Chronic Myelogenous Leukemia in a Patient with Advanced Adenosquamous Carcinoma*

Marie Aleli R. De Castro-Malig, MD, FSGOP, FPOGS

The coexistence of a hematologic malignancy with a gynecologic malignancy is extremely rare and as a consequence of this, there exist only a dearth of information on how to properly manage such a difficult case which led to the different treatment dilemmas encountered in the following patient.

The Case

T.V. was a 55-year old G3P3 (3003) who presented with intermittent vaginal bleeding for 2 months accompanied by weakness and easy fatigability. The only pertinent physical examination was that the cervix was converted to a 5cm x 5cm endophytic mass with extension to the right lateral vagina and bilateral parametria. A cervical biopsy was done which showed poorly differentiated adenosquamous carcinoma.

Her initial workups prior to definitive treatment included a complete blood count which showed hemoglobin of 102 g/L, WBC of 174.8 x 10^9/L and platelet count of 553 x 10^9/L. Differential count showed the presence of atypical cells as well as myelocytes, promyelocytes and metamyelocytes. Hence, a peripheral blood smear was done which showed markedly increased WBC with immature myeloid cells (Figure 1). A bone marrow biopsy was also performed which revealed markedly hypercellular marrow, moderate to marked megakaryocytic hyperplasia, marked granulocytic hyperplasia and severe myelofibrosis such that a myeloproliferative neoplasm probably Chronic Myelogenous Leukemia (CML) in accelerated phase was strongly considered. For confirmation, a fluorescent in-situ hybridization (FISH) assay was done which showed the presence of BCR-ABL fusion genes in 73.7% of the 555 cells examined (Figure 2).

A CT scan of the abdominopelvic area was also requested and this showed marked hepatosplenomagaly and a diffusely enlarged cervix with an irregular mass in the left posterior region measuring 5.27cm x 5.65cm x 3.01cm infiltrating the left parametrium and sigmoid colon. The included lung bases also showed nodular densities suggestive of pulmonary metastasis. The pulmonary metastases were also seen on chest x-ray. She was advised admission with the following diagnosis: G3P3 (3003) Adenosquamous Carcinoma, Cervix, Poorly Differentiated, Stage IVB, Chronic Myelogenous Leukemia, Accelerated Phase.

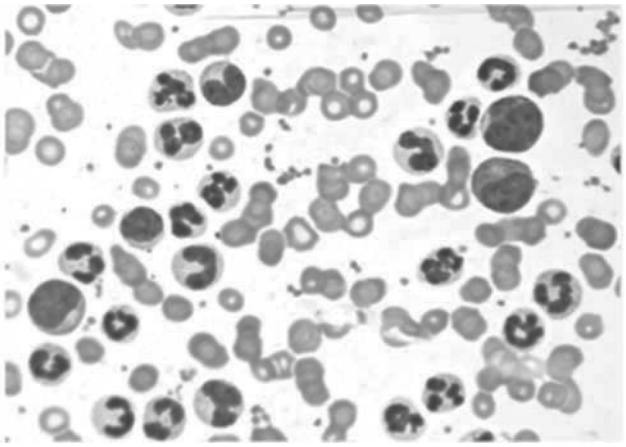

Figure 1. Peripheral blood smear showing markedly increased WBC with immature myeloid cells.

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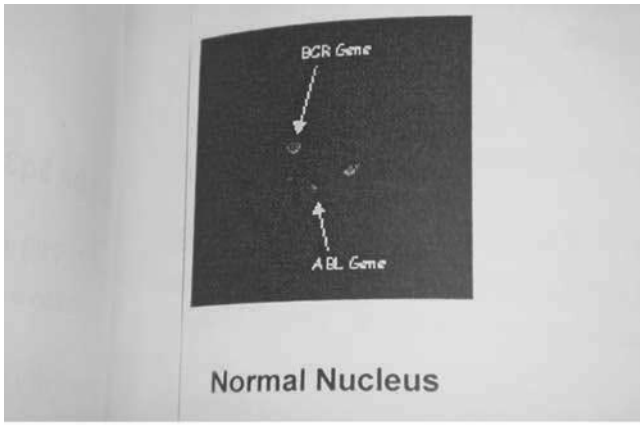

Figure 2. FISH assay showing positive for BCR-ABL fusion genes in 73.7% of cells analysed.

Course in the Ward

Patient was admitted by the Gynecologic Oncology Service and referred to the Hematology Service for co-management. The plan then was to prepare the patient for weekly chemotherapy using Cisplatin 40 mg/m^2 and Paclitaxel 40 mg/m^2 radiosensitizer dose concurrent with pelvic external beam radiation therapy. As for the CML, the plan was to control the leukocytosis and thrombocytosis first by using hydroxyurea and anagrelide then to eventually start the patient on imatinib through the Imatinib Program since the patient was not financially able to afford this standard treatment for CML.

Hydroxyurea and anagrelide were started on admission. When the white blood count decreased from 185 x 10^9/L to 14 x 10^9/L, chemotherapy with Cisplatin 60mg and Paclitaxel 60mg were started concurrent with radiation on the 21st hospital day. On the 36th hospital day, hydroxyurea and anagrelide were discontinued since the white blood count decreased to 3 with an actual neutrophilic count of 2.8. Concurrent chemoradiation was continued. On the 47th hospital day, the patient became anemic with hemoglobin of 85 and platelet count decreased to 64. Chemoradiation was deferred but after blood and platelet transfusion, only radiation treatment was restarted. On the 61st hospital day, she developed hospital-acquired pneumonia for which piperacillin-tazobactam was started and she also had abdominal distention secondary to partial gut obstruction due to hypokalemia. A transvaginal ultrasound was requested which revealed tumor progression with extension of the cervical mass to the parametria, upper vagina and isthmus. This also showed the presence of a cul-de-sac mass probably hemoperitoneum. On the 65th hospital day, the patient had cardiorespiratory arrest due to arrhythmia secondary to hypokalemia with potassium level of 1.5 but was revived. However, this was complicated by acute respiratory failure secondary to hospital-acquired pneumonia and piperacillin-tazobactam was shifted to meropenem. The patient's condition deteriorated until the 85th hospital day when the patient was comatose with Glasgow Coma Scale of 3, her relatives opted to bring her home.

Discussion

Mikami, et al. in 2004 reported one case of early stage squamous cell carcinoma and chronic lymphocytic leukemia. It was suggested that immunosuppression secondary to CLL may predispose to aggressive behavior of the secondary tumor. Activation of the human papilloma virus (HPV) due to immunosuppression may have played a role in the development of the invasive squamous cell carcinoma in the case report mentioned.[1] Our patient's underlying condition which was Chronic Myelogenous Leukemia led to immunosuppression which may have triggered the development of invasive and metastatic adenosquamous carcinoma.

The World Health Organization currently defines Chronic Myelogenous Leukemia as a myeloproliferative disease that originates in an abnormal pluripotent bone marrow stem cell and is diagnosed predominantly in adults. It is the most common myeloproliferative disease with an incidence of 1 to 1.5 cases per 100,000 population per year and makes up approximately 15% to 20% of all cases of leukemia. It is usually associated with the Philadelphia chromosome, also known as the BCR-ABL fusion gene.[2] The Philadelphia chromosome is generated by a reciprocal translocation between chromosomes 9 and 22. The genes involved in translocation are ABL on chromosome 9 and BCR on chromosome 22 (Figure 3). ABL encodes for a tyrosine kinase involved in normal cell proliferation while the BCR gene encodes

for proteins responsible in signal transduction and cell growth.[3]

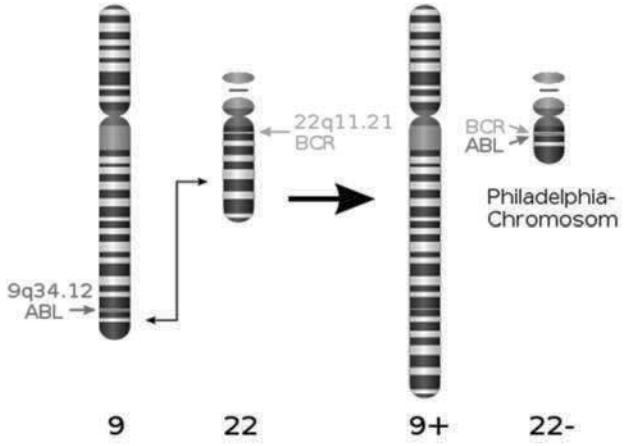

Figure 3. Philadelphia Chromosome Translocation.

Secondary to this mutation, signal pathways for proliferation become continuously activated, leading to unopposed growth, continuous proliferation and decreased cell apoptosis leading to early mobilization of immature cells. Thus, inhibition of the kinase activity of BCR-ABL is the principle on which modern CML therapies are based.[3]

Most patients with CML are in the 5th to 6th decade of life, asymptomatic and their disease is diagnosed only after routine white blood cell (WBC) counts are obtained. When symptomatic, the most frequently described symptoms are fatigue, anorexia, weight loss, fever, weakness, headaches, and night sweats. Mild anemia is a result of myelosuppression. Abnormal platelet counts and function can result in bleeding disorders. Splenomegaly and, less often, hepatomegaly can lead to a sensation of abdominal fullness. Our patient is a typical CML patient. She was in her 5th decade of life, previously asymptomatic with just a few months history of easy fatigability and weakness. Her hematologic condition was just discovered after blood workups for an obvious cervical malignancy.

CML is usually triphasic, having a chronic, accelerated and a blast phase. The patients whose CML is in the chronic phase have a far better prognosis than those in the blast or even in the accelerated phase, like this patient. The natural history of CML is one of progression from the initial asymptomatic chronic phase to the accelerated phase, with a final transformation into the blast phase. Since the blast crisis phase remains mostly incurable, survival is essentially determined by the time to transformation from chronic phase to accelerated phase. The disease phase is the strongest prognostic factor in CML, with patients diagnosed in the advanced phases carrying a significantly worse outlook.[4] This patient was diagnosed to be in the accelerated phase of CML, hence, she had a bleak prognosis made even worse by the fact that she had Stage IV adenosquamous cervical carcinoma.

Currently, imatinib therapy is accepted as being better than any other non-transplantation therapy but expensive for most such as our patient. Imatinib is a competitive inhibitor of the tyrosine kinase activity of BCR-ABL preventing it from phosphorylating its substrate.[5] The results for patients in the accelerated or blast phase of CML are still better than those obtained with other therapies. However, the response rate of patients in the accelerated phase is lower than that of patients in the chronic phase. The only curative approach is bone marrow or stem cell transplantation.[6] Hydroxyurea was given to this patient for palliative treatment of symptomatic leukocytosis, thrombocytosis and hepatosplenomegaly. Anagrelide was given to decrease thrombocytosis. Both can cause reversible myelosuppression.

It is no doubt that the combination of treatments contributed to the demise of this patient. Neutropenia from both weekly chemotherapeutic regimen, daily radiotherapy and daily hydroxyurea led to pneumonia which eventually resulted in acute respiratory distress syndrome and death. Moreover, diarrhea and vomiting secondary to concurrent chemoradiation led to severe hypokalemia resulting to fatal arrhythmia, hypoxic ischemic encephalopathy and death. This patient was treated according to the GOG 9803 Protocol published by DiSilvestro et al which made use of concurrent chemotherapy with Cisplatin 40 mg/m^2 and Paclitaxel 40 mg/m^2 with 45Gy/25Rx EBRT in 19 patients with Stage IB2-IVA cervical cancer with reported overall survival of 94%.[7] However, from the total of 19 patients included in this protocol, 2 had incomplete cycles, 9 experienced treatment delays

of up to 22 days and 4 patients required dose reductions due to grade 3-4 neutropenia. Hence, this study demonstrated unacceptable toxicity of combining the stated doses of concurrent Cisplatin and Paclitaxel chemotherapy with definitive radiotherapy for patients with advanced cervical cancer according to the expanded phase II part of the GOG 9803 protocol.[8]

How can we then best manage these difficult cases? For patients with advanced metastatic carcinoma, do we give systemic chemotherapy or best supportive care? It is undeniable that prognosis is unfavorable for patients with advanced, persistent, or recurrent squamous cell carcinoma of the cervix that can no longer be subjected to surgical resection or radiation therapy. Median survival for these patients is poor such that fewer than 20% survive in 1 year. The need for effective chemotherapy in this setting is well recognized, but the optimal treatment has yet to be determined despite numerous clinical trials. Metastatic, unresectable or recurrent carcinoma of the cervix are essentially incurable, and treatment such as systemic chemotherapy is generally palliative. Furthermore, many factors complicate the administration of conventional chemotherapeutic agents in this patient population such as co-morbid conditions or end-organ complications such as obstructive uropathy leading to renal dysfunction.[9]

Should chemotherapy be given, an efficacious, low-toxicity regimen is needed for this group of patients. The impact of single agent chemotherapy using cisplatin in patients with advanced metastatic cervical carcinoma is negligible.[9] Pectasides, et al. published a retrospective study in 2009 involving 51 patients with advanced, metastatic or recurrent carcinoma who were given the combination of carboplatin and paclitaxel every 3 weeks. Results showed that the combination of carboplatin and paclitaxel every 3 weeks is an effective and well-tolerated regimen against these group of patients. Given the palliative intent of treatment and the consideration of patient convenience and tolerance, carboplatin and paclitaxel might be an alternative outpatient regimen for advanced or recurrent cervical carcinoma.[10] This is one option that could have been given to our patient after the normalization of blood parameters. However, there should be prompt withdrawal of hydroxyurea or any form of treatment when neutropenia started to set in.

Another option is just to palliate vaginal bleeding which was the main complaint of the patient. A systematic review of 8 papers published on palliative radiotherapy for advanced cervical cancer showed that at present, there lacks adequate information to guide selection of adequate palliative radiation for patients with advanced cervical cancer and that treatment selection remains to be individualized.[11] Patients who are expected to have a short lifespan are often treated with palliative irradiation utilizing a large dose per fraction of external irradiation. High Dose Rate Brachytherapy can also be given for 2 fractions at 10 Gy/fraction to control bleeding. [12]

Conclusion

This case represents an interesting overlap of a gynecological and hematological disease. Unfortunately, this was associated with a relatively rapid and aggressive clinical course involving pulmonary metastases, pulmonary infection, neutropenia and death. Diagnosis and management in these extremely rare cases are quite challenging. A multidisciplinary approach involving the gynecologic oncologist, hematologist, pathologist and radiation oncologist is of utmost importance. The book Manual of Palliative Medicine by Medina states that death should not be regarded as treatment failure but part of the clinical course of a malignant disease, a part of the course of life even. Oncologists are trained to preserve or prolong life at all costs such that the decision to just give palliative care is somewhat a painful or difficult decision.[13] However, we all have to make a dutiful and rightful decision on the best treatment for our patients, the treatment that would give the best comfort and dignity especially for patients who are at the end of their lives.

