extent of disease utilizing imaging results in the form of transvaginal or holo-abdominal ultrasound, pre-operative CA-125 level, surgical procedure performed, intraoperative findings (such as presence of ascites and extent of disease, size of tumor and residual volume), stage and histopathologic diagnosis.

Data Analysis

For the descriptive analysis, the frequencies and percentages were presented for nominal and ordinal variables such as ECOG, stage, BMI, age group, ascites, preoperative and intraoperative extent of disease. In addition, the means and standard deviation were presented for discrete and continuous variables such as age and CA-125. The categorical baseline demographic characteristics were compared between patients with optimal cytoreduction and sub-optimal cytoreduction using Chi-squared test or Fisher's exact test (i.e. when the expected values per cell is less than five in more than 20% of the cells) while continuous normal variables were compared using the independent Student's t-test. For the inferential analysis, the odds ratio was estimated for all candidate predictors along with their 95% confidence interval and p-values. Both univariate and multivariate logistic regression analysis were done. P value of < 0.05 was considered significant. For this cohort study, the measurement of association used was relative risk or risk ratio (RR). This was computed by dividing the risk among exposed and unexposed.

Development of a model or set of predictors required two techniques. An exploratory univariate analysis was performed to identify crude predictors of optimal cytoreduction among the given clinical characteristics (full model). Once a full model was determined, this was then reduced using a backward selection process with a covariate retention threshold of p<0.20, after which final analysis would give the final model. All analysis was done using STATA/SE14.1(STATA CORP, Texas, USA).

RESULTS

A total of 218 patients were available for descriptive and inferential analysis. One-hundred forty-five patients had optimal cytoreduction while 73 had sub-optimal cytoreduction. The patients had a median age of 49 years. Majority of the patients were multiparous (58%), had a median BMI of 20 kg/m2 (40% of patients), finished high school (51%), were unemployed (49%), and had an ECOG score of 0. The distribution of patients into different levels of age group, Obstetric Score, BMI, highest educational attainment, occupation, and ECOG score were not statistically different for patients who had optimal or sub-optimal cytoreduction. Table 1 summarizes the key demographic characteristics of the participants.

About 6 in every 10 patients who had optimal cytoreduction or non-optimal cytoreduction had no comorbidity, 68% and 60%, respectively. Preoperatively, the extent of disease was limited to pelvic or retroperitoneal spread (I-low) in majority of patients who had optimal cytoreduction (95%) or non-optimal cytoreduction (80%). Most of the patients who had optimal cytoreduction had no preoperative ascites (75%) as compared to those who had non-optimal cytoreduction (41%). The median CA-125 value was 260 U/ml but discrepancy between those who had optimal cytoreduction or non-optimal cytoreduction was largely apparent – 144 and 1000 U/ml, respectively.

Intraoperatively, the extent of disease was limited to pelvic cavity (DS-low) in about 80% of patients who had optimal cytoreduction and 5% of patients who had non-optimal cytoreduction. Intraoperative ascites was noted in 70% of patients who had optimal cytoreduction and in 96% of patients with non-optimal cytoreduction. The median size of tumor for those who had optimal cytoreduction or non-optimal cytoreduction was 3400 cm^3 and 1200 cm^3, respectively. The median size of residual tumor in the non-optimal cytoreduction group was 4 cm. More than 80% of patients who had optimal cytoreduction had stage I or II malignancy while more than 95% of patients who had non-optimal cytoreduction had stage III or IV malignancy (Figure 1). Majority of tumors of patients who had optimal cytoreduction were mucinous (43%) while tumors of those who had non-optimal cytoreduction were of serous histology (56%) (Figure 2). Table 2 summarizes the clinical profiles of patients involved in the study.

A simple logistic regression analysis was done to determine the independent predictors of optimal cytoreduction (Table 3). The pre-operative extent and intraoperative extent of disease, presence of ascites, CA-125 value, size of primary tumor, stage of disease, and mucinous and serous histologic types were independent predictors of optimal cytoreduction. Specifically, a low preoperative extent of disease as compared to high extent of disease was associated with more than 14 times increased

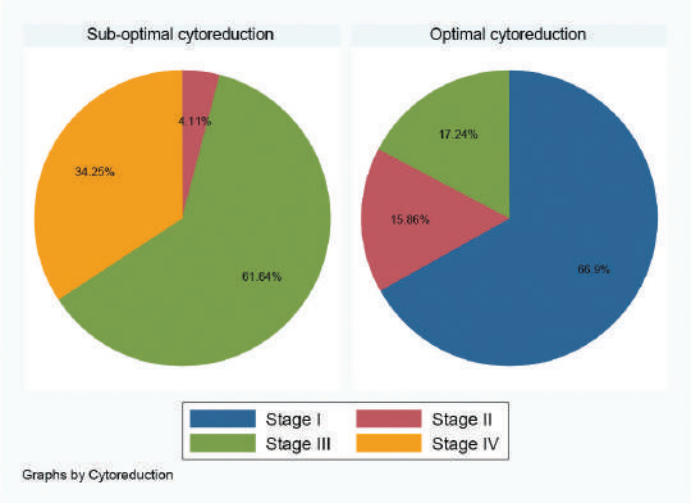

Figure 1. Distribution of stage of disease by cytoreduction outcomes

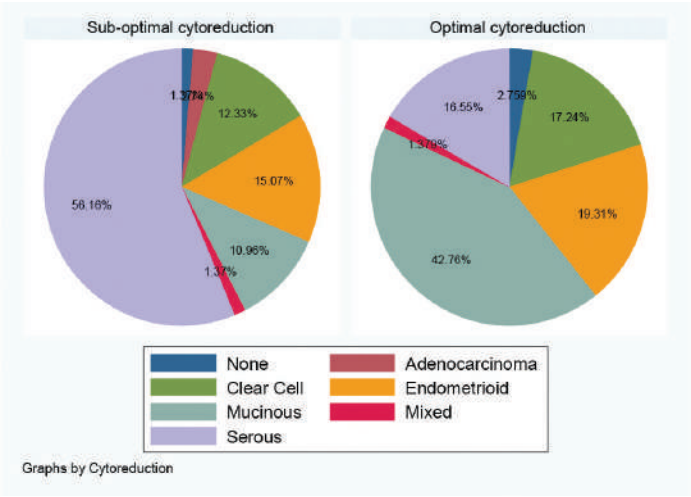

Figure 2. Distribution of histologic types by cytoreduction outcomes

odds of optimal cytoreduction (95% CI 1.68-121.22) but not mid extent (95% CI 0.38-42.18). Similarly, the absence of pre-operative ascites conferred more than four times increased odds of observing optimal cytoreduction (95% CI 2.38-7.90).

Likewise, a low and mid intra-operative extent of disease as compared to high extent, and the absence of intra-operative ascites were highly predictive of optimal cytoreduction. A CA-125 value of less than 500, in contrast with ≥ 500, was also associated with almost six times increased odds of optimal cytoreduction (95% CI 3.09-10.54). Furthermore, for every one centimeter increase in the size of primary tumor, there was an associated 8% increased odds of optimal cytoreduction (95% CI 1.04-1.12). A Stage I or Stage IV disease were perfectly predictive of optimal and non-optimal cytoreduction, respectively. A Stage II disease, as compared to Stage III, was associated with almost 14 times increased odds of optimal cytoreduction (95% CI 3.77-50.57). Histology-wise, a mucinous type tumor was associated with more than six times increased odds of optimal cytoreduction (95% CI 2.71-13.57). In contrast, the presence of serous tumor was associated with 85% decreased odds of optimal cytoreduction (95% CI 0.08-0.29).

In the multiple logistic regression analysis, the variables with p-value of less than 0.15 were included. The variable

"stage of disease", albeit having a highly statistically significant p-value in the simple logistic regression analysis, was not included in the final regression analysis since Stage I and Stage IV disease were perfectly predictive of optimal and non-optimal cytoreduction, respectively. Thus, after adjusting for the effects of covariates, only the pre-operative and intra-operative extent of disease were found to be significantly predictive of optimal cytoreduction. In particular, a low or mid intra-operative extent of disease, as compared to high extent of disease, were associated with more than 900 and 100 times increased odds of optimal cytoreduction (p-values < 0.001), respectively. A low preoperative extent of disease as compared to high extent appeared to be related to more than 15 times increased odds of optimal cytoreduction; however, this did not achieve a statistical significance (95% CI 0.99-241.06). Interestingly, a mid preoperative extent of disease as compared to high extent, was associated with more than 33 times increased odds of optimal cytoreduction (95% CI 1.21-923.31). Table 4 summarizes the adjusted odds ratios, 95% confidence intervals, and p-values of the variables included in the multiple logistic regression analysis.

DISCUSSION

This retrospective study explored the clinical characteristics predictive of optimal primary cytoreduction in patients diagnosed with epithelial ovarian carcinoma. The study identified the following as predictors of optimal cytoreduction: presence of ascites, CA-125 value, size of primary tumor, stage of disease and specific histology types and the extent of disease. However, the only statistically significant predictors of optimal cytoreduction were preoperative mid-extent of disease as well as low and mid intra-operative extent of disease.

Volume of ascites at primary surgery is a biomarker of

Table 1. Demographic Characteristics of the study population

VARIABLES	FREQUENCY			
	Optimal cytoreduction n=145 (%)	Non-optimal cytoreduction n=73 (%)	Total n=218 (%)	p-value
Age				
Median (range)	49 (42, 56)	52 (45, 57)	49 (42, 56)	
≤ 40	32 (22.07)	8 (10.96)	40 (18.35)	0.142
41-65	108 (74.48)	62 (84.93)	170 (77.98)	
> 65	5 (3.45)	3 (4.11)	8 (3.67)	
OB Score				
Median (range)	2 (0, 4)	2 (0, 4)	2 (0, 4)	
G0	42 (29.17)	20 (27.40)	62 (28.57)	0.897
G1-G5	83 (57.64)	43 (58.90)	126 (58.06)	
G6-G10	17 (11.81)	10 (13.70)	27 (12.44)	
G11-G15	2 (1.39)	0	2 (0.92)	
Body mass index				
Median (range)	20.2 (18, 23.29)	19.20 (16.9, 22.54)	20 (17.6, 23.1)	
Underweight (< 18.5)	45 (31.03)	31 (42.47)	76 (34.86)	0.328
Normal (18.5-22.9)	58 (40.00)	28 (38.36)	86 (39.45)	
Overweight (23-24.9)	22 (15.17)	7 (9.59)	29 (13.30)	
Obese I (25-29.9)	16 (11.03)	7 (9.59)	23 (10.55)	
Obese II (>30)	4 (2.76)	0	4 (1.83)	
Education				
College	41 (28.28)	18 (24.66)	18 (24.66)	0.291
High School	74 (51.03)	37 (50.68)	111 (50.92)	
Elementary	30 (20.69)	16 (21.92)	46 (21.10)	
No formal education	0	2 (2.74)	2 (0.92)	
Occupation				
Unemployed	73 (50.34)	34 (46.58)	107 (49.08)	0.879
Housewife	30 (20.69)	16 (21.92)	46 (21.10)	
Employed	42 (28.97)	23 (31.51)	65 (29.82)	
ECOG Score				
0	140 (96.55)	68 (93.15)	208 (95.41)	0.365
1	4 (2.76)	4 (5.48)	8 (3.67)	
2	0	1 (1.37)	1 (0.46)	
3	1 (0.69)	0	1 (0.46)	
4	0	0	0	

Table 2. Clinical Profile of the study population

VARIABLES	FREQUENCY			
	Optimal cytoreduction n=145 (%)	Non-optimal cytoreduction n=73 (%)	Total n=218 (%)	p-value
Co-morbidity				
With	47 (32.41)	29 (39.73)	76 (34.86)	0.296
Without	98 (67.59)	44 (60.27)	142 (65.14)	
Preoperative variables				
Extent of disease				
I - high	1 (0.69)	6 (8.22)	7 (3.21)	<0.001
I - mod	6 (4.14)	9 (12.33)	15 (6.88)	
I - low	138 (95.17)	58 (79.45)	196 (89.91)	
Presence of Ascites				
Absent	109 (75.17)	30 (41.10)	139 (63.76)	<0.001
Present	36 (24.83)	43 (58.90)	79 (36.24)	
CA-125 value				
Median (range)	144 (52.25)	1000 (338, 1127)	261.1 (76, 1000)	<0.001
< 500	105 (72.41)	23 (31.51)	128 (58.72)	
≥ 500	40 (27.59)	50 (68.49)	90 (41.28)	
Intraoperative variables				
Presence of Ascites				
Absent	43 (29.66)	3 (4.11)	46 (21.10)	<0.001
Present	102 (70.34)	70 (95.89)	172 (78.90)	
Extent of disease				
DS - high	1 (0.69)	50 (68.49)	51 (23.39)	<0.001
DS - mod	28 (19.31)	19 (26.03)	47 (21.56)	
DS - low	116 (80.00)	4 (5.48)	120 (55.05)	
Size of primary tumor (cm)				
Mean	20.9 x 17.3 x 11.67	15.7 x 11.9 x 8.15	19.1 x 15.5 x 10.5	-
Median	20 x 17 x 10	15 x 10 x 8	17.5 x 15 x 10	
Volume of primary tumor (cm^3)				
Mean (SD)	7093.21 (11328.87)	2327.27 (3699.67)	5497.27 (9736.11)	0.0006
Median	3960 (1368, 8400)	1200 (512, 2560)	2245 (720, 6000)	
Stage of Disease				
I	97 (66.90)	0	97 (44.50)	<0.001
II	23 (15.86)	3 (4.11)	26 (11.93)	
III	25 (17.24)	45 (61.64)	70 (32.11)	
IV	0	25 (34.25)	25 (11.47)	
Histology				
Adenocarcinoma	0	2 (2.74)	2 (0.92)	<0.001
Clear cell	25 (17.24)	9 (12.33)	34 (15.60)	
Endometrioid	28 (19.31)	11 (15.07)	39 (17.89)	
Mucinous	62 (42.76)	8 (10.96)	70 (32.11)	
Mixed epithelial	2 (1.38)	1 (1.37)	3 (1.38)	
Undifferentiated	0	0	0	
Transitional	0	0	0	
Serous	24 (16.55)	41 (56.16)	65 (29.82)	
None	4 (2.76)	1 (1.37)	5 (5.29)	

Table 3. Simple logistic regression analysis for independent predictors of optimal cytoreduction

Variables	Odds ratio, crude	p-value	95% CI
Age			
<40*			
41-65	0.44	0.051	0.19, 1.00
>65	0.42	0.292	0.08, 2.12
OB Score (n=215)			
G0*			
G1-G5	0.92	0.799	0.48, 1.76
G6-G10	0.81	0.661	0.32, 2.08
G11-G15	-	-	-
Weight (kg)	1.03	0.074	0.99, 1.05
Height (cm)	1.01	0.506	0.99, 1.03
Body mass index "Asian Criteria" (n=214)			
Normal (18.5 – 22.9)*	0.70	0.278	0.37, 1.33
Underweight (<18.5)	1.52	0.396	0.58, 3.97
Overweight (23 – 24.9)	1.10	0.846	0.41, 2.99
Obese I (25 – 29.9)	-	-	-
Obese II (≥ 30)			
Education (n=216)			
College*			
High School	0.82	0.643	0.36, 1.87
Elementary	0.88	0.708	0.44, 1.73
No formal education	-	-	-
Occupation			
Unemployed*			
Housewife	0.87	0.716	0.42, 1.81
Employed	0.85	0.626	0.44, 1.63
ECOG Score			
0*			
1	0.49	0.317	0.12, 2.00
2	-	-	-
3	-	-	-
4	-	-	-
Any comorbidity			
With*			
Without	1.37	0.286	0.77, 2.46
Pre-operative extent of disease			
I – High*			
I – Mid	4.0	0.249	0.38, 42.18
I – Low	14.27	**0.015**	1.68, 121.22
Preoperative Ascites			
Present*			
Absent	4.34	**<0.001**	2.38, 7.90
CA-125 value			
≥500*			
<500	5.71	**<0.001**	3.09, 10.54
Size of primary tumor[1]	1.08	**<0.001**	1.04, 1.12
Intraoperative extent of disease			
DS – High*			
DS – Mid	73.68	**<0.001**	9.36, 580.10
DS – Low	1,450	**<0.001**	158.07, 13,300.67
Presence of Intraoperative Ascites			
Present*			
Absent	9.84	**<0.001**	2.93, 32.96
Stage of Disease[2]			
I	-	**-**	-
II	13.8	**<0.001**	3.77, 50.57
III*	-	**-**	-
IV	-	**-**	-
Histology			
Adenocarcinoma	-	-	-
Clear cell	1.48	0.348	0.65, 3.36
Endometrioid	1.35	0.442	0.63, 2.89
Mucinous	6.07	**<0.001**	2.71, 13.57
Mixed epithelial	1.01	0.995	0.09, 11.29
Undifferentiated	-	-	-
Transitional	-	-	-
Serous	0.15	**<0.001**	0.08, 0.29

[1] largest diameter in cm treated as continuous variable

[2] Stage I disease predicts optimal cytoreduction perfectly while Stage IV disease predicts non-optimal cytoreduction perfectly

Table 4. Multiple logistic regression analysis

Variables	Odds ratio, crude	p-value	95% CI
Age			
<40*			
41-65	0.60	0.477	0.14, 2.48
>65	1.39	0.904	0.01, 282.28
Weight (kg)	1.01	0.851	0.95, 1.07
Pre-operative extent of disease			
I – High*	33.42	**0.038**	1.21, 923.31
I – Mid	15.45	0.051	0.99, 241.06
I – Low			
Preoperative Ascites			
Present*			
Absent	0.99	0.986	0.27, 3.58
CA-125 value			
≥500*			
<500	2.18	0.243	0.59, 8.07
Size of primary tumor (largest diameter in cm treated as continuous variable)	1.01	0.712	0.94, 1.092
Intra-operative extent of disease			
I – High*	110.11	**<0.001**	11.05, 1097.38
I – Mid	936.52	**<0.001**	85.50, 10257.65
I – Low			
Intra-operative Ascites			
Present*			
Absent	1.45	0.679	0.24, 8.45
Histology			
Mucinous	1.06	0.943	0.19, 5.83
Serous	0.32	0.082	0.08, 1.16

worse clinical outcomes. Various studies revealed that large volume of ascites are commonly correlated with suboptimal cytoreduction but these factors could only be correlated with other predictors rather than true predictors.[10,13] The present study confirms the findings of previous cohorts that identified ascites as risk factors for sub-optimal cytoreduction.[11]

Biomarkers such as CA-125 can be utilized to predict resectability. Given that CA-125 levels are elevated in more than 90 % of patients,[14] and can be a surrogate marker for the extent of tumor disease, several studies were conducted to identify threshold level at which optimal cytoreduction is not feasible. The predictive value of CA-125 was initially studied by Chi, et al. which was followed by succeeding studies in their respective populations.[3] Our study found that a CA-125 value of less than 500 U/mL, in contrast with ≥ 500 U/mL, was associated with almost six times increased odds of optimal cytoreduction (95% CI 3.09-10.54). This was consistent with a meta-analysis by Kang et al which concluded that CA-125 cut off value of 500 IU/ml (odds ratio = 3.7) is the critical value in the ability to predict suboptimal cytoreduction with a specificity of 63% and sensitivity of 69%.[15] However, a local study by Luna, et al. revealed that preoperative serum CA-125 level of 150 U/ml was able to predict optimal versus suboptimal cytoreduction with an accuracy of 87.7%, sensitivity of 78% and a false positive rate of 24%.[16]

Our study revealed that stage II, compared to stage III, was associated with almost 14 times increased odds of optimal cytoreduction (95% CI 3.77-50.57). In those with less extensive tumor spread, optimal cytoreduction can be achieved with relatively simple surgery. In our study, more than 80% of patients who had optimal cytoreduction had stage I or II malignancy while more than 95% of patients who had non-optimal cytoreduction had stage III or IV malignancy. Unfortunately, majority of the patients diagnosed with ovarian cancer present with advanced stage disease.[17-21] Residual tumor after surgery and before adjuvant chemotherapy is an important determinant of prognosis and this has been proven by studies on advanced EOC.[22-25] Despite aggressive surgical approaches in the management of patients diagnosed with ovarian carcinoma, the extent of the tumor bulk and its location may prohibit optimal resection at primary surgery. The success rate of achieving optimal cytoreductive surgery varies among reporting institutions, depending on their surgical skills and practices. Different high-volume institutions with a dedicated surgeon and multidisciplinary team frequently report an excellent rate of optimal cytoreduction.[26] In centers with particular interest in cytoreductive surgery, the rate of optimal resection ranges from 60-90%.[8,20]

There has been some evidence suggesting that some histologic types were more likely to be completely resected. A study by Bamias et al. suggested that histologic types such as mucinous tumors were more likely to be resected than a serous type.[27] Our study revealed that mucinous tumor was associated with more than six times increased odds of optimal cytoreduction (95% CI 2.71-13.57) while serous tumor was associated with 85% decreased odds of optimal cytoreduction (95% CI 0.08-0.29) but was not statistically significant after controlling the effects of other variables.

In this retrospective study, we observed that preoperative mid-extent of disease and low and mid intra-operative extent of disease were the only statistically significant predictors of optimal cytoreduction. The preoperative mid- extent of disease can be explained by the capability of the sonologist in detecting lymphadenopathy and utilization of International Ovarian Tumor Analysis (IOTA) that greatly contributed to the definitive management. Ultrasonography has high sensitivity to detect abnormality in the pelvis, omentum and inguinal nodes but has lesser sensitivity in other sites such as subdiaphragmatic surface, small bowel and mesentery.[28-30] However, it is important to note that although the mid pre-operative extent of disease was significantly predictive (i.e., p-value 0.038) of optimal cytoreduction using the high pre-operative extent as reference in the multiple regression analysis, the confidence intervals were too wide (i.e., OR 33.42, 95% CI 1.21-923.31) which could suggest an unstable estimate probably secondary to a small number of observations (i.e. n=15 in mid preoperative extent of disease and n=196 in low preoperative extent of disease). Thus, a larger number of observations in the mid-preoperative extent of disease category, as in the low preoperative extent of disease category, might be necessary in order to determine the true association between optimal cytoreduction and categories of pre-operative extent of disease.

Disease limited to pelvic, retroperitoneal spread or spread to the abdomen but sparing the upper abdomen (DS-low, DS-mid) was observed to be statistically significant predictors of optimal cytoreduction. This may be because majority of patients were diagnosed at an early stage (n=97).

There were some limitations to this study. First, this is a retrospective analysis of a single-center cohort of patients with epithelial ovarian malignancy. The important predictors vary between institutions depending on surgical practice and cytoreduction rates such that our results may not be applicable to other institutions. Second, since the study was conducted in a tertiary government hospital, preoperative imaging only in the form of ultrasound was done since not all patients could afford imaging by CT scan.

CONCLUSION AND RECOMMENDATION

In summary, preoperative mid-extent of disease and low and mid intra-operative extent of disease are the only statistically significant predictors of optimal cytoreduction. Identification of risk factors for suboptimal cytoreduction in small retrospective populations such as ours and all previously published cohorts, are not reproducible in alternate population. Ultimately, only a multi-institutional prospective trial would answer the question of whether or not an accurate and reproducible predictor model using clinical characteristics, serum biomarkers and imaging modalities could be developed for the prediction of surgical outcome. Such a predictor model would have to take into consideration the impact of variable surgical techniques and the surgeon's commitment to aggressive tumor debulking and skills.

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Survival outcome and prognostic significance of lower uterine segment involvement in early stage endometrioid endometrial carcinoma: A single institution study

Joan Kristel B. Abrenica, MD and Jennifer O. Madera, MD, FPOGS, FSGOP, FPSCPC

ABSTRACT

Background: Endometrial cancer is one of the most common gynecologic malignancies. Majority of patients present with early-stage disease and an over-all good prognosis. Treatment typically is surgery and the need for adjuvant therapy is based primarily on the stage of the disease and other prognostic factors. Lower uterine segment involvement (LUSI), though not included in the current FIGO staging for endometrial cancer, may play a role in its management.