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Gynecologic Malignancy in a Post-Renal Transplant Patient: Considerations and Management Dilemmas*

Victoria N. Sy-Fernando, MD, FSGOP, FPOGS

This is a case of a 49 y.o., G2P2 (2002), who presented with vaginal bleeding and a non-tender mass at the right lower quadrant of her abdomen of 1 year duration. She was diagnosed to have chronic kidney disease back in 1992 and underwent kidney transplant. She has hypertension and her medications included the following : prednisone, azathioprine, nifedipine and simvastatin.

She subsequently consulted a gynecologic oncologist. The abdominal examination revealed a 15cm x 12cm non-tender, movable solid mass at the right lower quadrant of the abdomen, the superior border of the said mass was about 5cm above the umbilicus. It was clearly delineable from the uterine corpus which was enlarged to about 18 weeks in size. On speculum examination, the cervix and vagina were smooth. The internal and rectovaginal examinations revealed normal external genitalia, parous vagina, the cervix was smooth measuring 3cm x 3cm, corpus was enlarged to 18 weeks size, the pelvic kidney was palpable at the right adnexal area. Both parametria were smooth and pliable. There were no masses at the cul-de-sac.

Transvaginal/transabdominal ultrasound were done, which revealed the following findings: the cervix measured 3.0cm x 2.8cm x 2.8cm with homogeneous echopattern. The endocervical cavity is distended by hypoechoic fluid (blood). The uterus measured 14.3cm x 11.7cm x 8.6cm. The corpus is midline with globular contour and heterogeneous echopattern. Distending the endometrial cavity is a 9.3cm x 9.1cm x 5.4cm heterogeneous mass which extends into the upper cervical canal and into the fundal myometrium. The subendometrial halo is indistinct due to posterior shadowing. Normal myometrial wall is noted anteriorly which measures 2.0 cm thick and posteriorly which measures 1.3 cm thick. Both parametria are intact. The kidney is noted at the right adnexal area and measures 7.2cm x 2.5cm x 4.0cm. At the right abdominal area, superior to the corpus is a 13.3cm x 6.4cm x 9.8cm movable solid-cystic mass. There is anechoic free fluid in the cul-de-sac. The impression was endometrial mass, consider submucous myoma, cannot rule out malignancy. Abdominal mass, consider ovarian new growth, probably malignant. CA-125 was elevated with the value of 203.7 U/ml. Chest x-ray was normal. Other preoperative labs were within acceptable levels including the kidney function tests.

She subsequently underwent Exploratory laparotomy, adhesiolysis, extrafascial hysterectomy with bilateral salpingo-oophorectomy, infracolic omentectomy, biopsy of peritoneal implants, appendectomy under epidural-general anesthesia. The intra-operative findings were as follows: There was 200 cc of clear, serous ascitic fluid. The liver, spleen, subdiaphragmatic surfaces, kidney surfaces were smooth and grossly normal. The renal graft was at the right pelvis. There were multiple tumorous superficial implants measuring <0.3cm at the right infundibulopelvic ligament, prevesical peritoneum, rectosigmoid peritoneal surface, epiploic fat, and appendix. The omentum was grossly normal and free

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of tumor. There were no enlarged palpable pelvic and para-aortic lympph nodes. The uterus was enlarged measuring 15cm x 12cm x 9cm with smooth serosal surface (cervix 3cm x 2cm x 2cm, grossly normal). On cut section, the uterine cavity measured 12cm, 3cm of which was the endocervical canal. Occupying the entire endometrial cavity was a 10cm x 4cm x 4cm creamy-white, friable solid mass with its lowest border located 2cm above the external cervical os. It has invaded more than 50% of the myometrium at the left anterofundal portion. The normal myometrium was 3.5cm thick anteriorly. The left parametrium measured 3cm while the right was 1.2cm. The right ovarian mass had filmy adhesions with the omentum and part of the small intestines. It was converted into a 19cm x 14cm x 7cm predominantly solid mass with cystic areas containing serous, hemorrhagic fluid. Cut section showed the solid portion (80% of the mass) to have a cream to yellow color, with necrotic and hemorrhagic areas. The right fallopian tube was 10cm long with cystic outpouchings at its distal end. The left ovary and left fallopian tube were grossly normal. The intraoperative assessment was Synchronous tumor: Ovarian New Growth, right, malignant, Stage IIIB and Endometrial malignancy, Stage IB with adenomyosis.

The patient's postoperative course was unremarkable and she was discharged on the fourth post-op day.

The final histopath result showed the following: Right ovary: Carcinosarcoma wth homologous sarcomatous component consisting of high-grade endometrial stromal sarcoma positive for lymphovascular space invasion. Endometrial adenocarcinoma, moderately to poorly differentiated, FIGO grade 3.

A month after her surgery, additional metastatic work-ups were done, prior to chemotherapy. Abdominal CT scan done showed mesenteric carcinomatosis. Chest CT scan done showed pulmonary nodules at the right lower lung. She was then upstaged to a Stage IV carcinosarcoma of the ovary.

The patient definitely warranted chemotherapy because of the residual disease in the peritoneum. Considerations were given to the possible effects of the chemotherapeutic agents on her renal graft and the fact that she is still on immunosuppressants. The decision was to give agents that would be least nephrotoxic and still with good efficacy for sarcomas. The combination of doxorubicin–cyclophosphamide-vincristine was given every 3 weeks.

After 3 cycles of chemotherapy, a repeat whole abdomen CT scan showed decrease in the thickening and mesenteric stranding. Chest CT showed clearing of the right lower lung nodules. There was a 0.4 cm left lateral base nodule. The patient already finished the 6 courses of chemotherapy, with no untoward reactions nor severe complications noted.

Discussion

Ovarian carcinosarcoma , otherwise also known as Malignant Mixed Mullerian Tumors of the Ovary (OMMMT), is a rare variant of the ovarian cancer, accounting for 1-4% of all ovarian tumors. These tumors contain both malignant epithelial and sarcomatous (mesenchymal) elements. The epithelial component is often serous, endometrioid or undifferentiated adenocarcinoma, but may also be clear cell adenocarcinoma or squamous carcinoma. The sarcomatous element may be homologous tissue native to the ovary or heterologous tissue not native to the ovary. Like those of the epithelial ovarian tumors, majority of the patients with ovarian carcinosarcoma usually presented with nonspecific symptoms, like abdominal fullness or discomfort, abdominal enlargement, bloatedness, fatigue, and abdominal mass. Thus, at the time of presentation, approximately 90% of patients with carcinosarcoma of the ovary will have disease spread beyond the ovary, and 75% of the women will have widespread metastasis (Stage III or IV). CA-125 is a highly specific tumor marker for epithelial ovarian tumors, specially for serous adenocarcinoma, and it has also been shown to be a useful tumor marker for ovarian carcinosarcoma.

FIGO staging had been use to stage ovarian carcinosarcoma. Our index patient is stage IV, with distant metastasis to the lungs.

Histologically, cytokeratin is positive for epithelial element. While S-100 and vimentin are positive for the mesenchymal element.

The histogenesis of carcinosarcoma arising in the ovary remains controversial. But immunologic and molecular studies have suggested that both malignant elements (carcinoma and sarcoma) originate from a transformation of a single aberrant (epithelial) clone, which subsequently diverges some into carcinomatous elements and the others into sarcomatous elements (Monoclonal/Combination Theory) as opposed to transformation occcurs independently from separate epithelial and mesenchymal origin (Collision Theory). It is now accepted the carcinosarcoma's are biphasic tumors, and that it is the epithelial component that dictates behavior.

Clinical prognostic factors associated with poor survival includes advanced stage at presentation, suboptimal debulking and older age.[1-4]

The survival of women with ovarian MMMT (OMMMT) was poor compared to women with Epithelial ovarian carcinoma (EOC). After adjusting for many factors, women with OMMMT were at 69% increased risk of death from any cause compared to women with EOC. Median survival for EOC was 40 months, while for OMMMT tumors was only 18 months.[5]

In the study done by Jonson, et al. comparing uterine from ovarian carcinosarcoma, with a median length of follow-up of 13 months (range 0-186 months). There was no difference in the overall survival between the two. The median survival for uterine carcinosarcoma was 16 months and 11 months for ovarian carcinosarcoma. The estimated 2 year survival for uterine carcinoma was 47.8%, while ovarian carcinosarcoma was 56.2%.[6]

The role of cytoreduction in EOC is well established. Recent studies showed optimal debulking surgery improves the survival for patients with ovarian carcinosarcoma. The median survival for those who were optimally debulked was 25 months vs only 8-16 months for those who were suboptimally debulked.[7-11]

Traditionally, ovarian carcinosarcoma has been managed similar to the more common epithelial ovarian cancer. Treatment generally consists of frontline surgical cytoreduction followed by chemotherapy in the adjuvant and relapsed settings.

In attempts to prolong survival, a number of different chemotherapy regimens have been employed in the treatment of ovarian carcinosarcoma. Non-platinum containging treatment regimens have met with little success, average response rate of only 23%.[12]

Response rates for patients treated with platinum-based chemotherapy, however, are more encouraging. A number of different regimens have been reported, all of which combined platinum with at least one other agent (Ifosfamide, Adriamycin/Doxorubicin, Dacarbazine, Cyclophosphamide and Paclitaxel). While response rates to platinum-based regimens range from 18%-100% in the literature, the overall survival remains poor, between 14-47 months.[12]

Based on uterine sarcoma data, many institutions combine ifosfamide with platinum, while others follow more traditional epithelial ovarian regimens and incorporate a taxane. The decision to substitute taxane for ifosfamide seems to be based largely on the improve toxicity profile and ease of administraion rather than proven efficacy. Ovarian carcinosarcoma patients have traditionally been felt to have a poor prognosis. This expected dismal outcome has led some to adopt a more conservative treatment approach, choosing to use taxane instead of ifosfamide.[13-15] As we can see in these 2 studies that Ifosfamide had a better response rate (88% vs 50%)and median survival (2 yr OS 81% vs 55%; P = 0.03) compared to Paclitaxel.[9,16]

A review of literature does seem to support the use of platinum based chemotherapy regimens, with a 54% overall response rate in the platinum group compared with only 23% response rate in the non-platinum containing regimens.[9,16]

It had been recommended that single agent Cisplatin or Carboplatin be given to those patients with poor performance score. For others, double chemotherapeutic agents has been suggested doublets: Cisplatin-Ifosfamide or Carboplatin-Paclitaxel combination. One can also consider the triple agent combinations of Platinum-Taxane-Anthracycline triples (such as Pacli-Epirubicin-Carbo TEC ot TIP Paclitaxel-Ifos-Cisp), with increase RR rate at the expense of increase toxicity. Despite the fact that ovarian carcinosarcomas are relatively chemosensitive tumors, the prognosis of these patients remains poor despite

the use of chemotherapy, lagging behind that of EOC.[12,17]

New treatment strategies are needed for this population. The use of biological targeted therapies has been proven successful in several tumor types. Whether such treatments could also be active in CS of the female genital tract is a big question. However, it is worth noting that in a recent phase II study of Doxorubicin in combination with anti-VEGF antibody Bevacizumab in patients with soft tissue sarcomas, the activity (RR 12%) was no better than that usually seen in Doxorubicin alone.[17]

There have been anecdotal reports of patients with ovarian carcinosarcoma treated with radiotherapy, in additon to or instead of chemotherapy. The role of radiotherapy in patients with early stage ovarian carcinosarcoma is unknown, but it should probably not replace chemotherapy. While there is little rationale for the use of radiotherapy in a disease that is usually diagnosed at advanced stages and usually behaves like epithelial ovarian carcinoma (ie, spreading through the peritoneal surface). So, radiotherapy may only be appropriate for patients with chemotherapy-refractory recurrent or persistent disease, restricted to the pelvis.[8,18,19,20]

Early diagnosis, optimal debulking and platinum-based adjuvant chemotherapy appear to offer the best chance for a prolonged survival in a patient with ovarian carcinosarcoma. Prospective trial cannot be performed in this disease due to its rarity, it has been recommended that data should be extrapolated from trials in uterine carcinosarcoma.

Synchronous Tumors of the Ovary and Endometrium

Synchronous tumors were defined as tumors that were either diagnosed concurrent with the primary tumor, discovered at the primary surgical procedure, or occurred within 1 year of the primary tumor diagnosis.[21]

Metachronous tumors were simply defined as tumors diagnosed greater than 1 year after the primary neoplasm.[21]

The presence of simultaneous carcinomas involving both the ovary and uterine corpus is relatively uncommon, and only 0.7–10% of patients with epithelial ovarian or uterine cancers have been found to have simultaneous tumors in large series. While in the retrospective studies, the incidence of synchronous uterine and ovarian carcinoma is 34% to 40% in autopsies and 5% to 15% in surgically resected specimens.[22]

If both the uterus and ovary are involved by malignancies, we are confounded with a question whether this is a case of metastasis or double primary carcinomas. In most cases, this is such an important question because not only such cases are stage differently, this may affect the prognosis of the patient and likewise, affect the therapeutic judgment of the clinician.

Many clinocopathologic features have been proposed over the years, the most commonly used is the one proposed by Young and Scully. The following are the criteria for interpreting concomitant uterine corpus and ovarian carcinoma:

Young and Scully's Criteria (1991)
Criteria for interpretation of nature of concomitant uterine corpus and ovarian carcinomas

Corpus Primary Ovarian Mets	Ovarian Primary Corpus Mets	Ovarian Primary Corpus Primary	Ovarian Mets Corpus Mets
Direct extension to ovary from large tumor	Direct extension to corpus from large ovarian primary	No direct extension to of either tumor	Usually no direct extension of tumors
Deep myometrial invasion from endometrium	Myometrial invasion from serosal surface	Myometrial invasion usually absent or superficial	Tumor characteristically in endometrial stroma. Myometrial invasion may be present
Lymphatic or blood vessel invasion in corpus, ovary, or both	Lymphatic or blood vessel invasion in corpus, ovary, or both	No lymphatic or blood vessel invasion	Lymphatic or blood vessel invasion frequent in corpus & ovary
Atypical hyperplasia of endometrium frequent	Atypical hyperplasia of endometrium usually absent	Atypical hyperplasia of endometrium frequent	Atypical hyperplasia of endometrium absent
Tumor present in fallopian tube	Tumor present on peritoneal surfaces and sometimes in fallopian tube	Usually both tumors confined to primary sites or have spread minimally	Tumors usually evident outside female genital tract
Tumor predominant on surface of ovary	Tumor predominant within ovary	Tumor predominant within ovary and endometrium	Ovarian tumor usually bilateral – ovarian surface involvement frequent
Usually no endometriosis in ovary	Endometrioisis sometimes present in ovary	Endometriosis sometimes present in ovary	Endometriosis absent
Histological types uniform and consistent with corpus primary	Histological types uniform and consistent with ovarian primary	Histological types uniform or dissimilar	Types of tumor inconsistent with or unusual for either organ

Malignancy in Renal Transplant Patients

Renal transplantation is now the treatment of choice for end-stage renal disease (ESRD).