Objective: The aim of this study was to investigate the prognostic significance of LUSI in early stage Endometrioid Endometrial Cancer in terms of survival outcome and recurrence free survival (RFS) and to detect its association with other prognostic factors.

Materials and Methods: This was a retrospective cohort study of patients with early stage endometrial cancer operated on in a single institution from January 2004 – December 2014.

Results: Of the 142 cases reviewed, 36 (25.4%) had LUS involvement. The 5-year over-all survival (OS) of patients with positive and negative LUSI were significantly different at 83.8% and 95.4% respectively, (p value = 0.039). There was no significant difference in the RFS at 87.5% and 87.8% respectively, (p value = 0.807). Involvement of LUS was a significant independent prognostic factor correlated with survival risk (HR: 2.37, CI: 1.15 - 6.84, p value = 0.019) and was significantly associated with deeper myometrial invasion (p value = 0.001), presence of lymphovascular space invasion (p value = 0.027) and tumor size of > 2 cm (p value = 0.023).

Conclusion: In surgically staged Endometrioid Endometrial Carcinoma confined to the uterus, LUSI is an independent significant poor prognostic factor associated with decreased OS. It as also associated with other poor prognostic factors such as deep myometrial invasion, tumor size of > 2 cm and positive LVSI. Involvement of LUS, more than an anatomical extension of the tumor, may be regarded as one of the valuable prognostic factors in managing endometrial cancer intra-operatively and post-operatively.

Keywords: *early stage endometrial cancer, lower uterine segment involvement, over-all survival outcome, recurrence free survival*

INTRODUCTION

Endometrial cancer ranked as the 13th most common cancer among both sexes and 8th among women in the Philippines with an estimated 2,451 new cases in 2015. One female out of 100 would have had a chance of developing endometrial cancer before the age 75. The estimated national standardized mortality rate was 1.4 per 100,000 and in the same year, it was the country's 13th leading cause of female cancer deaths with an estimated 565 mortality cases.[1]

Symptoms of endometrial carcinoma develop at an early stage leading to immediate diagnosis, increased survival rate and good prognosis. Treatment is usually surgery followed by individualized adjuvant therapy.[2]

The stage of the disease guides future treatment decisions and remains to be the major predictor of outcomes. Other well-established prognostic factors, though not all incorporated in the staging system, are included in many clinical management algorithms. These are tumor invasion to the myometrium, size, lymphovascular space invasion (LVSI), histologic grade, peritoneal fluid cytology (PFC) and lymph node metastasis.[2,3] Despite taking these variables into account, up to 10-20% of cases will still recur, emphasizing the need for more predictive prognostic markers.[4] At present, it is less clear if tumor location has a prognostic relevance in endometrial cancer.

In the previous editions of the clinical treatment guidelines of the Society of Gynecologic Oncologists of the Philippines (SGOP), isthmic or lower uterine segment involvement (LUSI) necessitated post-operative adjuvant radiotherapy irrespective of histologic grade or depth of myometrial invasion.[5,6] However, this was revised in 2005.[7] And in its latest edition, the Clinical Practice Guidelines (CPG) recognizes LUSI as a predictor of nodal spread in endometrioid carcinoma but not a prognostic factor indicating adjuvant treatment. A locally published study by Fabul et al. already demonstrated a significant correlation between LUSI and nodal involvement in patients with endometrial carcinoma.[8] But the study did not include its effect on outcome and prognosis.

This present study evaluated the effect in the outcome and prognostic significance of LUSI in patients with pathologically negative nodes. To date, there are no local studies that

From the Department of Obstetrics and Gynecology, Jose R. Reyes Memorial Medical Center, Rizal Avenue, Manila

Corresponding authors:
Joan Kristel B. Abrenica, MD; email: joank_05@yahoo.com
Jennifer O. Madera, MD, Department of Obstetrics & Gynecology, Jose R. Reyes Memorial Medical Center, Rizal Avenue, Manila; email: j_obiles@yahoo.com

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investigated its prognostic significance in early stage endometrial carcinoma. Understanding the survival outcome and prognostic value of LUSI can play a vital role in managing early stage endometrial cancer and counseling patients with the disease.

OBJECTIVE

The main purpose of this study is to investigate the survival outcome and prognostic significance of LUSI in early-stage Endometrioid Endometrial Cancer patients. The specific objectives are as follows: 1. To compare the 5-year over-all survival (OS) of patients with LUSI vs. patients without LUSI; 2. To compare the 5-year recurrence-free survival (RFS) of patients with LUSI vs. patients without LUSI; 3. To evaluate the association of LUSI with other poor prognostic factors such as deep myometrial invasion, tumor size (>2 cm), positive LVSI, and higher International Federation of Gynecology (FIGO) grade.

MATERIALS AND METHODS

This is an Institutional Review Board approved retrospective cohort study which included patients surgically staged Endometrioid Endometrial Carcinoma with disease confined to the uterus or stage I using the FIGO staging in a single institution from January 2004 – December 2014.

Retrieval and review of medical records and histopathologic results were done. LUSI was documented based on either histopathologic or gross pathologic description. Final Surgico-Pathologic reports were reviewed to determine the histopathologic LUSI described as the presence of malignant cells invading less than 1 cm above the internal cervical os. The Operative Techniques and intra-operative findings were the basis of the gross LUSI as visible endometrial tumor present less than 1 cm above the internal cervical os. The clinicopathologic characteristics such as myometrial invasion (either < 50% or > 50%), tumor size (< 2 cm or > 2 cm), presence or absence of LVSI, and FIGO grade (Grade 1, 2 or 3) were also obtained from the final Surgico-Pathologic reports.

A. Inclusion Criteria:

This study included patients with stage I Endometrioid Endometrial Carcinoma operated in a single institution from January 2004 – December 2014.

B. Exclusion Criteria:

Patients with advanced disease (stage II, III and IV) or non-endometrioid histology were excluded in the study to limit confounders. It is well-known that clear cell and serous papillary endometrial cancer naturally have aggressive behaviors even in early stages. Data of those with other primary gynecologic malignancies or other fatal comorbidities that may affect survival were omitted from the study. Those who were not operated in the same institution or with missing data or medical records were also not included in the study.

The data were collected from the Medical Records Section – Out Patient Department.

Descriptive statistics was used to summarize the demographic and clinicopathologic characteristics of the patients. Frequency and proportion was used for categorical variables and mean and SD for normally distributed continuous variables. Independent Sample T-test and Fisher's Exact/Chi-square test was used to determine the difference of mean and frequency, respectively, between patients with and without LUSI. OS and RFS were estimated using Kaplan Meier method. Univariate Cox regression model and corresponding 95% confidence intervals were used to analyze the prognostic significance of the different prognostic factors including LUSI. Multivariate comparative analysis was fitted to adjust for the potential confounding by other factors. All statistical tests were two tailed test. Shapiro-Wilk was used to test the normality of the continuous variables. Missing variables was neither replaced nor estimated. All p values < 0.05 were considered significant. STATA 13.1 was used for data analysis.

The primary outcomes of the study were OS and RFS at 5 years. Patients were divided into two groups based on the presence or absence of LUSI. Those with tumor localized in the corpus involving the LUS or localized entirely in the LUS formed Group A while tumors in the corpus without LUSI formed Group B.

OS was defined as the time from the date of surgery until the date of death from any cause. Survivors were censored from the date of last contact. RFS was defined as the time from surgery to disease recurrence or progression. Recurrence was classified as local if documented in the pelvis or vagina, or as distant if found beyond the pelvis such as bones, liver, lung, inguinal region, central nervous system or other distant sites.

Post-operative treatment was administered on an individual basis depending on different prognostic factors necessitating adjuvant therapy, either chemotherapy, radiation therapy or combination of these modalities. At completion of treatment, subjects were typically followed up at 3-month intervals for the first two years, at six month intervals for 3 additional years, and yearly thereafter. Standard surveillance included physical and pelvic examination and Papanicolau test with additional imaging studies and directed biopsies as indicated. All recurrent and progressive diseases were histologically and/or radiographically confirmed.

RESULTS

From January 2004 – December 2014, 286 endometrial cancer patients underwent exploratory laparotomy, peritoneal fluid cytology, hysterectomy, bilateral salpingo-oophorectomy and bilateral lymph node dissection. Some patients underwent radical hysterectomy due to initial consideration of cervical involvement. Most had extrafascial hysterectomy. After the surgery, only 142 patients satisfied the inclusion criteria and only 36 patients (25.4%) had positive LUSI (Group A).

Table 1 showed the demographic profile of patients included in the study. The mean age group was 52 years old. There were no significant differences on the distribution of patients' profile and risk factors between the 2 groups. Distribution of known prognostic factors was shown in Table 2. Overall, patients with LUSI were found to have higher rates of

Table 1. Demographic and Clinical Profile of the patients

	Total	Lower Uterine Segment Involvement		P-Value
		Positive	Negative	
	Frequency (%); Mean ± SD			
Age	52.11 + 9.24	53.03 ± 7.55	51.79 ± 9.75	0.435
BMI				0.449
Overweight 23 – 26.99	55 (38.7%)	14 (38.9%)	41 (38.7%)	
Obese > 27	62 (43.7%)	18 (50%)	44 (41.5%)	
Normal <22.99	25 (17.6%)	4 (11.1%)	21 (19.8%)	
Gravidity				0.631
1-5 Child	109 (76.8%)	27 (75%)	82 (77.4%)	
Nulliparity	31 (21.8%)	9 (25%)	22 (20.8%)	
>5 children	2 (1.4%)	0 (0%)	2 (1.9%)	
Hypertension				0.999
Positive	51 (35.9%)	13 (36.1%)	38 (35.8%)	
Negative	91 (64.1%)	23 (63.9%)	68 (64.2%)	
Diabetes Mellitus				0.518
Positive	14 (10%)	2 (5.6%)	12 (11.3%)	
Negative	128 (90%)	34 (94.4%)	94 (88.7%)	
Menopause				0.835
At 49 yo and above	44 (31%)	12 (33.3%)	32 (30.2%)	
Before 49 yo	98 (69%)	24 (66.7%)	74 (69.8%)	

Table 2. Prognostic factors of the patients

	Total	Lower Uterine Segment Involvement		P-Value
		Positive	Negative	
	Frequency (%)			
Myometrial Invasion				**0.001**
≥ 50%	69 (48.6%)	26 (72.2%)	43 (40.6%)	
< 50%	73 (51.4%)	10 (27.8%)	63 (59.4%)	
LVSI				**0.027**
Positive	39 (27.5%)	15 (41.7%)	24 (22.6%)	
Negative	103 (72.5%)	21 (58.3%)	82 (77.4%)	
Grade				0.452
3	15 (10.6%)	5 (13.9%)	10 (9.4%)	
1 or 2	127 (89.4%)	31 (86.1%)	96 (90.6%)	
Tumor Size				**0.023**
>2 cm	111 (78.2%)	33 (91.7%)	78 (73.6%)	
≤2 cm	31 (21.8%)	3 (8.3%)	28 (26.4%)	

deep myometrial invasion (p value = 0.001), presence of LVSI (p value = 0.027) and tumor size of > 2 cm (p value = 0.023).

The 5-year OS of stage I Endometrioid Endometrial Carcinoma patients with positive and negative LUSI were significantly different at 83.8% and 95.4% respectively, (p value = 0.039) (Figure 1). On the other hand, there was no significant difference in the RFS at 87.5% and 87.8% respectively, (p value = 0.807) (Figure 2). The median survival time was 55.2 months and the median recurrence free time was 56.5 months for Group A as compared to 59.5 months and 58.4 months respectively for Group B.

The impact of different prognostic factors on disease OS and RFS were depicted in Table 3 and Table 4. The most significant factor correlated with survival was LUSI (HR: 3.23, CI: 1.12 - 9.03, p value = 0.007). Furthermore, patients with deep myometrial invasion also had significant worse survival (HR: 5.85, CI: 1.68 - 10.37, p value = 0.018) compared to those with superficial myometrial involvement. In multivariate analysis, only LUSI (HR: 2.37, CI: 1.15 - 6.84, p value = 0.019) remained significantly correlated with survival risk. The results showed that after adjusting for myometrial invasion, LVSI, histologic grade and tumor size, patients with LUSI were 2.37 times more likely to die from the disease within 5 years from the time of surgery as compared to those who have no invasion to the LUS.

On the other hand, there was a trend towards a higher likelihood of recurrence among patients with LUSI (HR: 1.75, CI: 0.51 – 5.98, p value = 0.372) but this did not reach statistical significance.

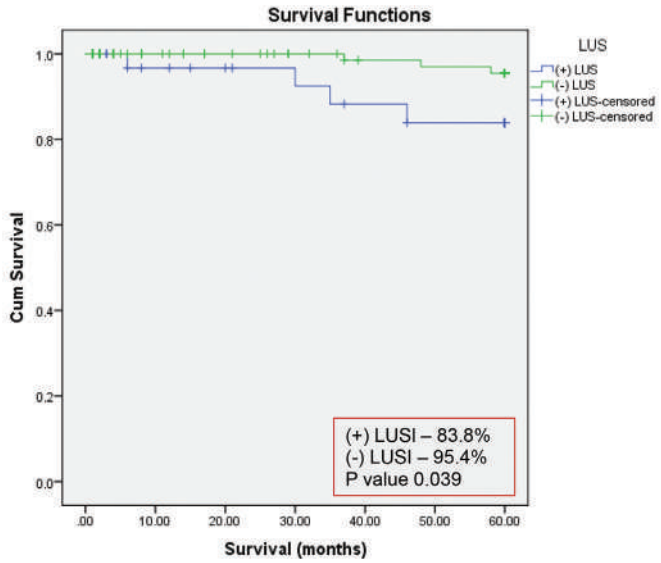

Figure 1. Kaplan-Meier Curve. 5-year OS using LUSI

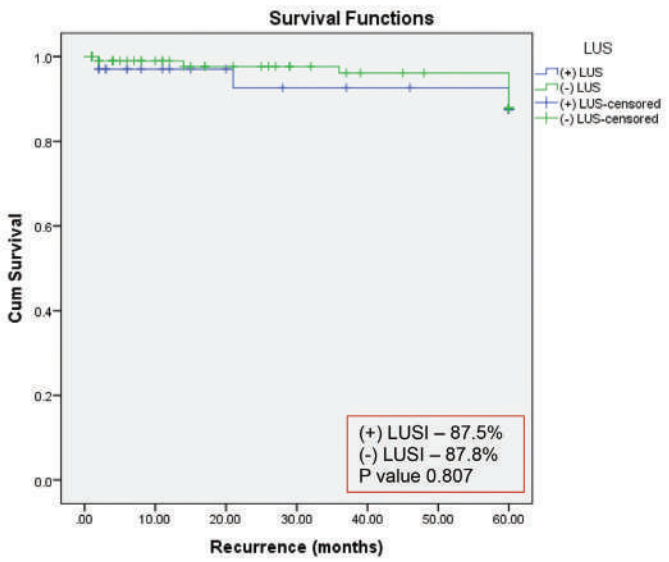

Figure 1. Kaplan-Meier Curve. 5-year RFS using LUSI

Table 3. Association of LUS and other Prognostic Factors to Mortality

	Univariate		Multivariate	
	Crude Hazard ratio (95% CI)	**P-Value**	**Adjusted Hazard ratio (95% CI)**	**P-Value**
LUSI Positive Negative	3.23 (1.12 to 9.03) (reference)	**0.007**	2.37 (1.15 to 6.84) (reference)	**0.019**
Myometrial Invasion ≥ 50% < 50%	5.85 (1.68 to 10.37) (reference)	**0.018**	4.35 (0.98 to 8.41) (reference)	0.068
LVSI Positive Negative	1.39 (0.26 to 7.61) (reference)	0.701	1.42 (0.36 to 3.73) (reference)	0.841
Grade 3 1 or 2	1.0 (reference)	–	1.0 (reference)	–
Tumor Size >2 cm ≤2 cm	0.31 (0.06 to 1.51) (reference)	0.148	0 0.36 (0.10 to 1.93) (reference)	0.367

DISCUSSION

The endometrium is pathologically divided into 2 parts: the uterine corpus (UC) or body and LUS or the anatomic division of the uterus representing the transition from the corpus proper to the cervix.[9] In general, only 3-6% of endometrial cancers originate from the LUS.[2,10,11] Histologically, LUS has characteristics of both the endometrium and cervix in the glandular epithelium and interstitium. It has a thin mucosal membrane and reduced hormonal stimulation response as compared with UC. Lymphatic drainage also differs between the lower and upper segments of the uterus. Therefore, the behavior of tumors in LUS was postulated to be more complex than that of tumors in UC. Because of its anatomical proximity to the cervix, it is likely that LUSI may act like stage II carcinoma and adversely affect over-all prognosis.[2,12,13] Hence, there were studies suggesting post-operative adjuvant treatment in endometrial cancer patients involving LUS.[13] Nevertheless, the current FIGO staging system does not differentiate between disease within the uterine fundus and disease within the LUS.[13,14]

Table 4. Association of LUSI and other Prognostic Factors to Recurrence

	Crude Hazard ratio	95% CI	P-value
LUSI			
Positive	1.75	0.51 to 5.98	0.372
Negative	(reference)	–	
Myometrial Invasion			
≥ 50%	1.33	0.40 to 4.34	0.641
< 50%	(reference)	–	
LVSI			
Positive	1.06	0.28 to 4	0.929
Negative	(reference)	–	
Grade			
3	1.0	–	–
1 or 3	(reference)	–	
Size			
>2 cm	0.52	0.15 to 1.78	0.297
≤2 cm	(reference)	–	

The reported prevalence of LUSI in endometrial cancer ranges from 4%-58%, implying that the threshold for making this diagnosis varies among different physicians. Furthermore, definitions used to describe LUSI in some reports were not clearly specified.[11-13] In this study where LUSI was defined based on gross and histopathologic findings, the 25.4% patients who were noted to have LUSI was comparable to that of Lavie et al which was 24%.[13]

There is no clear definition of the importance of LUSI in completely staged endometrial cancer patients with pathologically negative nodes. Foreign published studies on LUS are retrospective and have varying results.

This current study demonstrated that LUSI is an adverse prognostic factor influencing survival in early stage endometrial cancer. This is similar to that of Kizer et al and Gemer et al which both showed that invasion to LUS was significantly associated with decreased OS.[4,12] As in this analysis, both studies also limited the participants to early stage Endometrioid Endometrial Carcinoma and majority of the patients did not receive adjuvant treatment. Though the former report included some stage II endometrial cancer, it was just 1.2% of the whole population and sub-analysis of only stage I patients verified LUSI to be significantly associated with decreased OS. Other than LUSI, Kizer et al also confirmed grade and age as independent prognostic factors for poorer OS using multivariate analysis.[4] The second study by Gemer et al included a larger study population and also demonstrated an independent effect of LUSI on death and distant recurrence.[12]

Another study in 2008, revealed that patients with LUSI had lower RFS and worse OS compared to those without LUSI. Though it was reported that a greater number of these patients received adjuvant radiotherapy, radiotherapy itself was not found to be an independent factor affecting prognosis. Thus, it was considered that the final outcome results were not compromised by the post-operative treatment.[13] These authors suggested that LUSI influences outcome of patients with endometrial cancer and that it must be taken into consideration in managing patients and deciding upon possible adjuvant treatment.[4,12,13]

On the contrary, other literatures showed that involvement with LUS does not negatively affect outcomes and therefore, should not be considered as an indication of adjuvant treatment. Some authors revealed that it was not an independent prognostic factor for poor survival, but is associated with other poor prognostic factors such as more than one-half myometrial invasion, presence of LVSI, involvement of uterine serosa, lymph node metastasis and higher tumor

Table 5. Local and Distant Recurrences

	Local Recurrence	Distant Recurrence	Other Prognostic Factors
(+) LUS involvement	Pelvis (2)	Bones (1) Liver (1)	Tumor size > 2cm (2) (+) LVSI (1) (+) PFC (1)
(-) LUS involvement	Pelvis (3) Vagina (1)	Bones (1) Liver (1)	Tumor size > 2cm (3) ≥ 50% myometrial invasion (2) Age > 60 (1)

grade. However, these studies have different methodologies like including patients in advanced stages, having majority of their patients not undergoing lymph node evaluation, involving patients with poor histologic types or having a relatively small number of cases with LUSI, all might have altered prognostic outcomes. [9,10,11,15]

In the entire group of patients, only 10 (7%) had recurrences. Four had positive LUSI, and 6 had no LUS invasion, all having other poor prognostic factors. None among these prognostic factors turned out to be significantly correlated with recurrence (Table 4). However, the validity of this analysis may have been compromised by the small number of this adverse outcome. A larger series is necessary to elucidate significant effect of prognostic factors on recurrence while controlling other variables.

Results also showed that invasion to LUS was associated more with deep myometrial invasion, presence of LVSI and larger tumor size (> 2cm). These data suggest the possibility of considering LUSI as an alternative intra-operative pathologic evaluation when deciding whether or not to stage a patient with endometrioid histology.

The current CPG recommends that lymphadenectomy should be done on patients considered as high risk (tumor grade 3 with myometrial invasion > 50%). It may also be done on patients with intermediate risk (myometrial invasion > 50% or grade 3 superficial myometrial invasion) for staging purposes.[3] In a local study by Bagadiong et al, it was noted that there was no significant difference between the pre-operative and post-operative tumor grades.[16] Therefore, the pre-operative tumor grade from endometrial biopsy prior to the hysterectomy may be used as basis for doing lymphadenectomy.

However, precise evaluation of myometrial invasion may sometimes be difficult to achieve intra-operatively.[14] It is not unusual to find cancers that are classified as stage IA during surgery and turn out to be stage IB post-operatively. Likewise, presence of LVSI cannot be always assessed accurately even with intra-operative frozen section.[14] If the intra-operative diagnosis is uncertain, then the surgery may be inadequate. LUSI may also be considered and assessed at the time of pathologic gross and frozen section when in doubt if there is deep myometrial invasion or presence of LVSI.[14] Still, more prospective studies are warranted to determine if invasion to LUS alone can be used as an indication for lymphadenectomy and if its evaluation may be as reliable as gross or frozen section to permanent section for deep myometrial invasion, tumor grade 3 and presence of LVSI.

CONCLUSION

In surgically staged Endometrioid Endometrial Carcinoma confined to the uterus, LUSI is an independent significant poor prognostic factor associated with decreased OS. It as also associated with other poor prognostic factors such as deep myometrial invasion, tumor size of > 2 cm and positive LVSI. Involvement of LUS, more than an anatomical extension of the tumor, may be regarded as one of the valuable prognostic factors in managing endometrial cancer intra-operatively and post-operatively.

LIMITATIONS AND RECOMMENDATIONS

There are several limitations of this study. First, this is a retrospective analysis spanning a 10-year period involving a number of surgeons and pathologists with varying techniques and manner of describing gross and pathologic findings. Though the study used a strict definition of LUSI, a more accurate definition could have been achieved if all slides were available for review by a single pathologist. Second, adjuvant treatment in the form of radiation and/or chemotherapy was administered selectively to patients based on other prognostic factors and not on LUSI, which might have affected the results. Third, data gathered were limited by the availability and accuracy of the records retrieved at the Medical Records. The population was derived from a single tertiary hospital and results may not be generalizable to other population.

It is suggested that further prospective and multicenter studies with larger population and same objectives be done to strengthen the results of this current analysis. Additional studies may reveal the actual prognostic impact of LUSI on intra- and post-operative treatment for early staged endometrial cancer.

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Dermatomyositis as a paraneoplastic syndrome in high grade serous ovarian carcinoma: A case report and review of literature

Reya Andrea H. Hurtado, MD and Renee Vina G. Sicam, MD, FPOGS, FSGOP, FPSGE

ABSTRACT

Dermatomyositis occurring as a paraneoplastic syndrome in a high grade serous ovarian carcinoma is rare and treating the disease condition is a challenge.