In the early days of transplantation medicine, the clinicians were faced with fulminant acute rejection episodes and severe infections. With the introduction of more potent immunosuppressive medications, longer graft survival and older donors, as well as recipients, the 1-year survival rate of kidney transplant recipients with a functioning kidney is now more than 90%.[23]

Presently, the leading causes of mortality in renal transplant recipients in the US are cardiovascular disease, infection, and malignancy. While in ANZDATA 2008 report, posttransplant malignancy was the leading cause of death accounting for 32% of all deaths in 2008. Now, CVD and malignancy are becoming the major burden in transplantation medicine.[23,24,28]

An increased incidence of malignant tumors in transplant recepients was recognized as early as in the 1970's. The post-renal transplant de novo malignancy incidence ranges from 2.3% to 31% and for patients who followed up more than 20 years the incidence is 34%-50%. Incidence of malignancies increases with time, but interestingly it appears to occur immediately after transplantation.[25] In the study done by Wimmer, et al. transplant recipients developed 45% of all tumors within the first 5 years after transplantation and 71% within the first 10 years.[26] There was almost a linear increase in cancer incidence even more than 25 years after renal transplant, based on US data[27] as well as Australia and New Zealand Dialysis and Research Registry.[28]

Cancers tend to occur earlier, grow more rapidly and metastasize more widely than the general population. Female kidney transplant receipients experienced a 3-fold and men 2.5-fold greater risk for cancer incidence than the general population.[27,28]

It is noteworthy that not all cancers are equally increased in the transplant population. Information from the USRDS (US Renal Data System) and ANZDATA (Australia and New Zealand Dialysis and Transplant Registry databases showed that compared with the age-matched general population, the relative risk of common malignancies, such as colon, gastric, ovarian, prostate, lung, and breast were approximately two fold higher. Cutaneous melanoma,liver, gynecological, bladder, testicular tumors and leukemia are 3- to 5-fold higher. Kidney malignancies was 15-fold higher. While those mainly linked to oncovirus, such as non-melanoma skin cancer, lymphomas and Kaposi sarcoma, the risk was increased by >20-fold compared with the general population.[27,28]

All malignancies were found to be increased. The most common malignancies found in post renal transplant patients were related to chronic viral infections : skin, lip, anogenital cancers and posttransplant lymphoproliferative disorder (PTLD).[29]

In case of malignancy, the question of whether immunosuppression initiates the cancer or promotes its development, or both, remains debatable.

The various mechanisms by which the different immunosuppressive agents can induce or promote cancer development for cancer induction and promotion : impairs the repair of the DNA damage, induces the production of cancer promoters such as TGF-β and VEGF, intercalates with DNA, inhibits apoptosis, inhibits repair splicing and elicit codon misread.[30]

With regards to pathogenesis, malignancy after transplatation can develop in 3 different ways : De novo occurrence; recurrent malignancy in the recipient and transmission of malignancy from the donor.[29]

The risk factors for the development of de novo malignancy in the kidney transplant patient are as follows: First, immunosuppression, not only the use but also the type, duration and intensity of the immunosuppression are additional risk factors; Second, Conventional risk factors (i.e. age, smoking, analgesic abuse). The third is chronic viral infection, certain viral infections predispose transplant recipients to specific types of malignancies (Epstein_Barr virus with Lymphoma; Herpes Virus 8 with Kaposi sarcoma and Non-Hogdkins lymphoma; HPV with cervical, penile, vulvar carcinoma as well as Bowen disease, Non-melanoma skin cancer and skin and tonsillar cancer. While Hepatitis B and C virus with hepatocellular cancer). Fourth is genetic risk factors and fifth is the previous history of treatment with cytotoxic agents. Thus, the increased risk for cancer

development after transplantation is believed to be multifactorial. The immunosuppressive drug effects are added to possible environmental and preexistent genetic, immune and viral components for the pathogenesis of cancer.[29]

The treatment of tumors in patients who have received an organ transplant is challenging. Decisions are based on many factors such as the stage and type of cancer, aim of treatment (curative vs palliative) and effect of treatment on the graft.

The initial management of any malignancy in a transplant recipient is to modify immunosuppression. Reduction of immunosuppression to the minimum level where graft-organ function is still maintained is advised. For renal transplant patient, shifting to immunosuppression to a regimen with an antiproliferative effect, such as Sirolimus or Mycophenolate mofetil should be considered, these might help decrease the incidence of graft rejection and regress the malignancy.[30]

Surgery is the primary treatment for skin and solid cancers. In general, care should be taken to avoid damage to the vasculature of the enal graft. Surgery should be considered for every transplant recipient with localized solid malignancy.[30]

Radiotherapy is used either as a primary or adjuvant treatment to surgery. Radiotherapy to the lower abdomen or pelvis poses a challenge in patients who have undergone a renal transplant because of the pelvic location of the renal allograft. Therefore, when pelvic radiotherapy is indicated, options include changing the dose or field of irradiation to keep the renal allograft within the tolerance dose of the kidney or full dose of radiation with possible graft loss followed by dialysis.Three-dimensional conformal radiotherapy is advised in all patients and the dose delivered to the graft should be maintained below the threshold for late renal damage (below 23 Gy with 2 Gy per fraction). They are also at a higher risk of developing avascular necrosis of the femoral head because of the steroids given with chemotherapy and immunosuppression. This risk necessitates modification of radiation portals and reduction of the dose of the steroids. The end of the ureter can receive a high dose of radiotherapy combined with its tenuous blood supply can lead to ureteric stenosis and obstruction. Hence, radiation dose to this area should be kept to a minimum by ensuring that patients have a full bladder before treatment.[30]

Chemotherapy has an unfavourable effect on the subsequent availability of veins for the formation of AV fistula should the graft fail. Therefore, cannulation of the forearms and antecubital fossas should be avoided if possible, to avoid subclavian vein stenosis, which could compromise future AV fistula formation.[30]

Concerns raised regarding the use of chemotherapy in transplant recipients include the following : Increased risk of graft loss due to direct cytotoxic effects or as a result of interactions with antirejection drugs; and ncreased risk of sepsis as a result of the additive or synergistic effects of chemotherapy and immunosuppressant drugs.[31]

Chemotherapy or their active metabolites can be eliminated from the body through different metabolism, excretion in the urine, bile or feces, or through the respiratory tract. For those agents eliminated mainly by the kidneys, pharmacokinetic change in the face of renal dysfunction is decreased clearance into the urine, resulting in increased systemic exposure and increased toxicity. Therefore, dose adjustment in renal dysfunction is required for drugs eliminated by the kidneys either by dose reduction or by prolongation of the administration interval.[31]

Several issues like the ultimate treatment goal should be considered. This determines the selection of anticancer drugs. For curative treatment, aggressive drugs should be considered, while for palliative care, less aggressive drugs with lower toxicity are selected. The nephrotoxicity of anticancer drugs is also a major consideration. Many chemotherapeutic agents are nephrotoxic to some extent and can cause a further decline in GFR. Drugs with obvious nephrotoxicity, such as Cisplatin and Ifosfamide, should be avoided in patients with renal insufficiency. With regards to dose adjustments, there are at least two important factors for determining appropriate dose : the degree of renal impairment and the fraction of drug excretion normally contributed by the kidneys. For those drugs whose elimination is mainly via the kidneys, such as Carboplatin, dose adjustment should be calculated based on the patient's estimated renal

function. Otherwise, if drug elimination is primarily via non-renal pathways, such as with Paclitaxel, no dose adjustment is required.[31]

Chemotherapeutic regimens should be tailored according to the probability of cure or predicted benefit from palliation balanced against the risk of life-threatening bone marrow suppression, infection and possible graft rejection.

Combination of Paclitaxel – Carboplatin would be the chemotherapeutic agent of choice to be given for this patient, which has proven efficacy for both ovarian carcinosarcoma and endometrial carcinoma with mild nephrotoxicities based on different studies.[29]

In summary, this is a case of 49 year-old with advanced stage carcinosarcoma of the ovary and endometrial carcinoma. Ovarian carcinosarcoma is a rare variant of ovarian malignancy, which contains both malignant epithelial and sarcomatous elements. It is a very aggressive type of tumor with poor prognosis. It usually presents with non-specific symptoms and diagnosed at advanced stage. Primary management for both ovarian carcinosarcoma and endometrial carcinoma is surgical cytoreduction and chemotherapy is the adjuvant treatment for both using platinum-based chemotherapy.

Renal transplant recipients have a significantly higher incidence of cancer compared with the general population. The immunosuppressive therapy, oncogenic viruses, and direct oncogenic effects of immunosuppressive drugs are considered to be major risk factors for cancer development. Cancer and cardiovascular disease constitute the two main causes of death in this patient population.

Renal transplant recipients have a significantly greater incidence of cancer compared with the general population. The immunosuppressive therapy, oncogenic viruses, and direct oncogenic effects of immunosuppressive drugs are considered to be major risk factors for cancer development. Cancer and cardiovascular disease constitute the two main causes of death in this patient population.

Management of solid tumors in renal transplant recipients present various challenges. Multidisciplinary cancer management, preservation of allograft function and modification of immunosuppressant treatment are important goal in the management of cancer in transplant recipients. When renal-transplant patient recipients present with pelvic malignancies, surgery is the primary treatment of choice if feasible. Immune modulation is appropriate for most cases of gynecologic cancer. When radiotherapy is indicated, CT-based conformal planning is advised to keep the dose to the crucial structures as low as possible. If chemotherapy should be used, it should be used judiciously. Dose reductions might be need on the basis of baseline organ function, and concurrent medication. Chemotherapeutic regimens should be on the benefit of cure or from palliation balanced against the risk of life-threatening bone marrow suppression, infection and possible graft rejection.

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Primary Non-Hodgkin's Lymphoma of the Cervix*

Mary Evangeline Villa-Mercado, MD, FSGOP, FPOGS

Primary non-Hodgkin's lymphoma of the cervix is a rare entity. We report a case of a 52 year old woman who presented with three months history of vaginal discharge. Pelvic examination showed a cervical mass. Cervical biopsy was done which initially showed Glassy cell carcinoma. She subsequently underwent radical abdominal hysterectomy with bilateral adnexectomy and bilateral lymph node dissection. The histologic examination and immunohistochemical staining revealed ALK negative Anaplastic cell lymphoma of the cervix. She was clinically staged as IE based on Ann Arbor staging. Unfortunately, the patient expired 2 months post - surgery due to recurrence and complications of the disease. Review of the diagnosis and treatment is presented.

Key words: non-Hodgkin's lymphoma, anaplastic cell lymphoma, cervix

Non-Hodgkin's lymphoma (NHL) represents 70%-80% of all lymphomas. Extranodal NHL accounts for 20%-25% of all NHLs.[1,2] The female genital tract is more commonly secondarily involved by disseminated disease.[3] Primary genital tract lymphomas are rare and accounts for only 1%-1.5% of extranodal lymphomas.[4,5,6] Opinions on which of the gynecologic organs is the most common site are contradictory. Some authors suggest that the ovary is the most common while others believe that it is the cervix.[7,8]

The Case

Our patient is a 52 year old, G3P2 (2012), married, from Quezon City. Her chief complaint was foul smelling vaginal discharge. In 1993, she was diagnosed with hypothyroidism and underwent subtotal thyroidectomy. She is maintained on Levothyroxine tablet once daily. Family history is positive for lung and breast cancer and hypertension. Personal and social histories were unremarkable. Menarche was at 15 years old with subsequent menstruation occurring regularly on a monthly basis. Last menstrual period was August 8-13, 2013. Her condition started 3 months prior to admission, when she noted foul smelling vaginal discharge. No other symptoms were noted. Due to the persistence of symptom, she consulted a private gynecologist. Pap smear done revealed moderate inflammation. She was treated with unrecalled vaginal suppositories for 1 week. Due to the persistence of the vaginal discharge one month after, she followed up with the same gynecologist. A cervical biopsy was done. The diagnosis was Glassy cell carcinoma, cervix, stage IB1. She was advised to consult a gynecologic oncologist who advised her to undergo operation.

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On physical examination, the patient was conscious, coherent, ambulatory with stable vital signs. There were no cervical lymphadenopathies. The rest of the physical examination was unremarkable. Internal examination showed a normal external genitalia, smooth vagina, cervix converted to a 4cm x 2cm necrotic, exophytic mass without forniceal involvement, uterus small, parametria smooth and pliable.

Chest x-ray was normal. The abdominal CT scan showed a retroverted uterus with bulbous or enlarged cervix measuring 4cm x 4cm. The rest of the abdominal organs were unremarkable.

The patient subsequently underwent exploratory laparotomy, radical hysterectomy with bilateral salpingo-oophorectomy, and bilateral lymph node dissection. She had an unremarkable immediate postoperative course.

On gross examination of the specimen, there is a large fungating grayish-tan cervical mass measuring 4cm x 4cm x 1cm. The mass is located at the anterior lip (9 o'clock to 3 o'clock position). There is a 2cm x 1.5cm x 1cm extension in the 4-5 o'clock position. The cervical stroma measures 1.5cm thick and the mass seems to infiltrate less than ½ of the stroma. (Figure 1) Microscopically, sections from the cervical mass show large separate cells. Cells have vesicular nuclei and varying amounts of cytoplasm. Cytoplasm range from absent to moderate. Bizarre and multinucleated forms are present. There is ulceration of the epithelium and extensive necrosis. Tumor is limited to the cervix. (Figure 2) All other structures are negative for malignancy.

The histopathologic diagnosis is a High grade tumor of the cervix with invasion to less than ½ of cervical stroma. The following structures are negative for malignancy: endometrium, vagina, bilateral adnexa, bilateral parametria, right and left pelvic nodes. No lymph-vascular invasion demonstrated. Leiomyoma uteri, Intramural; Proliferative Endometrium; Chronic Cervicitis, Non Neoplastic Cervix. The differential diagnoses were: Sarcoma (Leiomyosarcoma, Lymphoma), undifferentiated carcinoma/sarcoma.

Immunohistochemistry was requested with the following results: Positive for LCA, CD30, EMA, Vimentin, Granzyme B (Figure 3 and 4); Negative for CD3, CD20, ALK, CK, SMA . Diagnosis based on Immunohistochemistry was compatible with ALK Negative Anaplastic Large Cell Lymphoma (WHO Classification). The final diagnosis was Anaplastic Large Cell Lymphoma, cervix, Stage IA; s/p Radical Hysterectomy with Bilateral Salpingo-oophorectomy, bilateral lymph node dissection.