A 46-year-old, nulligravid presented with an eight-month history of rash, joint pain, and progressive muscular weakness. Dermatomyositis was diagnosed in the background of cutaneous manifestations, progressive muscle weakness, elevated muscle enzymes and electromyographic findings. She was treated with prednisone, however during the course of treatment, she had an emergency exploratory laparotomy for a pelvic mass in complication. The patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, right hemicolectomy, and ileocolic side to side anastomosis. Histopathology revealed a high grade serous ovarian carcinoma, with a presumptive stage IIB. Post-operatively, the myositis partially improved. Steroid therapy was continued for two months. Chemotherapy was delayed because of repeated infections due to her immunosuppressed state.

Dermatomyositis is highly associated with malignancy. Early detection as well as treatment of the underlying malignancy can improve survival of this simultaneous condition.

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Keywords: *dermatomyositis, ovarian cancer, paraneoplastic syndrome*

INTRODUCTION

Dermatomyositis is a rare, acquired inflammatory myopathy with an incidence of 0.5-0.89 per 100,000.[1] It is characterized by progressive, proximal, symmetrical weakness, with cutaneous manifestations of erythema around the eyes and on sun exposed areas, with increased concentration of muscle enzymes. Majority of cases are considered to be idiopathic, however 15-30% of adult -onset dermatomyositis is associated with an underlying malignancy. Patients with dermatomyositis have a 6-fold risk of having cancer, with lung, breast, gastrointestinal tract and gynecologic as the most common sites.[1] The occurrence of dermatomyositis with ovarian malignancy is as high as 13.3 in one series.[2]

Dermatomyositis as a paraneoplastic syndrome associated with a high-grade serous carcinoma is a rare entity and only few case reports were reported worldwide. In such cases, malignancy is an established risk factor for poor prognosis and is the leading cause of death in patients with dermatomyositis (54.6%).[3] Thus, recognizing dermatomyositis and its predilection to occur before the diagnosis of ovarian carcinoma would prompt routine screening to rule out an adnexal mass in female patients. Early diagnosis of ovarian cancer associated with dermatomyositis significantly affects prognosis of this paraneoplastic syndrome.

Herein we report a case of dermatomyositis presenting as a paraneoplastic syndrome in high grade serous ovarian carcinoma. The disease course, treatment and outcomes of this case were reviewed with cited case reports.

CASE DISCUSSION

We present a case of a 46-year-old nulligravid with an eight-month history of facial rash and progressive symmetrical muscle weakness. Dermatomyositis was diagnosed based on cutaneous manifestations and muscle weakness, and elevated muscle enzymes: Creatinine Kinase Total 1368 U/L (nv: 30-135U/L), Creatinine kinase MM (skeletal muscle) 1328.68 U/L (nv:<115U/L), and Creatinine Kinase MB (heart) 39.50 U/L (nv: 0-16 U/L). Electromyography showed atrial fibrillations, complex repetitive discharge, and positive sharp waves. Skin biopsy revealed interface dermatitis consistent with dermatomyositis.

The primary physician initially treated her with prednisone 20mg/day, which slightly alleviated the skin lesions. On the second month, she experienced sudden right lower quadrant pain and was brought to a local hospital where she was diagnosed with a surgical abdomen. Explorative laparotomy was done by a general surgeon and referred intraoperatively to a gynecologist. Patient underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy, right hemicolectomy, ileocolic side to side anastomosis. Intraoperatively, there was a right pelvic mass involving the right ovary and fallopian tube adherent to the ascending colon and its mesentery. This adnexal mass was adherent to the right pelvic side wall. The specimen consisted of a right ovarian mass, solid whitish tan which measured 5

Department of Obstetrics and Gynecology, Section of Gynecologic-Oncology Philippine General Hospital, University of the Philippines, Manila

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Corresponding authors:
Reya Andrea H. Hurtado, MD; email: reyaandrea@yahoo.com
Department of Obstetrics & Gynecology, Section of Gynecologic-Oncology
University of the Philippines-Philippine General Hospital, Manila

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x 6 x 3 centimeter (cm). Contralateral ovary measured 3 x 2 x 1 cm, solid with creamy tan surface. Other pelvic structures were grossly normal. Final histology result was high grade serous carcinoma, bilateral ovaries, involving the right fallopian tube, mesenteric mass and nodes, and subserosal colonic wall. Peritoneal fluid washing cytology was positive. Based on these findings, the surgico-pathologic stage was IIB (inadequately staged). It was not reported, however, if all macroscopic tumor was resected.

Postoperatively, cutaneous manifestations and weakness temporarily improved. Serum cancer antigen 125 (CA-125) levels were normal at 20.27 U/mL (nv: 0-35 U/mL). However, two months after surgery, the patient had weakness of the upper extremities and reappearance of facial rash. She was prescribed prednisone and methotrexate with no improvement of symptoms. With persistent and worsening myositis, the patient was referred to a tertiary hospital for further management.

On physical examination, the patient had erythematous rash on sun exposed areas, particularly around the eyelids (Heliotrope rash) (Figure 1), the neck and the back (Figure 2). There were also erythematous papules known as Gottron's papules on the interphalangeal joints of the hands (Figure 3). On motor examination, muscle strength for the upper and lower extremities were 2/5.

Upon admission, methylprednisolone pulse therapy was started with improvement of her myositis symptoms. However, the patient developed pneumocystis carinii pneumonia and hidradenitis suppurativa and was treated with carbapenem. A repeat serum CA-125 level was elevated at 68.5 U/mL (nv:0-35 U/mL). Transvaginal ultrasound showed no pelvic mass at this time. The first cycle of Carboplatin Paclitaxel was given three months after the first admission at our institution. A month after the first cycle of chemotherapy, she eventually deteriorated and expired due to complications of the disease.

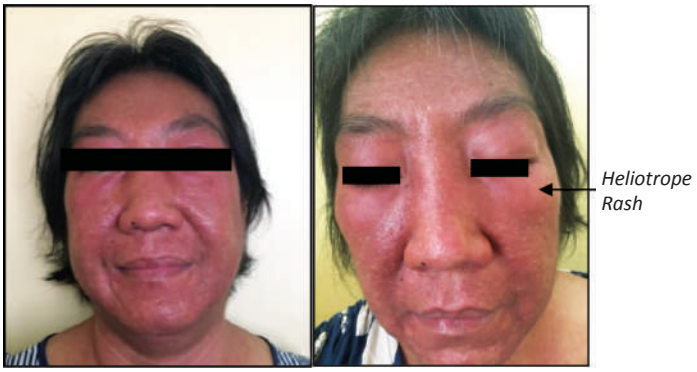

Figure 1. Characteristic cutaneous manifestations of dermatomyositis. A. Photosensitive areas of the face B. Heliotrope rash

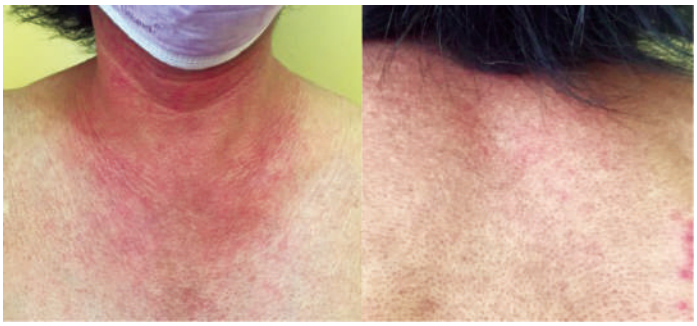

Figure 2. Erythematous rash on the neck and the back (V-sign and Shawl Sign of dermatomyositis)

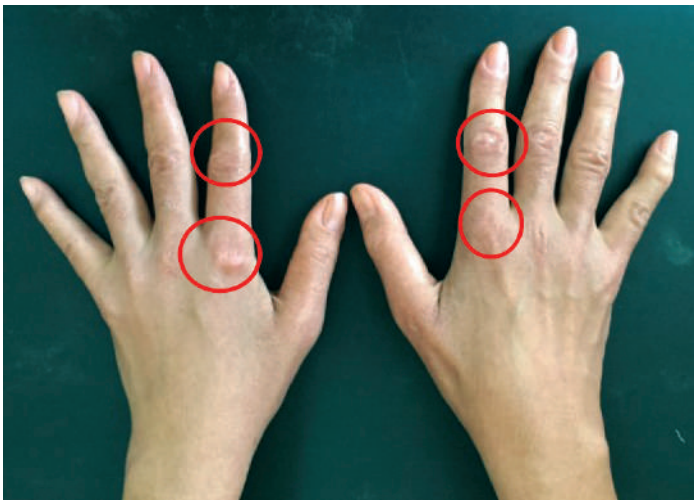

Figure 3. Gottron's Papule (erythematous papules on interphalangeal joints) as manifested by the patient

DISCUSSION

We are presented with a case of a patient with an ovarian malignancy and dermatomyositis. Dermatomyositis is diagnosed using the Bohan and Peter Criteria (1975). This includes cutaneous manifestations around the eyes (heliotrope rash), back (shawl sign) and neck (V-sign), proximal symmetrical muscle weakness, elevated muscle enzymes, and abnormal electromyography.[4] Paraneoplastic syndromes can be triggered by abnormal immune response to proteins from tumors. The inflammatory myopathy and cutaneous manifestations of our patient presented as the paraneoplastic phenomenon of her high grade serous ovarian carcinoma.

Review of literature has shown that dermatomyositis with ovarian malignancy is a rare condition. Several reports around the world have demonstrated that incidence is about 13-26%.[5] Malignancy can be diagnosed before, simultaneously with, or after the diagnosis of dermatomyositis. Onset of carcinoma ranges from 3 months to 6 years with a mean of 2 years after a diagnosis of dermatomyositis.[6] Thirty-five (35) case reports have been published reporting dermatomyositis with ovarian malignancy. These cases described paraneoplastic myositis secondary to ovarian cancer, and the majority were treated surgically with either primary debulking or bilateral salpingo-oophorectomy. The myositis paralleled the course of the ovarian cancer. Complete removal of the tumor usually resulted in an improvement in symptoms and decrease in biomarkers of myositis.[5]

Ten of these case reports presenting dermatomyositis with ovarian malignancy were associated with high grade serous ovarian carcinoma (Table 1). In these case reports,

Table 1. Review of case reports of dermatomyositis with high grade serous ovarian carcinoma describing temporal relationship, treatment given and outcomes.

Studies	Age of patient	Temporal relationship[1]	Stage	Treatment	Outcomes
Nakanishi (1999)	75 yo	Antecedent	IIIA	Tumor debulking then chemotherapy with carboplatin and paclitaxel x 6 cycles	Improvement of symptoms after surgery and chemotherapy No recurrence noted after 3 months
Venhuizen (2005)	48 yo	Antecedent	IIA	Unilateral salphingoopho-rectomy then chemotherapy with carboplatin and paclitaxel x 6 cycles	Improvement of symptoms after surgery and chemotherapy No recurrence of both condition after 16 months
Ngo (2009)	73 yo	Antecedent	IIIB	Hysterectomy with surgical staging	Improvement of symptoms after surgery
Mogami (2012)	2 cases: 1st case: 46 yo 2nd case: 58 yo	2 cases: Antecedent	1st case: 1B 2nd case: stage IV	1st case: Hysterectomy with complete surgical staging 2nd case: Neoadjuvant chemotherapy of carboplatin and paclitaxel x 4 cycles then tumor debulking, followed by 2 more cycles of chemotherapy	1st case: No evidence of disease for both condition for 2 years and 4 months 2nd case: ovarian cancer progression after completed chemotherapy Death from disease after 1 year and 4 months
Hong (2013)	48 yo	Antecedent	IIIA	Tumor debulking then chemotherapy with dose dense paclitaxel and carboplatin x 6 cycles	Improvement of symptoms after surgery Complete remission of ovarian cancer at 15 months after surgery
Christie (2013)	57 yo	Antecedent	unknown stage	Neoadjuvant chemotherapy with carboplatin and paclitaxel x 6 cycles then tumor debulking	Recurrence of ovarian carcinoma after 3 months paralleled with exacerbation of dermatomyositis symptoms Death from disease 18 months after diagnosis
Salmeron (2016)	50 yo	Antecedent	IC	Hysterectomy with complete surgical staging then chemotherapy of carboplatin and paclitaxel x 6 cycles	Improvement of symptoms after surgery and chemotherapy No evidence of disease for 2.5 years
Arshad (2016)	60 yo	Subsequent	IIIB	Tumor debulking	Improvement of symptoms after surgery
Raizman (2017)	63 yo	Antecedent	IIIA	Surgery (optimally debulked) then chemotherapy with carboplatin and paclitaxel 3 cycles	Improvement of symptoms for 5 months
Field (2017)	43 yo	Antecedent	IIIC	Tumor debulking (sub-optimally debulked) then chemotherapy with carboplatin and paclitaxel x 6 cycles and bevacizumab for 16 months	No evidence of disease for 1 year Ovarian cancer recurrence paralleled with recurring dermatomyositis symptoms

[1]*Antecedent: Dermatomyositis was diagnosed before diagnosing ovarian carcinoma.*
Subsequent: Dermatomyositis developed after the diagnosis of ovarian carcinoma.

dermatomyositis presented before the high grade serous ovarian carcinoma was diagnosed. Our case followed the same temporal pattern. The ovarian carcinomas in these case reports were diagnosed through either computed tomography scan or ultrasound as part of the recommended routine diagnostic imaging modality to rule out adnexal masses. As compared to our case, the ovarian malignancy was diagnosed not by imaging but by presenting with a surgical abdomen and subsequent laparotomy.

Dermatomyositis antecedent to ovarian carcinoma suggests a paraneoplastic phenomenon resulting from the ovarian malignancy as seen in our case. On the other hand, in one case reported by Arshad et al, the ovarian carcinoma preceded the development of dermatomyositis which suggests that proteins released by the tumor can stimulate an abnormal immune response leading to an inflammatory reaction affecting the muscle and skin. Either way, antecedent or following an ovarian carcinoma, dermatomyositis results from an abnormal immune response of the body to the ovarian carcinoma.

This is the second case of dermatomyositis associated with a high-grade serous carcinoma reported in a Filipino. The first case was reported last 2009 in which dermatomyositis was diagnosed before the discovery of a pelvic mass by computed tomography scan. It was reported that symptoms of the myositis resolved after surgery for the fallopian tube carcinoma and chemotherapy was advised after, subsequent follow ups were not reported in the case report.[7]

From the reviewed case reports (Table 1), the advantage of routine diagnostic imaging led to early detection of the ovarian malignancy prompting timely intervention with either surgery or chemotherapy which improved the dermatomyositis with ovarian carcinoma. Platinum based chemotherapeutic regimen was used as the first line treatment for the high grade serous carcinoma in these case reports and initiation of chemotherapy usually resulted to improvement and resolution of the dermatomyositis.

However, overall survival of these patients is still based on the stage of the ovarian carcinoma at the time of diagnosis and the severity of myositis. The longest recurrence free survival documented was more than 2 years in two case reports.[3,6] The ovarian carcinoma in these two case reports were of early stage of IB and IC. With our case diagnosed with stage IIB and not adequately staged, without the benefit of knowing if all tumors were resected, over- all survival is already compromised comparing with patients with early stage ovarian carcinomas and adequately staged.

Severity of myositis indirectly affect the prognosis of ovarian cancer, since it delays the initiation of treatment of the carcinoma. This was seen in two cases reported by Chen and Lee, wherein the severe myositis led to failure of initiating treatment for their ovarian cancer which resulted to cancer-related death.[8] In our case, chemotherapy was already delayed from the time she was operated on and was further delayed due to the debilitating status of her myositis that needed immediate intervention. Furthermore, treatment with glucocorticoids left our patient in an immunosuppressed state making her susceptible to subsequent infections which in turn also became contraindications for her to receive her first cycle of chemotherapy.

Generally, there are no present guidelines in the timing of treatment for both conditions. It is advised that both malignancy and myositis should be controlled. However, treatment of the underlying malignancy should be prioritized first unless the myositis needs urgent treatment. Several case reports indicated that treatment for myositis may not be effective without treatment of ovarian carcinoma and response to treatment or resolution of the myositis improves with chemotherapy.[9] This was contrary to our case, wherein control of the myopathy was prioritized due to its severity.

Treatment for dermatomyositis includes control of the muscular and cutaneous symptoms while the standard treatment for ovarian malignancy is surgery and chemotherapy. Glucocorticoids, most commonly prednisone, are routinely given initially at a dose of 1 mg/kg/day to address the muscular symptoms.[9] This was the maintenance treatment given to our patient upon the diagnosis of dermatomyositis. In cases when there is severe muscle impairment, induction therapy with intravenous methylprednisolone pulses is often recommended which was given to our patient during her admission at our institution. Patients with dermatomyositis are often immunocompromised and as such present a challenge during the course of treatment. In our case, the patient developed pneumonia and hidradenitis suppurativa which prevented initiation of chemotherapy.

A unique feature of this condition discussed in the case reports was the reappearance of the cutaneous manifestations in parallel with ovarian recurrence. Hence, dermatomyositis symptoms can be used to monitor treatment and recurrence of the underlying ovarian malignancy. As such, monitoring for relapse of both conditions would include monitoring of muscle enzymes such as creatinine kinase for dermatomyositis, CA-125 as well as periodic history and physical examination for the ovarian carcinoma.[9]

Pathogenic molecular mechanism of dermatomyositis with malignancy still remains unclear. But several insights and hypothesis have been discussed in case reports and studies describing the possible immunopathogenesis and carcinogenesis with dermatomyositis. Hypothesis included certain autoantibodies in association with dermatomyositis. Generally, these myositis – specific antibodies, attack directly the blood vessels of the skin and skeletal muscle which manifest as the skin lesions and muscle weakness characteristic of dermatomyositis.[10] These myositis – specific antibodies were highly expressed in patients with a primary tumor resulting to development of myopathy.

In 2006, Tariff et. al. discovered a novel autoantibody, the anti TIF1- gamma uniquely associated with adult-onset dermatomyositis and malignancy.[11] A number of published studies have also established this association. One study done recently by Fujimoto et al, has associated the occurrence of malignancy with dermatomyositis. It reported the typical cutaneous manifestations and muscular weakness, and detection of the novel anti- TIF1- gamma/ alpha antibodies. In this study, adult patients with dermatomyositis detected with these autoantibodies (anti-TIF1-gamma and alpha) had the typical heliotrope rash and Gottron's papule, with an incidence

of 42-75% of malignancy as compared with those negative for these autoantibodies. Both the heliotrope rash and Gottron's papule were present in our patient, and detection of this novel auto anti-body if feasible is a good documentation associating these antibodies with dermatomyositis associated with a high grade serous ovarian carcinoma.

The studies reviewed hypothesized that in the presence of an occult neoplasm, as in our case, these autoantibodies developed during the antitumor immune response that could result to the paraneoplastic syndrome of dermatomyositis.[10] Presently, there is no clear evidence how these autoantibodies cause the paraneoplastic syndrome in patients diagnosed with high grade serous ovarian carcinoma. But discovery of these autoantibodies is clinically significant in the future in screening patients with dermatomyositis who might have an underlying malignancy.

CONCLUSION

Dermatomyositis presenting as the paraneoplastic phenomenon of high grade serous ovarian cancer is rare and treating this condition is a challenge. Early detection and initiation of treatment for the ovarian malignancy in dermatomyositis connotes a better outcome for this condition. Autoantibodies, if available, can be used to screen patients with dermatomyositis but routine screening for malignancy is foremost and a must. Severity of myositis affects prognosis of these simultaneous conditions. Reappearance of cutaneous lesions of dermatomyositis suggests recurrence of the ovarian carcinoma; hence, a thorough physical and diagnostic examinations are needed for reevaluation of status of the ovarian cancer.

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Radiation: Cure or curse?
A case report on radiation-induced endometrial cancer after cervical cancer treatment

Joan Kristel B. Abrenica, MD and Benjamin D. Cuenca, MD, FPOGS, FSGOP

ABSTRACT

Radiation-Induced Malignancies (RIM) are rare clinical entities that encompass different histological types, majority being high grade and deep tumors with worse prognosis, hence becoming a therapeutic challenge. The reported incidence of an endometrial cancer developing after radiation therapy for cervical cancer is 0.5% - 0.8%. After a thorough literature search, this probably is the first case of endometrial cancer reported as a second primary malignancy following radiation therapy for cervical cancer in the local setting. A 60-year-old para 4 was diagnosed with stage IIB squamous cell carcinoma of the cervix who underwent concurrent chemoradiotherapy with brachytherapy. She had an incidental history of chronic Hepatitis B infection and Rheumatic Heart Disease. She remained asymptomatic with no evidence of disease (NED) for 11 years until abdominal pain ensued. A transvaginal ultrasound showed fluid-filled uterine cavity and intracavitary mass. On exploratory laparotomy, peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, resection of rectal mass and biopsy of mesenteric implants were performed. Final histopathology revealed an advanced stage adenosquamous carcinoma of the endometrium.

Keywords: *cervical cancer, endometrial cancer, radiation-induced malignancy, second primary malignancy*

INTRODUCTION

Cervical cancer is the 4th most common cancer among women worldwide. In the Philippines, it ranks second among females with about 6,670 new cases diagnosed yearly.[1] Though advances in screening as well as in surgical and treatment approaches have collectively improved survival in the recent years, survivors may be faced with other related issues after the treatment. Among others, no matter how infrequent it may be, is the development of a second primary malignancy.[2,3]

Several possible etiologies and postulates were advanced to justify such occurrence. First, cervical cancer survivors share the risk with other Human Papillomavirus (HPV)-associated cancers such as those of the anus, oropharynx, vulva and vagina. Second, survivors of cervical cancer may share similar socioeconomic status and lifestyle-related predispositions such as smoking and sexual practice. Third, treatment modalities, using chemotherapy, radiotherapy or both, may induce another primary malignancy.[2]

Radiotherapy, in particular, has been described as a "two-edged sword" because, though it has become a life-saving and primary treatment for locally advanced cervical cancer, it can also cause second primary malignancy which may develop even several years following its administration.[4,5]

The knowledge of Radiation-Induced Malignancies (RIM) came from survivors of the atomic bomb attacks in Japan in 1945 where tumor development among survivors was increased as compared to non-irradiated individuals. Currently, they comprise the majority of second primary malignancies.[4-6] For cervical cancer alone, a study evaluating second cancers following radiation therapy reported that 5% of second primary cancers were attributable to radiation.[7]

Radiotherapy used to treat the first malignancy can induce minor changes to the nuclear DNA that predispose the cellular DNA to different mutations, carcinogenesis and teratogenesis. The exact molecular processes involved in increasing the susceptibility to develop RIM are not well understood. However, three mechanisms may explain its pathogenesis. First, ionizing radiation produces direct effect causing single and double strand DNA breaks. These may cause gene mutation and trigger the cascade towards malignant transformation of the radiated cells. Second, indirect effect happens when ionizing radiation comes in contact to water or oxygen around the target cells producing free radicals and super oxide radicals causing damage to the cells and gene instability. Other indirect effects include abnormal intracellular signaling, production of cytokines, and inflammatory responses. Third is the bystander effect, which is a phenomenon observed after radiation and chemical exposure, in which the untreated cells demonstrate abnormalities mimicking exposure, such as chromosomal instability, after radiation therapy. This may be the mechanism of RIM in non-targeted tissues.[4,6,8-10]

This case report highlights a case of a radiation-induced endometrial cancer after treatment of cervical carcinoma

Department of Obstetrics and Gynecology, Jose R. Reyes Memorial Medical Center, Rizal Avenue, Manila

Corresponding authors:
Joan Kristel B. Abrenica, MD; email: joank_05@yahoo.com
Benjamin D. Cuenca, MD; email: bjdcuenca@yahoo.com
Department of Obstetrics & Gynecology, Jose R. Reyes Memorial Medical Center, Rizal Avenue, Manila

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and aims to impart the clinical relevance of its diagnosis, management and outcome.