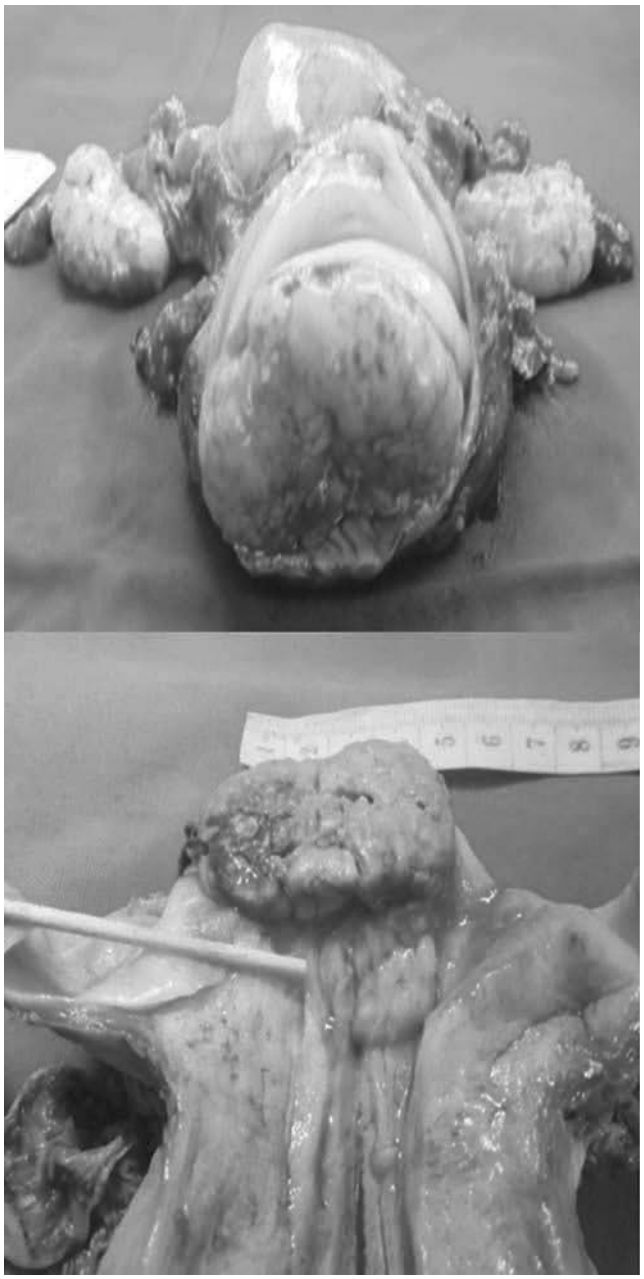

Figure 1. (a) Gross picture of specimen showing the cervical mass (b) cut section of the uterus showing the cervical mass.

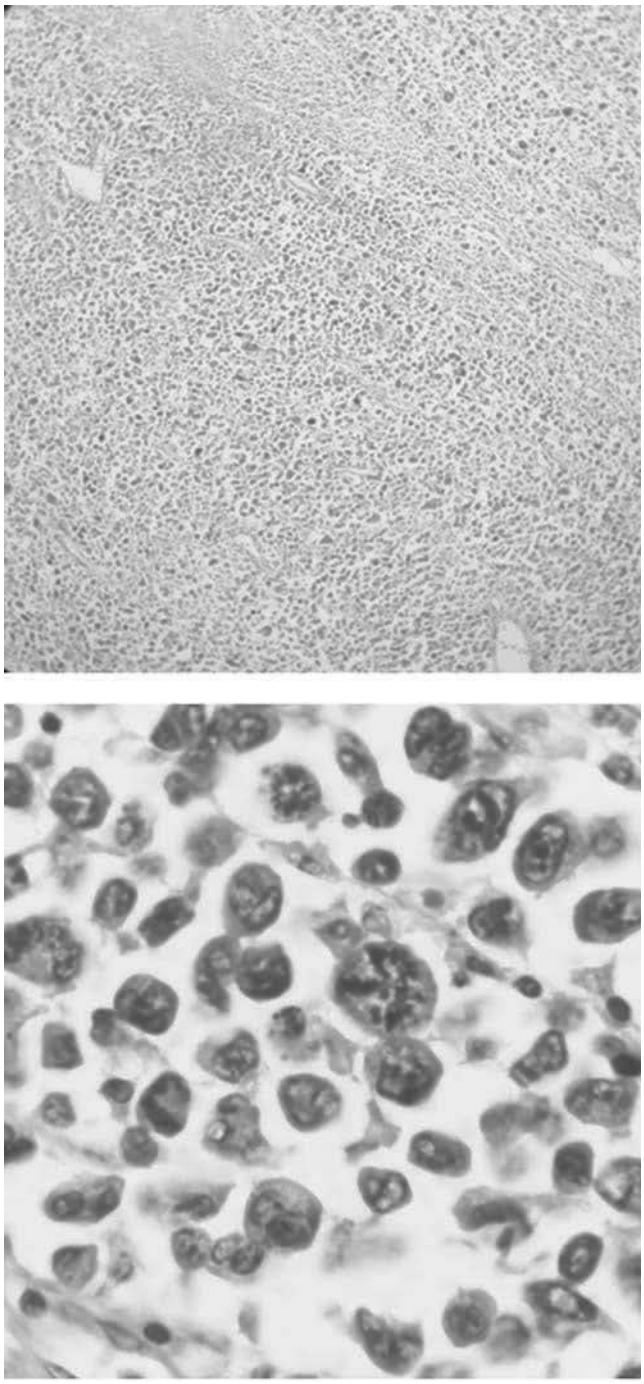

Figure 2. Microscopic section of the cervical mass (a) Low Power Field (b) Oil Immersion Field.

Discussion

Primary cervical lymphomas are defined as lymphomas which originate and localize from the uterine cervix without myometrial involvement and without any evidence of leukemia at the time of diagnosis.[9,10] It accounts for only 0.12%-0.6% of all extranodal lymphomas.[11] It occurs in approximately one in every 730 cases of NHL.[12] Published cases are mostly in the form of case reports and small case series and less than 60 cases were reported.[13]

These tumors usually occur from 20 to 80 years, with median age varying between 40 to 59 years old. Majority of which were premenopausal.[14] Cervical lymphoma tends to occur in younger patients compared to other non-Hodgkin lymphomas.[15]

Etiology and pathogenesis of cervical NHL are still unclear. Some authors have suggested the possibility that Epstein Bar virus or human papillomavirus plays a role in the development of cervical lymphoma[8,16]; however, there is no reliable evidence on the role of these viruses. The possible association of chronic inflammation and cervical lymphoma has been proposed but has not been adequately proven. Aozasa, et al.[7], in a study found formation of lymph follicles in one of four such cases of cervical lymphoma, suggesting the presence of preceding inflammation in the cervix.

Signs and symptoms are non specific and vary with abnormal vaginal bleeding as the most commonly reported symptom either as postmenopausal bleeding in the older age group or menometrorrhagia and postcoital bleeding in younger patients.[17,18,19] Other symptoms include vaginal discharge, pelvic pain, dyspareunia, urinary retention or perineal discomfort. Although B symptoms such as fever, weight loss, night sweats, and fatigue ,are often associated with systemic lymphoma, they are uncommon in cervical lymphoma.[15,20] Our patient presented only with persistent vaginal discharge without any B symptoms.

In general, cervical lymphomas may manifest from very subtle to gross abnormalities. Approximately one in five patients was asymptomatic and had the cervical lymphoma discovered on routine physical examination or as incidental finding at the time of hysterectomy for other indications.[14,15,21] In one case report, the pelvic examination revealed a large cervical ectropion with contact bleeding.[22] They may likewise present as polypoid masses[23] or a submucosal mass mimicking leiomyoma.[24] Occasionally, gross findings may vary from an unremarkable bulky cervical

or pelvic mass with vaginal or parametrial involvement.[13,15,25] It may also present as a rapid endophytic or exophytic pattern of growth, half of all reported cases exceeded 4cm in diameter.[14]

Primary cervical lymphomas are rarely diagnosed with cervical smear because lymphomas originate from the cervical stroma and the overlying squamous epithelium is generally unaffected. According to Harris and Scully[26], up to 67% of these tumors present with subepithelial abnormality and tumors arise from cervical stroma with the overlying squamous epithelium initially preserved. Only 20% of the patients were positive for malignancy smears. In 22 malignant lymphomas collected by Whitetaker[27], only 5 of 13 cases cytologically examined were positive. In 2005, a case series found that only 50% of cervical lymphomas had an abnormal pap smear.[13] The cytologic features of malignant lymphoma reported by investigators included isolated malignant cells of medium to large size, increased N/C ratios with scanty cytoplasm and prominent nucleoli with irregularly clumped chromatic or chromocenters.[28, 29] Positive cytology in the absence of ulceration is still possible due to penetration of the malignant cells through the surface membrane into the vaginal discharge according to Krumerman and Chung.[29] Although, cytologic diagnosis of malignant lymphoma is not always possible, cytology, if abnormal, may give the initial clue to the correct diagnosis.

Colposcopic findings are, likewise, not conclusive but may aid in the diagnosis. It was suggested that the most important colposcopic finding is diffuse cervical enlargement with or without erosion , a polypoid mass, or a barrel shaped diffuse enlargement of the cervix.[3,26, 30] One study reported showed findings of extended transformation zone without abnormal findings.[22] In one case report, a raised lesion occupying the entire transformation zone was the only finding noted.[31]

Deep biopsy of the lesion is necessary for the diagnosis of this malignancy.[26] This examination reveals preliminary histopathological features that may indicate lymphoma. Futhermore, the authors recommend a deep incisional or excisional biopsy to establish a definitive diagnosis when the initial biopsy is non-diagnostic such as findings of atypical epithelial cells coexisting with lymphoid infiltrates.[13]

Histologically, cervical lymphoma appears similar to lymphomas arising from other sites. It presents as diffuse infiltration of the stroma by monomorphic population of malignant lymphoid cells. The cells had intermediate to large, round to ovoid and irregular nuclei surrounded by scanty neoplasm. Unfortunately, a lot a disease entities overlap in morphologic features and may mimic lymphoma, which could be the reason why for our index patient, lymphoma was not diagnosed on initial biopsy. It was only in the hysterectomy specimen that the diagnosis of cervical lymphoma was confirmed.

Differential diagnoses are ample and include a variety of benign and malignant conditions such as chronic cervicitis, poorly differentiated carcinoma of which glassy cell carcinoma is subclassified, sarcoma, or lymphoma like lesion. Other hematopoietic lesions, malignant mixed mullerian tumors, endodermal stromal tumors, and melanoma should be ruled out. Epithelial tumors such small cell neuroendocrine carcinoma and lymphoepithelioma like carcinoma may also present diagnostic difficulty.[3,8,13,15]

In this dilemma, immunohistochemistry techniques proved to be extremely useful and invaluable in coming up with the specific diagnosis. In most of the reported cases, the immunohistochemical staining which has been documented, were of B-cell lineage. The most common histologic subtype is diffuse large B cell type (70%).[8,32] However, other B lymphomas such as mucosa-associated lymphoid tissue lymphomas[23], marginal zone B cell lymphoma, and follicular lymphoma have been reported.[8] T lymphomas and natural killer cell lymphomas[34] as well as Burkitt's lymphoma were reported.[34] In our case, the tumor stained positive for LCA, CD30, EMA, Vimentin, Granzyme B and negative for CD3, CD20, ALK, CK, SMA. This is consistent with the diagnosis of ALK negative Anaplastic Large cell lymphoma which is classified under Mature T cell and Natural Killer Cell neoplasm in the current WHO Classification updated in 2008.

Once cervical lymphoma is diagnosed, a complete clinical staging workup is usually requested after the biopsy prior to definitive treatment or post

operatively after the diagnosis is firmly established as in our patient. This includes CT or MRI of the abdomen and pelvis, CT scan of the chest , and bone marrow biopsy.[35] More recently, PET imaging has been increasingly used in the staging and follow up, although its precise role has not yet been determined.[36]

Although sonography is the initial or primary modality for evaluating female genital organs, it has limitation in the evaluation of the cervix. Thus, uterine cervical lymphoma has rarely been reported in sonographic findings in the literature.[37,38] The terms "posterior enhancement" and "pseudocystic appearance" are commonly used to describe the sonographic features of lymphoid tissues in non-Hodgkin's lymphoma.[39,40] They appear as such because the lymphoid tissue consists of homogenous cellular sheets and the sonographic beam encounters a few interfaces.

The Ann Arbor staging system is routinely used for staging both HL and NHL. (Table 1) Our index patient was given a stage I because the mass was localized in the cervix. A large series suggests that most patients with extranodal NHL present with stage IE tumor (73%) and IIE tumor (24%).[41,42]

Due to its low incidence, there is no widely accepted consensus on its management. According to case reports and series, therapy consists of radiotherapy alone, surgery alone, chemotherapy alone or a combination of the above methods.

The approach usually depends on the stage. Although the standard treatment has not yet been established, according to literature, the mainstay of treatment appears to be radiotherapy alone or in combination with surgery and/or chemotherapy for stage I and II.[8,42] Muntz, et al.[14], advocated primary surgery, followed by individualized radiation therapy for those with stage IE disease localized in the pelvis.

Some authors suggest that surgical resection in localized lymphoma may improve survival.[43] Complete surgical resection is sometimes an acceptable approach in well-selected cases of cervical lymphomas.[44] However, Perren, et al.[42], following an extensive review of literature, reported that there is no evidence radical surgery is in any way advantageous in terms of survival benefits and thus, might not be necessary.

For women with stage IE diffuse bulky disease, they recommended high dose radiotherapy with brachytherapy. On the other hand, others have suggested combination chemotherapy with radiation particularly in patients with bulky stage I and II.[35] Chemotherapy is the only therapeutic option in cases of advanced disease (Stage III or IV) with or without surgery or radiotherapy, although poor results are reported in terms of disease-free and overall survival.[35] Some authors have advocated surgery or radiotherapy in addition to combination chemotherapy to decrease the risk of central recurrence.[35,42] But combination chemotherapy with tailored radiotherapy is the preferred first line option. So far, only 2 cases have been presented where neoadjuvant chemotherapy followed by surgery was successfully instituted.[11,25] In patients with locally advanced and/or high grade lymphoma, more aggressive management should be used.[42,45]

For patients desirous of future pregnancy, options reported include combination chemotherapy and neoadjuvant chemotherapy followed by uterine preserving surgical approach. To preserve hormonal function, ovarian transposition is sometimes carried out.[14] Literature data show that up to 40% of women in childbearing age treated with chemotherapy for systemic non-Hodgkins lymphoma may conceive.[46] Sandvei, et al.[48], reported a case of successful pregnancy in a young woman treated with chemotherapy and no further treatment. Lorusso, et al.[48], in 2007, described a case of a patient who had a successful pregnancy 3 years after undergoing neoadjuvant chemotherapy followed by cold knife conization treatment for B-cell non Hodgkins lymphoma.