CASE PRESENTATION

A 60-year-old, G4P4 (4004), Filipino, widow was diagnosed with Cervical Squamous Cell Carcinoma, Large Cell Non-Keratinizing (SCCA, LCNK) Stage IIB and underwent pelvic external beam radiation (50 Gy) with weekly Cisplatin chemotherapy followed by Low Dose Rate (LDR) brachytherapy (40 Gy) 11 years ago. She sought consult due to one-month history of dull, hypogastric pain, grade 5/10, radiating to the flank, relieved by rest, not associated with vaginal bleeding. She was previously diagnosed with Chronic Hepatitis B infection and Rheumatic Heart Disease, maintained on Penicillin. She had a two-pack year smoking history. Her family history is negative for any familial disease. She had been having annual follow up with unremarkable pelvic examination, normal Papanicolau smear and imaging studies post treatment for the cervical cancer until the present symptom occurred. Transvaginal ultrasound showed an endometrial mass with minimal color flow on Doppler and more than 50% myometrial invasion with possible hydrometra (Figure 1). The cervix was normal and no adnexal mass was seen. On examination, cervix was 2 x 2 cm, smooth with enlarged corpus of about 4 months size and thickened but free bilateral parametria. The rest of abdominal organs had unremarkable findings on whole abdominal ultrasound. Chest x-ray and bone scan all revealed normal findings.

A whole abdominal CT scan with triple contrast may have been done prior to the surgery to better evaluate the extent of the disease. However, with a physical examination suggestive of an early stage disease, transvaginal ultrasound with a uterine mass confined to the corpus, normal whole abdominal ultrasound and chest x-ray, patient was scheduled for operation.

Dilatation and curettage with evacuation of hematometra and endometrial biopsy revealed endometrioid adenocarcinoma with squamous differentiation. Accordingly, the patient underwent exploratory laparotomy, peritoneal fluid cytology, extrafascial hysterectomy with bilateral salpingo-oophorectomy, resection of rectal mass and biopsy of mesenteric implants.

On laparotomy, the patient had approximately 100 cc of serous ascitic fluid. The surfaces of the palpable abdominal organs were studded with minute carcinomatosis (Figure 2A). There was no palpable pelvic lymph node. However, there was a note of a 1.0 x 1.0 cm solid, fixed left para-aortic lymph node. The corpus was densely adherent to the cul de sac posteriorly, bilateral pelvic sidewalls laterally and bladder anteriorly. It measured 5.7 x 7.2 x 2.8 cm with a solid tumor at the fundal serosal surface measuring 5.0 x 7.1 x 1.7 cm, extending to the right fallopian tube. On cut section of the corpus, the endometrial canal measured 4.8 cm with a friable necrotic mass measuring 4.0 x 5.2 x 3.7 cm attached at the right posterior area invading up to the serosa (Figure 3A). Lowest border of the mass extended up to 1.1 cm above the internal cervical os. The cervix was smooth and measured 2.0 x 1.8 x 1.5 cm. The endocervical canal was also smooth.

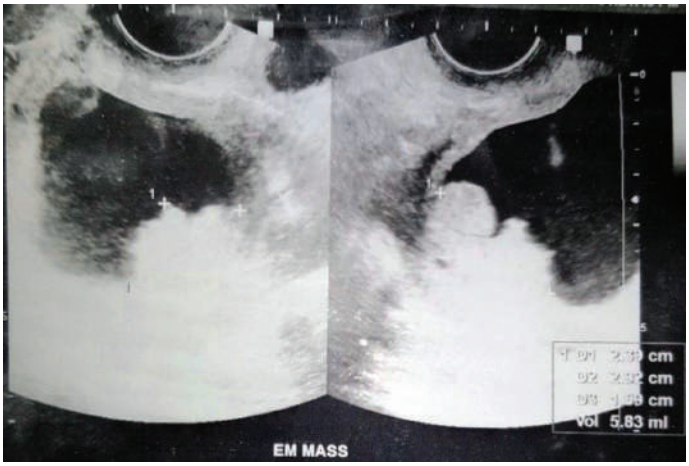

Figure 1. Transvaginal ultrasound showing endometrial mass with ore than 50% myometrial invasion, possible hydrometra

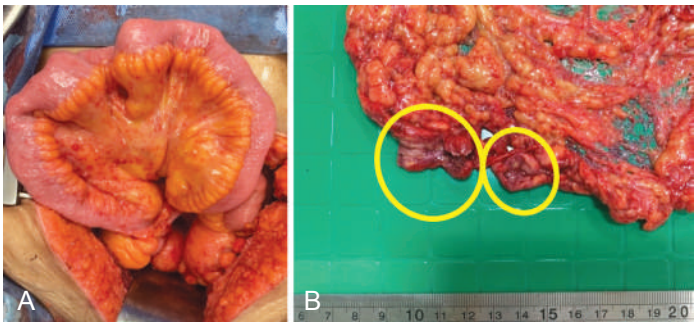

Figure 2. Evidence of extrapelvic disease A. Carcinomatosis B. Omental solid masses

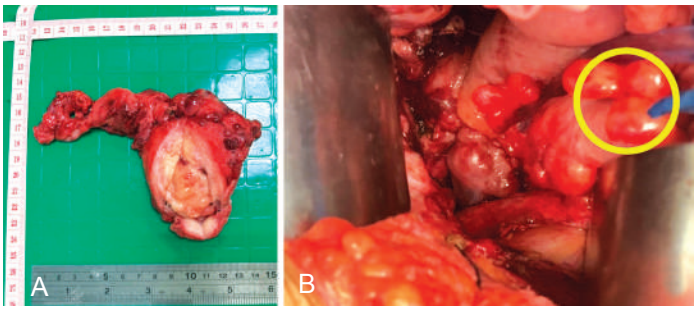

Figure 3. Evidence of pelvic disease A. The corpus with tumor extending to the serosal surface and right fallopian tube B. Solid rectal mass

Bilateral ovaries were atrophic. The left fallopian tube was grossly normal. The right fallopian tube had tumor extension. After adhesiolysis and hysterectomy, there was a rectal mass noted measuring 4.0 x 3.0 cm, solid with friable area near its base (Figure 3B). The omentum was matted with 2 solid masses measuring 1.0 x 2.3 x 0.4 cm and 3.5 x 1.6 x 0.8 cm. Cut section of these masses revealed hemorrhagic and necrotic areas (Figure 2B).

Microscopic sections of the uterus showed tumor cells composed of an admixture of malignant squamous and glandular cells (Figure 4A, B, C and D) with lymphovascular space invasion (Figure 5). The omentum, cervix, bilateral fallopian tubes, bilateral parametria, rectal mass and mesenteric implants were all positive for tumor involvement.

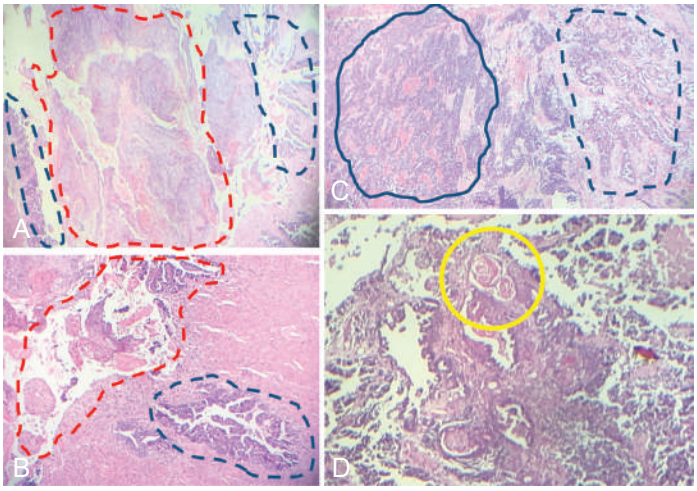

Figure 4. A & B. The uterus showing tumor cells composed of an admixture of malignant glandular cells (blue lines) and malignant squamous cells (red lines). C. The malignant glandular component forming vague glandular pattern, forming nest of moderately (broken line) to poorly (solid line) differentiated cells. D. The malignant squamous cells exhibit marked cellular pleomorphism, nuclear atypia and mitotic spindles with some keratin pearls (yellow line). (hematoxylin-eosin stain, low magnification)

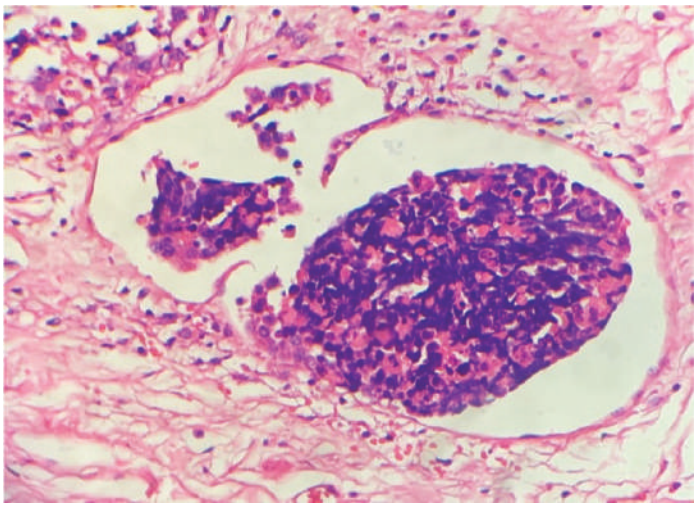

Figure 5. Lymphovascular space invasion with malignant cells (hematoxylin-eosin stain, low magnification)

DISCUSSION

RIM are more common with high linear energy transfer (LET) radiation doses such as alpha particles and neutrons than with low LET doses like gamma rays and x-rays. Ionizing radiation is classified as low LET and in general is considered a weak carcinogen.[4] The incidence of endometrial carcinoma after radiation therapy for cervical cancer is low at 0.5% - 0.8%.[11]

Radiotherapy can induce a wide variety of malignancies which cannot be distinguished histologically from naturally occurring tumor in the absence of genetic testing and biomarkers. It was suggested that excess deletions and balanced inversions were the two mutational signatures of ionizing radiation in second malignancies.[4,12] In lieu of genetic testing, Cahan's criteria, originally used to define radiation-induced sarcoma in 1948, are currently being used as the gold standard for identifying RIM, Cahan's criteria consist of the following: (1) a RIM must have arisen in an irradiated field, (2) a sufficient latent period, preferably longer than 4 years, must have elapsed between the initial irradiation and the alleged induced malignancy, (3) the treated tumor and alleged induced tumor must have been biopsied and the two tumors must be of different histology, (4) the tissue in which the alleged induced tumor arose must have been normal.[4,8]

The patient satisfied all criteria in Cahan's definition of RIM. She had her second malignancy of the endometrium which was irradiated 11 years ago for her cervical carcinoma. She had cervical SCCA LCNK and eventually developed adenosquamous carcinoma of the endometrium. Lastly, she was previously well with no known history of any malignancy or other familial disease. Pelvic examinations and Papanicolau smears done during her annual follow-up were normal. Imaging studies on surveillance all revealed atrophic uterus and normal cervix with no signs of malignancy.

The patient is non-obese, non-hypertensive, non-diabetic, with smoking history and use of combined oral contraceptive pills; all these factors place her at low risk of having endometrial cancer. Penicillin intake for her Rheumatic Heart Disease was found to be a risk factor for lung and breast cancer but no reports were found relating it to endometrial cancer. Her family history does not include any hereditary predisposition to RIM. What factors, then, caused the patient to develop radiation-induced endometrial cancer?