The regimens used for cervical lymphoma are the same regimens usually employed for systemic NHL. Chemotherapeutic regimens have evolved from single agent vincristine to different combination chemotherapy. The most common chemotherapy regimen is CHOP. Six courses of cytotoxic chemotherapy according to the CHOP protocol (Day 1 cyclophosphamide 750 mg/m^2, Adriamycin 50 mg/m^2, vincristine 1.4 mg.m^2 IV. Days 1-5 Prednisone 100mg/m^2 p.o) are administered on a monthly basis. Other reported chemotherapeutic regimens used were

MACOP-B (methotrexate, adriamycin, cyclophosphamide, vincristine, prednisone, bleomycin), THP-COP, CVP (cyclosphosphamide, vincristine, and prednisone) CHOP-R . Combination chemotherapy has been proven effective , resulting in excellent response rate and long term cure.[15,25]

Prognostic factors are the same as that for other extranodal lymphomas. The prognosis seems to correlate with the stage and grade of the disease.[26] Moreover, Stroh, et al. developed an international index score consisting of age of patient, Ann Arbor Stage, number of extranodal sites affected, performance status and serum Lactic dehydrogenase values, which could predict the outcomes for cervical lymphomas.[35] The size of tumor and type of lymphoma are also important prognostic features.[49]

Survival rates are scarcely reported in literature. Cervical lymphomas have generally a better prognosis than the nodal lymphomas with an overall median survival of 4 years.[36] Relapse rates was reported to be similar in the groups of patients treated by surgery and radiotherapy, surgery and chemotherapy, and surgery, radiotherapy and chemotherapy.[14] In a series described by Harris and Scully, 93% 5 year overall survival and 84% 5 year survival in 14 patients with cervical lymphomas stage IE treated with radiotherapy and/or surgery. Moreover, overall and disease free survival was only 33% in 3 cases of Stage IIE. Recently, in a review by Dursun, et al.[15], regarding 31 cases, 8 patients (26%) diagnosed with stage IE were treated exclusively with chemotherapy alone and no relapse were observed with a follow up 6 months to 8 years. This suggests that this option is effective over time.

However, note that reports on treatment and prognosis were mostly based on the most common histologic type of cervical lymphoma which is the B-Cell lymphoma. Our patient is diagnosed to have an ALK negative anaplastic large cell lymphoma which is known to have a very aggressive systemic counterpart. Our patient expired 2 months post surgery due to recurrence of the disease and its complications.

Summary

Primary malignant lymphoma of the cervix is an uncommon clinical entity. The clinical symptoms are non-specific and frequently mimic other benign or malignant diseases. Cytological differential diagnosis can be misleading and a deep cervical and oftentimes excisional biopsy is required. Immunohistochemistry is necessary and invaluable in establishing an accurate diagnosis. Furthermore, the management of such is controversial. Nevertheless, clinicians and pathologists should be aware of this diagnosis and should include cervical lymphomas in the differential diagnosis of any gynecologic cancers.

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The Health-Related Quality of Life Survey of Cervical Cancer Patients Before, During and After Pelvic External Beam Radiotherapy Concurrent with Weekly Cisplatin in a Tertiary Care Government Hospital: A Preliminary Report*

Rommel A. Garcia, MD; Merlind M. Montinola - Morales, MD and Lilibeth L. Sia Su, MD, FSGOP, FPOGS

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

Objectives: Quality of life should always be a primary consideration among patients being treated for cancer. Quality of life is a secondary endpoint used in addition to survival data in developing modes of treatment for cancers. There is paucity of studies in the Philippines on quality of life of cancer patients. This study aims to utilize the European Organization for Research and Treatment of Quality of Life Questionnaire (EORTC QLQ-C30) and the supplemental module (EORTC QLQ-CX24) in determining the health-related quality of life of cervical cancer patients before, during and after pelvic external beam radiotherapy concurrent with weekly Cisplatin and to determine the association of health related quality of life with treatment outcome. This preliminary data reports on the acceptability and validity of these tools in Filipino patients with cervical cancer.

Methods: Data were collected from cervical cancer patients at a tertiary institution using the EORTC QLQ-C30 and QLQ-CX24 supplemental module. Patients undergoing concurrent chemoradiation were evaluated before during and after treatment.

Results: Eighty-two patients were included in the initial analysis with ages ranging from 26 - 71 years of age, with a mean age of 48.8 years. Majority of patients are in the FIGO st. II - III and had no co-morbid illnesses. Half of the patients are with treatment and half had no treatment. For the core questionnaire, the subjects generally have high mean scores for the physical, cognitive, and role functions; but intermediate in terms of the global health status, emotional and social functions. They have generally low reported symptoms except for the financial difficulty which is high (82%). Statistical analysis for the QLQ-CX24 module showed that the internal consistency (Cronbach $\alpha > 0.70$) was satisfactory in almost all scales in the cervical cancer module except for the sexual/vaginal functioning scale (Cronbach $\alpha = 0.657$). But almost all scales did not show good convergent validity.

Conclusion: The EORTC QLQ-C30 and the QLQ-CX24 questionnaires can be used as a tool for the clinicians to assess the health - related quality of life issues of Filipino patients with cervical cancer. Completion of the sample size and recomputation of the factors should be done in order to have more evaluable data in determining the questionnaire validity and assessing the quality of life of patients before, during and after concurrent chemoradiation.

* First place, 2013 SGOP Research Contest.

Cervical cancer is the most common female genital tract malignancy in the Philippines and the second most common cancer affecting females after breast cancer with an incidence of 11.7/100,000 in 2010[1]. The treatment facilities for the management of cervical cancer are scarce and available only in specialized tertiary government hospitals and some private hospitals.

Treatment for cervical cancer can either be surgical or medical (radiotherapy with chemotherapy)[2]. In the local and international guidelines, radical hysterectomy is the treatment of choice for early stages of the disease. Meanwhile, concurrent chemoradiation is a treatment option applicable to all stages of the disease. According to the 2012 Annual Statistics for Gynecologic Oncology cases in our institution; 83% of cervical cancer patients are diagnosed with advanced stage of the disease.[3] Hence, the majority of cervical cancer patients are treated with chemoradiation and only a very few undergo radical hysterectomy. The impact of treatment with chemoradiation is not only limited to the adverse events and treatment complications but also involves other aspects that affect self-image, daily activities, family life, social functioning and financial situation of the family.

The concept of "quality of life" refers to an individual's total well-being, which includes all emotional, social, and physical aspects of the individual's life. When it is used in reference to medicine as Health Related Quality of Life (HRQoL), it refers to how the individual's well-being may be impacted over time by a disease, a disability, or a disorder including treatment. This includes physical and mental health perceptions and their correlates—including health risks and conditions, functional status, social support, and socioeconomic status[6].

To quote one of the earlier and better known concepts of HRQoL in cancer patients – "Quality of life is a difficult concept to define and to measure. A hypothesis is proposed which suggests that the quality of life measures the difference, or the gap between the hopes and expectations of the individual and that individual's present experiences at a given period of time. Quality of life can only be described by the individual and must take into account many aspects of life."[7]

In the field of medical research, especially concerning clinical trials, HRQoL is currently considered as an endpoint, in the same manner as disease free survival (DFS) and over-all survival (OS). It is a dynamic process. Changes over time must be measured several times along treatment and follow-up. Being a subjective event, it is gauged according to the patient's perception and not from the observation of the therapeutic team[8].

It is not acceptable to pursue curative treatment with the hope of improving life expectancy when one does not give due consideration to treatment morbidity and patient-centered decision-making and quality of life implications[9].

There are a variety of survey tools used for measuring patients' health related quality of life, the results of which can be used to determine treatment options based on past results from other patients. When it is used as a longitudinal study device that surveys patients before, during, and after treatment, it can help health care providers determine which treatment plan is the best option, thereby improving healthcare through an evolutionary process [10].

Quality of life should always be a primary consideration among patients being treated for cancer. Some clinical trials have reported quality of life as a secondary endpoint used in addition to survival data in choosing chemotherapeutic agents for the treatment of advanced cervical cancer.[11, 12] Some studies have noted that patient-reported HRQoL measurements may be an important prognostic tool in advanced cervical cancer[12, 13]. Quality of life has been shown to predict survival in numerous disease settings[9,14,15]. Data from the Gynecologic Oncology Group (GOG) suggest that baseline HRQoL scores may predict survival and may serve as an early barometer of patients who may or may not respond to aggressive treatment.[9,16,17]

Cancer patients, doctors and health care researchers have different perspectives and may rate the same objective situation differently which lead to the currently accepted practice of assessing HRQoL using patients' questionnaires. These are validated, multi-dimensional instruments that systematically asks

questions covering physical, socio-economic, emotional, cognitive, work- or role-related aspects as well as a wide variety of disease related symptoms and therapy induced side effects. These have yielded several important and at times, unexpected results[8]. Patient- reported outcomes are now widely considered an excellent methodology to evaluate the utility of treatment[9]. These patient questionnaires are psychometric assessment tools that have met certain quality standards, most importantly with regards to their reliability and validity. There are hundreds of validated intruments that have been developed but the more commonly used for gynecologic cancers include the Functional Assessment of Cancer Therapy (FACT—with gynecologic and symptom subscales), the European Organization for the Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30), Hospital and Anxiety Depression Scale (HADS), Profile of Mood States (POMS), Rotterdam Symptom Checklist(RSCL), MOS-Short Form 36 (SF-36), and Visual Analogue Scale (VAS).

Majority of cervical cancer patients at the UP-PGH are diagnosed at initial consult with locally-advanced disease. These patients are treated with chemoradiation. Thirty seven percent of these patients will actually start treatment and only 16% of them will be able to complete the treatment. Only 10% will have no evidence of disease on short-term follow-up[3].

This study is conducted to determine the health related quality of life among cervical cancer patients before, during and after chemoradiation. It seeks to describe and compare the patients' HRQoL during these periods and will attempt to determine if HRQoL measurements are associated with dropping-out, non-completion of treatment, protraction of treatment time and if these measurements are also associated with tumor progression/persistence and eventual treatment failure.

Talking to and listening more to patients may just be as important as the clinical parameters and numerous laboratory tests done on them. It is actually the quality of life studies that give credence to the hard to prove but frequently encountered scenarios wherein patients perceive disease progression before it is clinically evident [14]. Clinicians have to look at the person behind the patient.

It is no longer appropriate to just help patients to simply survive one's illness, but rather avoid giving the "killing cure", to allow patients to enjoy life and function productively while interacting with their environment during multimodality cancer treatment.[18]

Review of Related Literature

The treatment for patients with cervical cancer has changed significantly over time. In the past, treatment of locally advanced disease involves extensive radiotherapy with external pelvic irradiation and brachytherapy. More recently, concurrent chemoradiotherapy has become the treatment of choice for patients with locally advanced cervical cancer. Cisplatin added to radiotherapy (chemoradiation) has shown better survival of patients with advanced cervical cancer than with radiation alone[4]. However, the addition of chemotherapy to radiotherapy may increase the radiation-related side effects on the bladder, as well as sexual functioning and could impact negatively on the quality of life, during and after treatment.[5] In a study by Torbe, et al. which compared the treatment results and side effects of patients who had concurrent chemoradiation and those who had radiotherapy alone showed that there was no significant difference between the two groups in terms of over-all survival, local relapse free-time and distant metastasis free-time, and in the frequency of rectovaginal and vesicovaginal fistulas. Concurrent chemoradiation had better results in the group of patients without anemia. However, side-effects (including nausea, vomiting, leucopenia, thrombocytopenia, early side effects on the intestines and both late and early side effects on the urinary bladder) were significantly increased the group treated with concurrent chemoradiation The study concluded that chemoradiation shows better results if there is no anemia but it increases the frequency of early and late side-effects that could impact negatively on the quality of life during and after treatment[5].

A critical review of patient-rated quality of life studies of long-term survivors of cervical cancer was done by Vistad, et al. Twenty-three studies were

included and were published between 1966 and August 2005. A quality assessment using methodological and treatment-related criteria was performed to distinguish between studies with good and less good methodology. The studies with good methodology focused primarily on sexual and social function after treatment, and less on physical and psychological well-being. The trend is that radiotherapy is more associated with reduced quality of life dimensions than surgery or chemotherapy. Reviewed studies indicate that quality of life in cervical cancer survivors is reduced compared to the general female population following radiotherapy, but less so following surgery[20].

In 1986, the European Organization for Research and Treatment of Cancer (EORTC) initiated a research program to develop an integrated, modular approach for evaluating the quality of life of patients participating in international clinical trials. The EORTC QLQ-C30, the current core questionnaire, was developed to incorporate nine multi-item scales: five functional scales (physical, role, cognitive, emotional and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale with inclusion of several single-item symptom measures. An international field study on the practicality, reliability and validity of the EORTC QLQ-C30 was performed. The questionnaire was administered before treatment and once during treatment to 305 patients with advanced non-resectable lung cancer from centers in 13 countries. The result supported the hypothesized scale structure of the questionnaire with the exception of role functioning (work and household activities), which was also the only multi-item scale that failed to meet the minimal standards for reliability either before or during treatment. Validity was shown by 3 findings. First, all interscale correlations were statistically significant. Second, most of the functional and symptom measures discriminated clearly between patients differing in clinical status as defined by the Eastern Cooperative Oncology Group performance status scale, weight loss, and treatment toxicity. Third, there were statistically significant changes, in the expected direction, in physical and role functioning, global quality of life, fatigue, and nausea and vomiting; for patients whose performance status had improved or worsened during treatment. The reliability and validity of the questionnaire were highly consistent across the three language-cultural groups studied: patients from English-speaking countries, Northern Europe and Southern Europe. The study concluded that the EORTC QLQ-C30 is a reliable and valid measure of the quality of life of cancer patients in multicultural clinical research settings.[22] Presently, the questionnaire has been translated and validated into 81 languages, including Tagalog, and is used in more than 9,000 studies worldwide. It is supplemented by disease-specific modules for breast, lung, head and neck, esophageal, ovarian, gastric, cervical, multiple myeloma, prostate, colorectal and brain cancer.[29]

In 2006, the EORTC group developed and validated the Quality-of-Life Questionnaire Cervical Cancer Module (EORTC QLQ-CX24) to supplement the EORTC QLQ-C30 core questionnaire. It consists of 3 multi-item scales and 5 single-item scales. Multi-trait scaling analyses revealed high internal consistencies and the questionnaire fulfilled convergent and discriminant validity. It was administered in a multi-cultural setting which included 9 European countries, Australia, Brazil, Korea and Taiwan. A total of 346 patients who underwent radical hysterectomy and received radiotherapy and chemotherapy were included. Most patients completed the core questionnaire and the cervical module in <15 minutes and two thirds did not require any assistance to complete the questionnaires.[25]

Asian countries then followed and adapted the EORTC QLQ-CX24 module. It was translated and validated in Sri Lanka and South Korea.[26, 32] In these studies, psychometric evaluation assessed the instrument for scale structure, scale reliability, validity and acceptability. The QLQ-CX24 was found to be patient-friendly with high compliance and low missing data and was concluded to be a valid instrument in the assessment of health-related quality of life issues for patients with cervical cancer.[26, 32.]

Locally, the EORTC QLQ-C30 Tagalog translation of the core questionnaire has been validated by Zafranco, et al. in 2009 in a study on the health related quality of life in Filipino breast cancer patients which also included the breast cancer module.[30] The questionnaire was also used by Vergara, et al. in their

study published this year on the quality of life and nutritional status of cancer patients (breast, colorectal and hematologic cancers) undergoing chemotherapy in the National Kidney and Transplant Institute.

The cervical cancer module (EORTC QLQ-CX24) has not yet been translated locally and has not been used in the local setting in assessing the health-related quality of life issues of patients with cervical cancer ongoing concurrent chemoradiation.

A lot of research and journals on quality of life have been published in paper and online, but all of them focused on the health related quality of life *after* treatment with radiotherapy or concurrent chemoradiation. Searches done in the print media and internet failed to come up with a study on quality of life changes while patients are undergoing concurrent chemoradiation. There is also no known previous study on quality of life before, during and after chemoradiation in our institution.

Objectives

General Objective

To determine the health-related quality of life of cervical cancer patients with stage I to III disease before, during and after pelvic external beam radiotherapy concurrent with weekly Cisplatin; and to determine the association of health-related quality of life with treatment outcome.

Specific Objectives

1. To compare the health-related quality of life of cervical cancer patients before, during and one month post treatment with concurrent chemoradiation.
2. To compare the quality of life scores across pertinent clinical variables such as cancer stage, histologic type and presence or absence of adverse events (anemia, neutropenia, uremia, infection and electrolyte imbalance).
3. To compare the quality of life scores across demographic variables like age, educational level and income classification.
4. To determine the association of quality of life scores with treatment outcome (dropping-out, non-completion of treatment, protraction of treatment time and tumor persistence/ progression).

Scope and Limitation

The study aims to only compare the HRQoL scores of cervical cancer patients in relation to the phases of chemoradiation. The other dimensions of quality of care such as the level of patient satisfaction is beyond the scope of this study.

Research Design

This is a prospective descriptive cohort.

Target Population

The target population consisted of patients diagnosed with cervical cancer stages I to IIIB who are scheduled to undergo treatment with chemoradiation.

Inclusion Criteria

The study included patients diagnosed with cervical cancer stage I-IIIB and that:

- diagnosis of the disease was confirmed by biopsy
- were scheduled for pelvic external beam radiotherapy concurrent with weekly Cisplatin (radiosensitizing dose) followed by brachytherapy as their primary treatment
- have informed and signed written consent for this study
- good periodic follow-up as scheduled by the section and the research investigator
- with complete medical records that would allow adequate evaluation for the purpose of the study
- for the purpose of evaluating the impact of the disease and treatment on the HRQoL on

these patients, only those who have started chemoradiation and finished *at least* 10 days of radiotherapy and/or 2-3 courses of Cisplatin chemotherapy were included in the study.

Exclusion Criteria

The following patients were excluded from the study:

- patients with stage IV cervical cancer
- patients who had neo-adjuvant chemotherapy
- patients who had abdominopelvic surgeries related to the treatment of the cervical cancer (radical hysterectomy, extrafascial hysterectomy, bilateral salpingo-oophorectomy)
- patients with previous abdominopelvic radiation therapy
- patients with other types of cancers (concurrent or previously treated)
- patients who were pregnant at the time of chemoradiation

The Research Instrument

The EORTC QLQ-C30 incorporates 9 multi-item scales: five functional scales (Physical, Role, Cognitive, Emotional and Social Functioning); 3 symptom scales (Fatigue, Pain and Nausea/Vomiting); and a Global Health Status/QoL scale. Six single item scales were also included (Dyspnea, Insomnia, Appetite Loss, Constipation, Diarrhea and Financial Difficulties). The EORTC-QLQ-C30 has been translated to the Filipino Tagalog and validated locally. The Filipino Tagalog version of the EORTC-QLQ-C30 is available online at the EORTC website. Permission to use in this study had been granted.

Translation

The cervical cancer-specific supplemental questionnaire EORTC-QLQ-CX24 was also internationally validated.[25-27] It consisted of questions relating to symptom experience, body image, sexual/vaginal functioning, lymphedema, peripheral neuropathy, menopausal symptoms, sexual worry, sexual activity and sexual enjoyment. There was no available Filipino/ Tagalog version of this supplemental questionnaire. The translation and back translation process to Filipino - Tagalog followed the EORTC Quality of Life Group Translation Procedure Manual instructions. The initial translation was done with a staff of the Sentro ng Wikang Filipino, University of the Philippines-Manila. The principal investigator checked the translation then coordinated with the translation officer of the EORTC for the translation and back translations to the native Filipino language.

Pilot Testing

The pilot testing of the translated questionnaire was performed on 15 cervical cancer patients to identify and solve any potential problems in translation and to identify difficult-to-understand words and upsetting or offensive expressions; and whether the patient would have asked the question in a different way without changing the wording of the original item but expressing it clearly in Filipino Tagalog. The obstacles in patients' understanding and completing the questionnaires were reviewed and used to modify the questionnaires by the translation group. The revised questionnaire was then submitted to the EORTC committee for approval. The final translated questionnaire was then approved for study use.

Procedure

The study was conducted in a tertiary institution. Informed consent from the patents was obtained by the principal investigator prior to inclusion into the study. The medical records of all consenting patients were retrieved and case report forms were filled up.

The patients' HRQoL were documented on three occasions – before, during and one month after chemoradiation. The respondents were asked to enter a quiet room and to answer the pre-tested self-administered questionnaire. Equal opportunity for all cervical cancer patients who satisfied the inclusion criteria were considered –patients who could not read and/or write were included in the study. They were assisted in answering the questionnaire by their

companions, by family members, or by a research assistant.

To ensure that the questionnaire would not be perceived as a quality of care questionnaire, it was explained to the respondents on initial meeting to answer truthfully, that the study is not about the quality of care – that it is not about rating or grading their attending oncologist. The principal investigator emphasized that the study is on quality of life and all their answers are strictly confidential such that even their attending oncologist would not know their answers to the questions.

The case registry form was completed to identify important demographic and clinicopathologic characteristics of the patients (see case registry form). Important information recorded included age of the patient, civil status, obstetric score, monthly family income, family size, co-morbid illness, stage of the disease and histologic type. Clinical laboratory factors including hemoglobin level, absolute neutrophil count, serum creatinine/ creatinine clearance, urinalysis and electrolytes were recorded each time the patient answered the self-administered questionnaire – data serve as surrogate markers for the presence or absence of adverse events (anemia, neutropenia, uremia, infection and electrolyte imbalance).

Ethical Considerations

The research protocol was approved by Research Ethics Board. In the recruitment of patient respondents, it was fully understood that these respondents invited to participate in the study were cancer patients, and as such, were vulnerable individuals. The issue of vulnerability was addressed by the principal investigators by explaining adequately that the management would not be altered by participation or non-participation into this study. It was also explained that participation in the study does not guarantee better outcomes than those who choose not to participate, and that any decision to discontinue their participation during the course of the study will likewise not affect primary management. The patients were also informed that participation into this study does not entail additional expenses on the part of the patient outside the usual protocol in the management.

This study was undertaken as a partial fulfillment of the requirements for completion of training, as such all expenses for the conduct of the study were shouldered by the principal investigator.

There is no conflict of interest with other agencies/ sections/departments arising from this study.

Results and Discussion

Validation Study

Demographic Data

Eighty-two patients with cervical cancer were recruited for questionnaire validation from June 2012 to June 2013. Their ages ranged from 26 – 71 years with a mean age of 48.8 years. Majority of patients were in the FIGO st. II – III and had no co-morbid illnesses. Half of the patients had treatment and half had no treatment. The demographic data of the patients are shown in Table I.

The majority of the women (70%) completed the modules in <15 minutes and most (65%) did not require any help. Patients related that the questions are clear and easy to understand. There was good item compliance with < 3% missing values except in the optional questions relating to sexual function. Only 6 patients opted to answer the questions.

Table 2 shows the scores of the patients for the QLQ-C30 and the QLQ – CX24 questionnaires. The scale scores were transformed to a scale from 0 to 100 based on the recommendations in the EORTC QLQ-C30 Scoring Manual. Meanwhile, the items in the cervical cancer module (EORTC QLQ-CX24) were categorized and transformed according to the procedures in the study of Greimel et, al. (2006). The QLQ-C30 questionnaire was not statistically validated anymore since, it was previously validated locally.[30] A high mean score for the functional scale and the global health status represented a high/healthy level of functioning, while a high score for the symptom scale/ item represents a high level of symptomatology or problems. Based on the results, the subjects generally have high mean scores for the physical, cognitive and role functions (76.5%, 73% and 69.9%, respectively);

Table 1. The sociodemographic data of patients.

	(n = 82)	Percent
Age (mean ± SD)	48.8 ± 9.29	
Graviditye		
≥ G4d	51	62.2
≤ G3	31	37.8
Education		
Elementary	22	26.8
High School	47	57.3
College	13	15.9
Civil Status		
Single	20	24.4
Married	50	61.0
Separated	6	7.3
Widow	6	7.3
Place of Residence		
Metro Manila	33	40.2
Provinces	49	59.8
Monthly Income		
P 5,000 -10,000	5	6.1
P 10,000- 15,000	52	63.4
P 15,000 – 20,000	20	24.4
P 20,000 – 25,000	2	2.4
P > 25,000	3	3.7
FIGO Stage		
I	3	3.7
II	33	40.2
III	44	53.7
IV	2	2.4
Histologic Type		
Squamous cell	66	80.5
Adenocarcinoma	16	19.5
Co-morbid Illness		
None	54	65.8
With (e.g. HPN, DM)	28	34.1
Treatment		
Yes	45	54.9
No	37	45.1

but intermediate in terms of the global health status, emotional and social functions (52.1%, 59.8% and 49%). They have generally low scores reported symptom scores (10.2% – 41%) except for the financial difficulty which is high (82%).

Table 2. Quality of life scores according to QLQ-C30 version 3.0.

Areas	Mean	SD
Physical function	76.5	18.3
Role function	69.9	28.2
Emotional function	59.8	29.0
Social function	49.0	36.1
Cognitive function	73.0	22.5
Global QOL	52.1	20.5
Pain	53.9	29.7
Fatigue	40.1	25.2
Nausea/vomiting	10.2	19.6
Dyspnea	22.4	27.2
Insomnia	41	37.5
Appetite loss	30.9	30.4
Constipation	35.4	37.5
Diarrhea	14.2	25.7
Financial difficulties	82.1	33.2

The Tagalog translation of the cervical cancer module, QLQ-CX24 was tested for internal inconsistency and construct validity. Multi-trait scaling analyses were employed to examine correlations between items and the hypothesized scales within the EORTC QLQ-C30 and EORTC QLQ-CX24, separately. Convergent validity for each scale was assessed by calculating the correlation between each item and its own scale corrected for overlap. The correlation values were then compared for the correlation of each item with other scales to examine discriminant validity. A scaling error for an item was obtained when the correlation between an item and its own scale was lower than its correlation with any other scale. Correlations were determined by using the Pearson product-moment coefficient. Since the cervical cancer module contained optional items (sexuality items), pair-wise deletion of individuals with missing values were used in the multitrait analysis. The internal consistency of the multiitem scales was calculated by using the Cronbach á coefficient. Values of $\alpha \geq 0.70$ were considered acceptable for group comparisons. On the other hand, to be able to determine the relationship between the EORTC QLQ-C30 and EORTC QLQ-CX24, the scales in the cervical cancer module were correlated with the QLQ-C30 scales using also the Pearson product-moment coefficient.

Table 3. Multitrait scaling analyses with pearson correlations between scales items on the supplemental 24-item cervical cancer module.

Scale	Mean ± SD[a]	Cronbach α	Item-ownscale correlation[b]	Item-other scale correlation[c]	Scaling errors (%)
Symptom experience (items 31-37, 39, 41-43)	33.92 ± 17.16	0.7488	0.1863 - 0.6232	0.0000 - 0.9691	26 (29.55%)
Body image (Items 45-47)	33.47 ± 28.61	0.7689	0.5724 - 0.6206	0.0000 - 0.7661	2 (8.33%)
Sexual/vaginal functioning (Items 50-53)	12.5 ± 12.64	0.657	0.1463 - 0.6742	0.0000 - 0.9487	14 (43.75%)
Lymphoedema (Item 38)	11.38 ± 25.24	NA	NA	0.1640 - 0.7746	NA
Peripheral neuropathy (Item 40)	22.36 ± 27.24	NA	NA	0.1251 - 0.9691	NA
Menopausal symptoms (Item 44)	31.3 ± 32.01	NA	NA	0.0876 - 0.4201	NA
Sexual worry (Item 48)	70 ± 33.15	NA	NA	0.0353 - 0.6036	NA
Seuxal activity (Item 49)	22.22 ± 23.57	NA	NA	0.0295 - 0.5108	NA
Sexual enjoyment (Item 54)	33.33 ± 21.08	NA	NA	0.0000 - 0.7746	NA

[a] SD - Standard deviation
[b] Corrected for overlap
[c] The opposite value is displayed for negative correlations

Based on the results, the questionnaire showed that the internal consistency (Cronbach $\alpha > 0.70$) is satisfactory in almost all scales in the cervical cancer module except for the sexual/vaginal functioning scale (Cronbach $\alpha = 0.657$). However, removing the item concerning pain during sexual intercourse or other sexual activities would increase the Cronbach α of the sexual/vaginal functioning scale to 0.8864. This may be due to the small number of patients who answered this part of the questionnaire (6 out of 83 patients) since these items were labeled as optional items.

For the convergent validity, almost all scales did not show good convergent validity because almost all item-own scale correlations were less than 0.40 except for body image (0.5724–0.6206). Besides, scaling error was seen in the scales. The highest scaling error was observed in the symptom experience scale (29.55% or 26 out of 88).

The mean scores for all scales in the cervical cancer module indicate that the patients generally experience low level of symptomatology / problems except for the sexual worry scale (70 ± 33.15).