The development of RIM may be caused by a complex interaction of many etiological variables which can be classified into three major categories: 1. Radiotherapy which includes radiation technique and type of radiation; 2. Patient's factors comprised of family history, age at radiation, current age, gender and latency period; and 3. Other miscellaneous factors such as history of smoking, chemotherapy and infection (Table 1).[2,4-7,13-16]

Conventional Radiotherapy directs high energy photons in a step and shoot fashion towards a target tumor. A more advanced technique, Intensity Modulated Radiotherapy (IMRT) involves radiation source moving around the tumor while separating the radiation beam into beamlets to distribute adjusted intensity, direction and shape of the radiation beam. The change from conventional radiotherapy to IMRT is postulated to double the incidence of RIM since it involves increased field size and larger volumes of normal tissues to be exposed in low doses of radiation.[4-6] The patient had external beam radiation using Conventional Radiotherapy with Cobalt 60 Telegraphy. One difference between Cobalt 60 and the currently more available Conventional Linear Accelerator is the size of penumbra which is used to spare nearby critical structures from scattered beam (Figure 6).[13,17] The larger penumbra used in Cobalt 60 involves increased in field size and more tissues irradiated which might have contributed some risks in the patient's RIM.[6,13]

The patient had LDR brachytherapy and was given a total of 40 Gy in 60 hours. This type of brachytherapy might have also increased her risk for developing RIM since it involves

Table 1. Risk factors for development of radiation-induced malignancy

FACTORS	RISKS	COMMENTS
Radiotherapy		
Technique	PEBRT: Conventional < IMRT [4,5,6] Brachytherapy: LDR > HDR [4,14]	Cobalt 60 > LINAC [13] ↑ Fractionation = ↓ Risk [4,14]
Field	↑ Field = ↑ Risk [4,6]	Cobalt 60 > LINAC [13]
Dose	↑ Dose = ↑ Risk [7,15]	Based on distance from the cervix
Patient		
Familial disease	Deficient DNA repair mechanisms [4,10]	Retinoblastoma, Neurofibromatosis, Li-Faumeni [4,6]
Age at exposure	↓ Age = ↑ Risk [4,6,16]	< 30 years old = ↑ Risk [7,15]
Current age	↑ Age = ↑ Risk [2]	≥ 60 years old = independent risk factor
Latency	↑ Latency = ↑ Risk [7,15]	Increasing risk ratio that may persist throughout the lifetime
Gender	Female = ↑ Risk [16]	
Miscellaneous		
Smoking	At time of radiation treatment [6,10]	Risk for lung cancer [16]
Concurrent chemotherapy	May ↑ Risk [2,6,16]	Carboplatin, Flurouracil [2]
Chronic infection	↑ Risk [9]	Chronic Hepatitis B infection = extrahepatic disease [9] ↑ Oxidative stress [6]

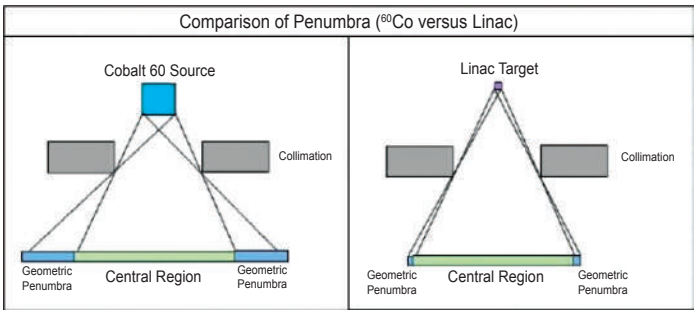

Figure 6. Cobalt 60 vs Linear Accelerator [15]

continuous distribution of radiation allowing no fractionation or breaking up of the radiation that was distributed to the tumor. Fractionation decreases the risk for RIM since it gives time for the normal cells to repair sublethal DNA damage. HDR brachytherapy, on the other hand, allows treatment on an outpatient basis and significantly decreases treatment times. Patient risks for deep vein thrombosis, prolonged immobilization and hospitalization are therefore minimized. Additionally, adaptive treatment planning and dosimetry are possible with each fraction in HDR brachytherapy as compared to having treatment based on single application on LDR brachytherapy.[4,14]

Researches analyzing second malignancies due to radiation for cervical cancer used the distances of the organs from the cervix to assess the dose response relationships for cancer risk. Organs were divided into three based on their distances from the cervix, wherein the bladder, rectum, uterine corpus, large intestine, ovaries, bone, and connective tissue were considered to be closest to the cervix and have received highest doses of radiation compared to other organs. These organs were also the ones found to have higher incidence rates of second primary malignancy compared to those more distant from the cervix.[7,15] In general, the risk of developing radiation-associated cancer of the endometrium after treatment for cervical malignancy is 1.3%. This is equivalent with that of bone tumors but is far below those computed for the bladder (4.5%), vagina (2.7%), Non-Hodgkin's lymphoma (2.5%), stomach (2.1%), leukemia (2.0%), and rectum (1.8%).[7]

Considering the age of radiation, children and young adults are more likely to develop the late effects of radiation for two reasons. They have more cells that are dividing and more tissues that are fast growing and their longer life span gives cancer more time to develop.[4,6,16] For cervical cancer patients, the relative risk of developing RIM was significantly elevated for those under age 30 at the time of exposure which was 4.2%. The patient was started on radiotherapy at 48 years old giving her a lower relative risk of 1.2%.[7] The patient does not have any familial disease related to defective DNA repair mechanisms such as retinoblastoma and neurofibromatosis that would make her at risk for RIM.[4,6,10] These were suggestive that other individual factors might have been the underlying cause of her radiation-induced endometrial cancer.

The patient's current age and gender may be risk factors for RIM since age of > 60 years was found to be an independent factor for developing second malignancy among cervical cancer patients.[2] Also, Dracham et al. indicated that for a given dose of radiation, women are more prone to develop second malignancies as compared to men.[16]

Latency period is defined as the time from the initial radiation therapy to the development of endometrial cancer. Studies on second malignancies after cervical cancer treatment have shown that the risk of radiation-induced tumors of the rectum or anus, bladder, ovary, and uterus persists about 10 years, with statistically significant increasing trends even after 40 years. Similar to prior studies, these findings indicate that the risk of radiotherapy-induced cancers among adults are higher when treated at younger ages and that the increased risk may persist throughout life.[7,15]

Associations of chronic inflammation to tumor development and progression are now generally accepted. Thus, another factor that may possibly explain the patient's higher risk for acquiring radiation-induced endometrial cancer was her chronic hepatitis B infection.[9] The patient had several blood transfusions for recurrent bleeding due to cervical cancer. Few years after completion of her treatment, she was diagnosed to have chronic hepatitis B infection. In a study by Jiang et al,[9] endometrial carcinoma may also be associated with HBV infection. In endometrial cancer group, the prevalence of HBsAg and hepatitis B carrier were significantly elevated as compared with the control group, 12.8% vs 6.0% (p value = 0.001) and 9.3% vs 5.5% (p value = 0.013), respectively. Moreover, HBsAb tested positive prevalence and HBV serum markers in endometrial cancer group were significantly lower than the control group, 41.2% vs 68.5% (p value = 0.001) and 36.9% vs 15.6% (p value = 0.001), respectively. One reason involved in HBV infection and endometrial cancer is the possibility of extrahepatic disease. Although these extrahepatic disorders are primarily the result of an immunopathological reaction, viral replication in the extrahepatic tissues may play a role in the development of these diseases. Many extrahepatic sites were already proven to support HBV infection and replication including peripheral blood mononuclear cells, bone marrow, the spleen, kidneys, bile ducts, the colon, the heart and lymph nodes. Whether the endometrium is also an extrahepatic site in chronic HBV infection needs to be verified histologically.[9] While further studies are still needed to determine the impact of HBV infection on the risk of endometrial cancer, the role of chronic infection in increasing oxidative stress with radiation effect to previously normal irradiated cells is an acceptable pathogenesis of RIM.[6]

Chemotherapy is also a known risk factor for its development since it may lead to delay or prevention of the cell's reparative process thus aggravating the disease. Carboplatin and Fluorouracil, were found to be independent risk factors for developing second primary malignancy.[2,6,10] However, the patient was only given low dose Cisplatin as radiosensitizer for 6 cycles.

A study by Kumar et al[11] compared radiation-induced endometrial cancer and second sporadic endometrial cancer, (endometrial cancer among those who did not receive pelvic radiation but subsequently developed the disease). The first group of patients were described to have a longer latency period and a much greater incidence of advanced stage lesions relative to the second sporadic group endometrial cancer. This supports the hypothesis that the first group has prolonged in situ development without becoming apparent for early diagnosis; a feature well-displayed by sporadic endometrial cancers. The mode of presentation of the patients with the radiation-associated endometrial cancer were described to be nonspecific such as abdominal pain or cramping, different for the latter group who mostly presented with vaginal bleeding.

Similar with the radiation-associated endometrial cancer group, the patient came in due to abdominal pain radiating to the back. Radiation-induced cervical stenosis, in her case, prevented vaginal bleeding. The finding of a fluid-filled endometrial cavity in the transvaginal ultrasound suggested a stenotic cervix blocking the passage of blood and causing hematometra. This also caused some delay in the diagnosis of her second primary malignancy because the stenotic cervix led to difficulty of doing the traditional pipelle biopsy, hence the need to do endometrial biopsy under anesthesia after securing medical clearance.

Final histopathology revealed adenosquamous carcinoma of the endometrium. The histopathology was based on both malignant glandular and malignant squamous components of the specimen. By definition of mixed carcinoma, the second cell type must account for at least 10% of the tumor volume. This was the reason why the endometrial biopsy result was different from the final histopathology after hysterectomy. The smaller amount of tissue collected from the curettage compared to the whole uterine specimen in the hysterectomy might have led to the diagnosis of the squamous part as benign and metaplastic rather than neoplastic and malignant. The importance of recognizing adenosquamous carcinoma of the endometrium is the marked difference between its prognosis and that of a pure adenocarcinoma, the first lesion having worse prognosis.[18,19]

The differentiation of the squamous component of endometrial carcinomas closely parallels the histologic differentiation of the glandular component in most tumors. But outcome is predicted better by the grade of the glandular component.[20] The patient had poorly differentiated glandular component (Figure 4C) which indicates worse prognosis, typical in RIM. Reports on endometrial carcinomas arising after radiation for cervical cancer show that these cancers are poorly differentiated and are diagnosed at an advanced stage, resulting in poorer prognosis with a 5 year over-all survival rate of only 21%.[11,21]

There is no difference in the recommended treatment for radiation-induced and sporadic endometrial cancer. She was supposed to have her adjuvant therapy, however, the patient did not consent for any other treatment after the surgery until she eventually expired.

CONCLUSION AND RECOMMENDATION

This is a case of a 60 year old female who developed second primary malignancy of endometrial adenosquamous carcinoma after concurrent chemoradiotherpy for cervical SCCA, LCNK. This presents a less common but more serious effect of radiotherapy in cervical cancer treatment. With the increasing trend of young patients diagnosed with

cervical cancer, receiving the more advanced techniques of radiotherapy, and having longer expected survival time, it is critical that clinicians and patients be aware of the potential development of RIM which can occur decades after treatment. Clinically, it should be remembered that the benefits of radiotherapy in cervical cancer outweigh the risks and that initial treatment should not be compromised due to the concern over the development of a second primary malignancy. However, patients at higher risk of developing the disease should be identified and counselled well.

Furthermore, RIM may be an unavoidable side effect of radiation and in times when prevention is not possible, early detection is the key for prompt management and better prognosis. This points to the significance of thorough monitoring of atypical signs and symptoms in these patients. For radiation-induced endometrial cancer, vaginal bleeding may not occur due to cervical stenosis and patient may present with vague symptoms such as abdominal pain, cramping or enlarged uterus just like in our patient.

The Clinical Practice Guidelines of the Society of Gynecologic Oncologists of the Philippines recommends high risk patients, those with advanced stage treated with primary chemoradiotherapy or radiation alone or surgery plus adjuvant therapy, to be observed closely after treatment with physical and pelvic examination and Papanicolau test every 3 months for the first 2 years followed by every 6 months for 3 additional years, then yearly thereafter.[22] The most important key point raised in this report is that careful annual monitoring should be continued and patient should be advised to seek consult anytime if with new symptoms, even if she is free of disease for many years, as other complications such as second malignancy may occur after a long latency period, such as 11 years in the patient.

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