Most of the scales in the cervical cancer module were negatively correlated with the functioning scales in the core questionnaire. This indicates that high levels of the patients'functions are related with low levels of symptomatology / problems related to cervical cancer. There was a weak non-significant positive correlation between the financial difficulty scale and almost all the scales in the cervical cancer module. This means that high levels of financial difficulties experienced by the patients are slightly related to high levels of symptomatology / problems related to cervical cancer All correlations with scales related to sexuality items were non-significant although some items have high correlation coefficients. This may be attributed to the small number of patients who answered the said items (N=6). Decrease in the sample size was associated with decrease in the power of the statistical test

Quality of life scores were negatively correlated with symptom experience, sexual/vaginal functioning, lymphedema, menopausal symptoms, and sexual activity. Meanwhile, they were positively correlated with body image, peripheral neuropathy, sexual worry and sexual enjoyment.

Based on the above results, the cervical cancer module showed internal consistency was acceptable except for the sexual functioning scale which showed a low coefficient which maybe due to the small number of patients who answered the questionnaire because these items were optional and majority of the patients were not sexually active.

The low convergent validity and high scaling error could be attributed to the small sample size.

Main Study – Preliminary Result

The computed sample size for the study to determine the health-related quality of life of cervical cancer patients with stage I to III disease before, during

Table 4. Correlations between the European Organization for Research and Treatment of Cancer (EORTC) Quality-of-Life Core Questionnaire and the supplemental 24-item Cervical Cancer Module of the EORTC Quality-of-Life questionnaire.

	EORTC-QLQ-CX24 scales								
EORTC-QLQ-C30	Symptom experience	Body image	Sexual/ Vaginal functioning	Lymphedema	Peripheral neuropathy	Menopausal symptoms	Sexual worry	Sexual activity	Sexual enjoyment
Global Health Status									
Quality of life	-0.3443[b]	0.3138[b]	-0.0001	-0.2592[a]	0.1405	-0.1603	0.2821	-0.1394	0.3611
Functioning scales									
Physical functioning	-0.4332[b]	-0.2597[a]	-0.3592	-0.1625	-0.1276	-0.2186[a]	-0.3315	0.0355	-0.3627
Role functioning	-0.3293[b]	-0.3088[b]	0.1479	-0.0910	-0.1580	-0.2580[a]	-0.2871	0.0307	-0.4258
Emotional functioning	-0.4289[b]	-0.3687[b]	-0.0184	-0.1977	-0.2611[a]	-0.2142	-0.2661	0.1078	-0.1757
Cognitive functioning	-0.4997[b]	-0.4565[b]	0.1203	-0.3940[b]	-0.3561[b]	-0.3347[b]	-0.3643	-0.0827	0.1924
Social functioning	-0.4697[b]	-0.4754[b]	0.4694	-0.3482[b]	-0.1648	-0.3458[b]	0.2793	-0.2257	-0.3216
Symptom scales									
Fatigue	0.4556[b]	0.3480[b]	0.5898	0.3954[b]	0.1431	0.2614[a]	0.3432	-0.3834	0.3537
Nausea and vomiting	0.2978[b]	0.2223[a]	0.0001	0.3742[b]	0.3021[b]	0.0663	0.3007	0.2325	0.5223
Pain	0.5504[b]	0.4977[b]	-0.3229	0.1879[a]	-0.1421	0.0806	0.2370	0.5678	0.0001
Single item scales									
Dyspnea	0.1848	0.0840	-0.4172	0.1041	0.2053	0.0842	-0.4470	0.0000	0.0000
Insomnia	0.3803[b]	0.3526[b]	0.1614	0.2103	0.0303	0.1160	0.4240	0.4744	0.3875
Apetite loss	0.3561[b]	0.2104	-0.3612	0.4115[b]	0.1823	0.1075	0.3887	-0.1768	0.0001
Constipation	0.4706[b]	0.4554[b]	0.5109	0.1056	0.0221	0.0948	0.5107	-0.5393	0.3062
Diarrhea	0.2213[a]	0.1094	0.0789	0.1704	0.3044[b]	0.1024	0.1159	0.0000	0.7560
Financial difficulties	0.0889	0.1325	0.0000	0.0986	0.0836	0.0299	0.5193	0.3536	0.0001

[a] $p<0.05$
[b] $p<0.01$

and after pelvic external beam radiotherapy concurrent with weekly Cisplatin was 121.

This paper presents the interim analysis with a total of 45 patients included in the study from June 2012 – June 2013. Table 4 shows the socio-demographic characteristics of the sample population. The patients' ages ranged from 26 – 64 years old, with a mean age of 47.4 years.

Twenty nine of 32 patients (90%) who have completed treatment had protracted treatment times ranging from 63 to 163 days. The ideal time of treatment was 55 to 60 days, beyond which pelvic control of the tumor suffered by 1% for every day beyond 60 days. Protraction of treatment time was due to lack of funds and anemia which necessitated blood transfusions.

For the treatment outcomes, 24 patients (75%) who completed treatment had no evidence of disease on follow up while 8 patients (25%) developed persistence. Patients with tumor persistence were advised systemic chemotherapy.

The quality of life scores before, during and after concurrent chemoradiation were computed and analyzed once the sample size had been reached in order to assess the quality of life of the patients over time.

Conclusion

In conclusion, the study provides a Filipino-Tagalog translation of the EORTC QLQ-CX4 questionnaire. Completion of the sample size and recomputation of the factors should be done in order to have more evaluable data in determining the questionnaire validity and assessing the quality of life of patients before, during and after concurrent chemoradiation.

Table 4. The sociodemographic data of patients who underwent concurrent chemoradiation.

	(n = 82)	Percent
Age (mean ± SD)	47.4 ± 9.52	
Gravidity		
≥ G4	24	53.3
≤ G3	21	46.7
Education		
Elementary	14	31.1
High School	22	48.9
College	9	20.0
Civil Status		
Single	10	22.2
Married	28	62.2
Separated	4	8.9
Widow	3	6.7
Place of Residence		
Metro Manila	20	44.4
Provinces	25	55.6
Monthly Income		
P 5,000 -10,000	5	11.1
P 10,000- 15,000	20	44.4
P 15,000 - 20,000	17	37.8
P 20,000 - 25,000	2	4.4
P > 25,000	1	2.2
FIGO Stage		
I	2	4.4
II	25	55.6
III	18	40.0
Histologic Type		
Squamous cell	34	75.6
Adenocarcinoma	11	24.4
Co-morbid Illness		
None	31	68.9
With (e.g. HPN, DM)	14	31.1
Treatment Status		
Completed?		
No	N =13	28.9
Persistence	6	13.3
Did not continue	7	15.6
Yes	N =32	71.1
Protracted? Yes	29	64.4
No	3	6.6
Outcome	N=32	
NED	24	53.3
Persistence	8	17.8

The EORTC QLQ-C30 and the QLQ-CX24 questionnaires can be used as a tool for the clinicians to assess the health – related quality of life issues of Filipino patients with cervical cancer. The questionnaires were well-accepted and easy to understand and with high rates of completion, although only a few patients opted to answer the sexual and vaginal function scales. For our part as clinicians, it is thus imperative that we should improve on our discussion and counseling of issues relating to sexual health to our patients.

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The Research Instrument

EORTC QLQ-C30 (version 3)

Kami ay interesado sa iilang bagay tungkol sa iyong kalusugan. Pakisagot lamang po ang mga tanong sa pamamagitan ng pagbilog sa bilang na tumutukoy sa iyo. Walang "tama" o "maling"sagot sa tanong. Ang impormasyon na iyong ibinigay ay mananatiling lihim.

	Di Masyado	konti	bahagya	labis
1. Nababalisa ka ba ng mga gawaing mahihirap tulad ng pagdadala ng mabigat na "shopping bag"?	1	2	3	4
2. Ang mahabang paglalakad ba ay nakakaligalig sa iyo?	1	2	3	4
3. Nakakaligalig din ba ang panandalian paglalakad mo sa bahay?	1	2	3	4
4. Kinakailangan mo bang manatili sa higaan o sa upuan sa araw?	1	2	3	4
5. Nangangailan ka ba ng tulong sa pagkain, pagbihis, paghugas sa sarili o sa paggamit ng kubeta?	1	2	3	4

Sa nakaraang linggo:

	Di Masyado	konti	bahagya	labis
6. May limitasyon ka ba sa pagsasagawa mo ng iyong trabaho o iba pang gawaing pang araw-araw?	1	2	3	4
7. May limitasyon ka ba sa pagsasagawa ng iyong mga libangan o ibang gawain?	1	2	3	4

	Di Masyado	konti	bahagya	labis
8. Kinakapos ka ba sa paghinga?	1	2	3	4
9. May sakit ka bang nararamdaman?	1	2	3	4
10. Kinakailangan mo bang magpahinga?	1	2	3	4
11. May problema ka ba sa pagtulog?	1	2	3	4
12. Nakakarandam ka ba ng panghihina?	1	2	3	4
13. Nakakaramdam ka ba ng kawalan ng gana sa pagkain?	1	2	3	4
14. Nakakaramdam ka ba ng pagduduwal?	1	2	3	4
15. Nasusuka ka ba?	1	2	3	4
16. Nahihirapan ka ba sa pagdumi?	1	2	3	4
17. Nakaranas ka ba ng pagtatae?	1	2	3	4
18. Napapagod ka ba?	1	2	3	4
19. Ang sakit ba na iyong nararamdaman ay naging sagabal sa iyong pang araw-araw ng gawain?	1	2	3	4
20. Nahihirapan ka ba sa pagbibigay tuon sa mga bagay tulad ng pagbabasa ng pahayagan o panonood ng telebisyon?	1	2	3	4
21. Nakakaramdam ka ba ng nerbiyos o pagkabahala?	1	2	3	4
22. Nag-aalala ka ba?	1	2	3	4
23. Nararamdaman mo ba ang pagkayamot?	1	2	3	4
24. Nakakaramdam ka ba ng lungkot?	1	2	3	4
25. Nahihirapan ka ba sa pag-aalala ng ilang bagay?	1	2	3	4

	Di Masyado	konti	bahagya	labis
26. Naapektuhan ba ang kalagayan mo ngayon o ang pagpapagamot ba sa iyo ay nakakahadlang sa iyong gawaing pampamilya?	1	2	3	4
27. Naapektuhan ba ang kalagayan mo ngayon o ang pagpapagamot ay hadlang ba sa iyong gawaing panlipunan?	1	2	3	4
28. Nagdudulot ba ng suliraning pananalapi ang pagpapagamot at ang kalagayan mo ngayon?	1	2	3	4

Para sa sumusunod na mga katanungan, pakibilugan lang ang bilang sa pagitan ng 1 at 7, na siyang pinakamabuting tumutukoy sa iyo:

29. Paano mo bibigyang halaga ang kabuuang kalusugan sa nakaraang linggo?

1	2	3	4	5	6	7
napakasama						napakagaling

30. Paano mo tantiyahin ang buong kalidad ng iyong buhay sa nakaraang linggo?

1	2	3	4	5	6	7
napakasama						napakagaling

EORTC QLQ - CX24

Iniuulat minsan ng mga pasyente na nararanasan nila ang mga sumusunod na sintomas o problema. Mangyari lamang tukuyin kung gaano mo naranasan ang mga sintomas o problemang ito nitong nakaraang linggo. Pakisagutan ang mga sumusunod sa pamamagitan ng pagbilog sa bilang na pinaka-naglalarawan ng iyong kalagayan.

Sa nakaraang linggo:

	Di Masyado	konti	bahagya	labis
31. Ikaw ba ay nakaranas ng pangingirot sa iyong tiyan?	1	2	3	4
32. Nahirapan ka ba sa pagkontrol ng iyong pagdumi?	1	2	3	4
33. Nagkaroon ba ng dugo sa iyong dumi?	1	2	3	4
34. Ikaw ba ay madalas naglalabas ng tubig o ihi?	1	2	3	4
35. Nakaramdam ka ba ng pananakit o mainit na pakiramdam kapag naglalabas ng tubig o umiihi?	1	2	3	4
36. Ikaw ba ay nagkaroon ng pagtagas ng iyong ihi ?	1	2	3	4
37. Nahihirapan ka bang ilabas lahat ng ihi sa pantog?	1	2	3	4
38. Mayroon ka bang pagmamanas sa isa o dalawang binti?	1	2	3	4
39. Nakaramdam ka ba ng pananakit ng balakang?	1	2	3	4
40. Ikaw ba ay nagkaroon ng pamimintig o kawalan ng pakiramdam ng iyong mga kamay o mga paa?	1	2	3	4
41. Ikaw ba ay nagkaroon ng iritasyon o pananakit ng iyong ari o kaluban?	1	2	3	4
42. May lumalabas ba na likido mula sa iyong pwerta?	1	2	3	4
43. Ikaw ba ay mayroong abnormal na pagdurugo sa iyong pwerta?	1	2	3	4
44. Ikaw ba ay nakaramdam ng madalas na pag-iinit ng katawan o pamamawis?	1	2	3	4
45. Ikaw ba ay nakaramdam ng pagiging hindi kaakit-akit sa pisikal na anyo bunga ng iyong sakit o gamutan?	1	2	3	4
46. Ikaw ba ay nakaramdam ng kabawasan sa iyong pagkababae bunga ng iyong sakit o gamutan?	1	2	3	4
47. Pakiramdam mo ba ay hindi ka kontento sa pangangatawan mo?	1	2	3	4

Sa nakaraang linggo:

	Di Masyado	konti	bahagya	labis
48. Nangamba ka ba na ang pakikipagtalik ay magiging masakit?	1	2	3	4
49. Ikaw ba ay naging aktibo sa pakikipagtalik?	1	2	3	4

Sagutin ang mga sumusonod na katanungan kung ikaw ay nakipagtalik nitong nakaraang apat (4) na lingo:

	Di Masyado	konti	bahagya	labis
50. Nakaramdam ka ba ng panununuyo ng iyong pwerta kapag nakikipagtalik?	1	2	3	4
51. Nakaramdam ka ba ng pag-igsi ng iyong pwerta?	1	2	3	4
52. Nakaramdam ka ba ng paninikip ng iyong pwerta?	1	2	3	4
53. Nakaramdam ka ba ng pananakit kapag nakikipagtalik o sa iba pang gawaing sekswal?	1	2	3	4
54. Ang mga gawaing sekswal ba ay nakakapagpaligaya sa iyo?	1	2	3	4

Treatment Outcome After Loop Electrosurgical Excision Procedure (LEEP) for Pre-Malignant Cervical Lesions: A Five Year Review in a Tertiary Care Government Hospital*

Ma. Margarita M. Montecillo, MD and Lilibeth L. Sia Su, MD, FSGOP, FPOGS

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

Appropriate management of women with cervical intraepithelial neoplasia (CIN) is a critical component of cervical cancer prevention.[1] Cervical intraepithelial neoplasia II - III are classified as high grade pre-cancerous lesions. There are many treatment options for the precancerous lesions varying from ablative methods, i.e. cryotherapy, electrocautery and laser vaporization, to excisional methods, i.e. cold knife conization (CKC) and loop electrosurgical excision procedure (LEEP) (Panna, 2009).[2]

In our institution, excisional therapy includes cold knife conization and loop electrosurgical excision procedure (LEEP). The indications for both procedures are almost similar and the decision is made by the preference of the clinician. Presently, there is no local data on the treatment outcome after loop electrosurgical excision procedure (LEEP) for pre-malignant cervical disease.

This study was conducted to determine the incidence of persistence, recurrence and progression of the cervical intraepithelial neoplasia, the incidence of underlying invasive carcinoma, the incidence of stenosis and obstetrical complications after loop electrosurgical excision procedure (LEEP) for pre-malignant cervical disease.

This is a retrospective descriptive study of patients who underwent loop electrosurgical excision procedure (LEEP) at a tertiary care government hospital using review of medical records for data collection. Medical records were reviewed for the treatment outcome of cold knife conization. Only patient charts that fufill the inclusion criteria were included. All patient information were kept strictly confidential.

Key words: Loop Electrosurgical Excision Procedure (LEEP), cervical cancer

Cervical cancer is a common disease worldwide. It is a leading cause of cancer-related death for women in developing countries.[2] In 2008, the Philippines estimated age-standardized national incidence rate was 11.7 per 100,000.[3] Cervical cancer is considered as a preventable cancer because it has a long period of precancerous lesion. Cervical cancer screening strategies such as cytology screening and visual inspection with acetic acid (VIA) are effective methods for detecting the premalignant lesions. Appropriate management of women with cervical intraepithelial neoplasia (CIN) is a critical component of cervical cancer prevention.[1]

Cervical intraepithelial neoplasia II - III are classified as high grade pre-cancerous lesions. There are many treatment options for the precancerous lesions varying from ablative methods, i.e. cryotherapy,

* Second place, 2013 SGOP Research Contest.

electrocautery and laser vaporization, to excisional methods, i.e. cold knife conization (CKC) and loop electrosurgical excision procedure (LEEP).[2]

Cervical conization is the treatment of choice for high grade precancerous lesions. Loop electrosurgical excision procedure (LEEP) is one of the accepted techniques for cervical conization. This is because the technique allows the simultaneous collection of specimens for further histopathological and therapeutic diagnostics and can be performed in an outpatient setting using local anesthesia.[4]

In our institution, excisional therapy includes cold knife conization and loop electrosurgical excision procedure (LEEP). The indications for both procedures are almost similar and the decision is made by the preference of the clinician. Presently, there are no local data on the treatment outcome after LEEP for pre-malignant cervical disease. This study was conducted to determine the incidence of persistence, recurrence and progression of cervical intraepithelial neoplasia, the incidence of underlying invasive carcinoma, the incidence of stenosis and obstetrical complications.

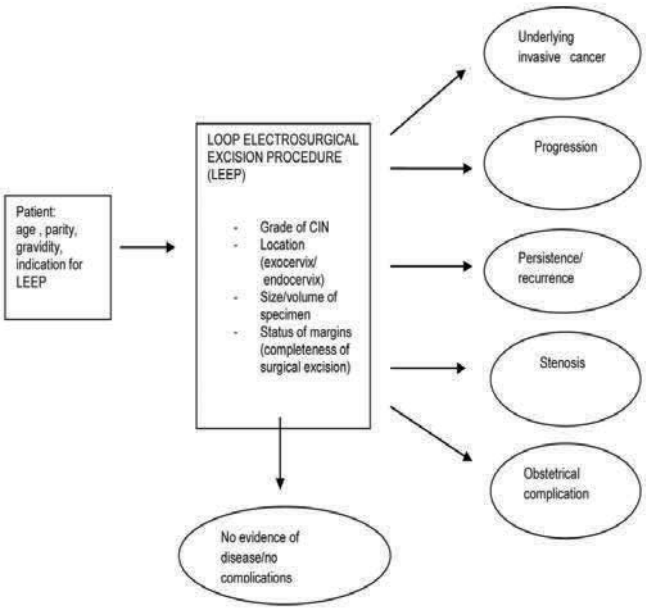
The search for abstracts and full text journals articles was done using the terms "cervical intraepithelial neoplasia (CIN)", "treatment outcome", "long-term outcome", "loop electrosurgical excision (LEEP)", "cold knife conization", "residual and recurrent disease".

Since LEEP was introduced by Prendiville in 1989 for the evaluation and treatment of cervical intraepithelial neoplasia, it has rapidly gained acceptance among gynecologists due to many advantage reasons such as providing adequate cervical specimens for pathological examination, the convenience to perform in an outpatient setting, and the high success rate with low surgical morbidity. Morbidity is lowered by shorter operative times, elimination of general or regional anesthesia and reduced blood loss. The possible complications are intraoperative hemorrhage, early and late postoperative hemorrhage, and postoperative infection.[6] A pathologic specimen is provided for histologic review and confirmation. Often, this specimen is smaller, yet adequate for evaluation when compared to other conization techniques.

Reported success rates in the treatment of dysplasia with LEEP are high, ranging from 63% - 97% and are comparable with older ablative procedures.[7] Despite the effectiveness of LEEP, recurrent dysplasia occurs in 5% - 64% of patients.[8] In previous studies, risk of persistent or recurrent disease has been consistently associated with large lesion, endocervical extension and incomplete LEEP excision.[5] Incomplete excision is associated with an increased risk of residual disease, 7%-85% of patients with positive margins later present with residual disease, recurrence or invasive disease.[9]

Many women who require treatment for cervical intraepithelial neoplasia (CIN) are in the reproductive age group. Thus, it is important to consider the potential negative effects of this treatment on future pregnancies.[10] LEEP conization can lead to a fragility of cervical connective tissue during pregnancy which may predispose patients to preterm births. For depths over 17 mm, there was a significant risk of preterm delivery.[11] Perhaps resecting a large amount of cervical stroma decreases the structural integrity of the cervix and thus the ability to carry a pregnancy to term. When obtaining informed consent for LEEP, it is important to counsel women about the increased risk of preterm delivery in subsequent pregnancies.[10]

Based on the review of related literature, the proposed conceptual framework for the present study focused on the factors that has a potential to affect the outcome after LEEP for pre-malignant cervical lesion.



This study was conducted to determine the incidence of persistence, recurrence and progression of the cervical intraepithelial neoplasia, the incidence of underlying invasive carcinoma, the incidence of stenosis and obstetrical complications after loop electrosurgical excision procedure (LEEP) for pre-malignant cervical disease.

Specific Objectives

1. To describe the demographic characteristics of the loop electrosurgical excision procedure (LEEP) patient in terms of age, gravidity, parity and the indication for the conization.
2. To describe the surgico-pathologic features in terms of the grade of neoplasia, location of the lesion, size or volume of the specimen, status of surgical margins.
3. To determine the incidence of persistence, recurrence and progression of the cervical intraepithelial neoplasia.
4. To determine the incidence of underlying invasive cervical cancer.
5. To determine the incidence of loop electrosurgical excision procedure (LEEP) complications (e.g. stenosis and obstetrical complications).

Materials and Methods

The Study Design

The study is a retrospective descriptive study. A flowchart of the study is seen below.

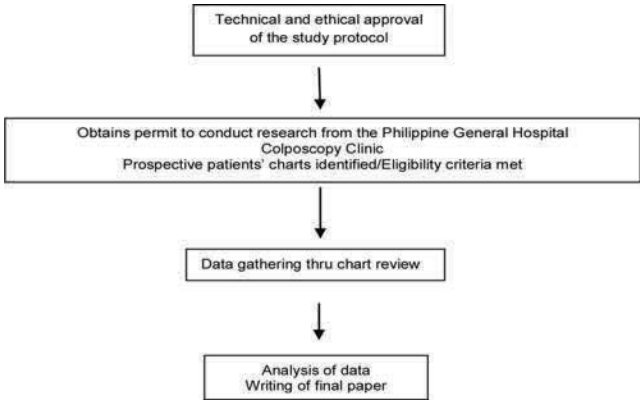


Figure 2. Flowchart of study activities.

Target Population

The target population consisted of patients who underwent loop electrosurgical excision procedure (LEEP) for pre-malignant cervical lesion from January 2008 to December 2012 at the Philippine General Hospital Colposcopy Clinic.

Inclusion and Exclusion Criteria

Inclusion Criteria

- All patients who had loop electrosurgical excision procedure (LEEP) for cervical intraepithelial neoplasia from January 2008 to December 2012 at the PGH Colposcopy Clinic.
- Patients who had loop electrosurgical excision procedure (LEEP) in other hospitals but are doing follow-up or having treatment for sequelae or complications at the PGH Colposcopy Clinic from January 2008 to December 2012.
- Had good follow-up and/or complete medical records for the purpose of this study.

Exclusion Criteria

- Patients who had other methods of excisional procedure for the treatment of cervical pre-malignant lesion.
- Patients who had loop electrosurgical excision procedure (LEEP) for indications other than cervical intraepithelial neoplasia or cervical pre-malignant lesion.
- Those with incomplete medical records.

Sampling Design and Sample Size

The study is a retrospective descriptive study. Sample size calculation is not necessary as all patients who had at the PGH Colposcopy Clinic LEEP from 2008 to 2012 were considered for inclusion into the study. It would be an exhaustive sample size of all patients who had loop electrosurgical excision procedure (LEEP) within the specified time frame.

Procedure

The study was conducted at the Philippine General Hospital Colposcopy Clinic.

After study protocol approval, the principal investigator secured permit to conduct research and retrieve medical records from the PGH Colposcopy Clinic. The medical records of patients who underwent LEEP from 2008 to 2012 were identified through the logbooks and record books of the Colposcopy Unit, Department of Obstetrics and Gynecology, Philippine General Hospital. The medical records of patients who satisfied the inclusion criteria were included in the study. Data gathering was thru chart review.

Data Collection Tool

A case registry form for each patient was filled up by the principal investigator. The case registry form recorded the patient clinical and demographic characteristics, the loop electrosurgical excision procedure (LEEP) surgico-pathologic features gathered from the Surgical Pathology Reports and the treatment outcomes. (See Appendix, Case Registry Form).

Data Analysis

Descriptive analysis was used for the patients' clinical and demographic characteristics, surgico-pathologic features and treatment outcomes.

The data obtained from the study were analysed using descriptive statistics (mean, range and percentage).

Results

A total of 37 patients were included in this study. The mean aged of the patients was 43.7 years. Their ages ranged from 26 to 76 years. The median age of the patients was 43 years. Forty percent (40%) of the patients were 30 - 39 years of age while 10% are aged 40 - 49. Three patients (8%) were below 30 years old.

The median number of pregnancies of the patients (gravidity) prior to the loop electrosurgical excision procedure was 2 with a corresponding range of 0 to 8 pregnancies. Twenty seven percent of patients had been pregnant for 2 times at the time of loop electrosurgical excision procedure. The median number of children born by the patients (parity) prior to the loop electrosurgical excision procedure was 2. One patient was nulligravid at the time of the procedure.

Patients who underwent loop electrosurgical excision procedure at the Philippne General Hospital Colposcopy Clinic were diagnosed with suspicious cervix (5.4 %), abnormal cytology (LSIL 2.5%, HSIL 21.6%, ASCUS 2.5%) and cervical pre-malignant lesion (CIN I - 5.4%, CIN II - 46%, and CIN III 16.2%) (Table 2).

Five out of 37 (13.5%) patients had no evidence of neoplasia on the LEEP specimen. The specimens were read as chronic cervicitis. Thirty two patients (32 out of 37) had evidence of disease on the LEEP specimen. Thirteen had CIN I (35.1%), 14 had CIN II (14%), 4 had CIN III (4%). The incidence of

Table 1. Clinical and demographic characteristics of the patients.

ID #	Age (years)	Gravidity/ Parity	Pre-LEEP lesion	Histopath diagnosis of LEEP specimen	Location of lesion	Surgical margin	Size of LEEP	Outcome
2008								
ML	35	G3P3	Abnormal Pap smear (HSIL)	CIN III	Endocervix	(-)	3.4x1.5x0.6	Recurrence
LF	58	G6P5	Abnormal Pap smear (LSIL)	CIN I	Exocervix	(-)	1.3x0.8x0.5	NED
MB	36	G1P1	CIN II - III	CIN II	Endocervix	(-)	4.5x2.7x1.5	NED
MB	30	G2P2	Abnormal pap smear (HSIL) CIN III	CIN II	Exocervix	(-)	4.5x1.5x0.6	NED
MS	39	G0	CIN II	CIN III	Exocervix	(-)	2.5x1.5x0.5	Recurrence

2009								
MF	29	G3P2	Abnormal Pap smear (HSIL)	CIN I	Exocervix	(-)	2x2x1.5	NED
EA	52	G4P4	CIN II	CIN II	Exocervix	(-)	4x1x0.5	NED
AG	42	G2P2	Abnormal Pap smear (ASCUS)	Cervicitis			2.2x1.4x1.1	NED
MD	46	G5P4	Abnormal Pap smear (HSIL)	CIN I	Exocervix	(-)	2x2x1.5	Lost to ffup
VC	45	G5P5	Suspicious cervix	Cervicitis			2.5x2x1.5	Lost to ffup
WC	30	G4P3	Abnormal Pap smear (LSIL) CIN I	CIN I	Exocervix	(-)	3.3x2.5x1.1	NED
MVM	43	G4P3	CIN II	CIN I	Exocervix	(-)	2.1x1.1x0.5	NED
MB	34	G4P4	Abnormal Pap smear (HSIL)	Cervicitis			2.8x1x0.6	Lost to ffup
LP	54	G3P3	Abnormal Pap smear (HSIL) CIN I	CIN I	Exocervix	(-)	3x1x1.1	NED
2010								
AL	28	G2P2	CIN I	CIN II	Exocervix	(-)	3.2x1.9x1.1	NED
RS	39	G3P3	Suspicious cervix CIN II	CIN II	Exocervix	(-)	4.3x2.2x1.5	NED
RB	55	G2P2	Abnormal Pap smear (HSIL)	CIN I	Exocervix	(-)	2.2x1.4x1.1	NED
RF	38	G6P6	Suspicious cervix CIN II	CIN II	Exocervix	(-)	3.6x1.5x1.3	Lost to ffup
NK	38	G3P3	Abnormal Pap smear (HSIL)	CIN III	Exocervix	(-)	2x2.5x1.5	Lost to ff-up
HA	37	G2P2	CIN II	Cervicitis			1x0.8x0.5	Lost to ffup
DT	53	G5P5	CIN III	SCCA LCNK	Endocervix	(-)	3.3x1.5x1.2	SCA cervix IB1
EN	56	G2P2	CIN II	CIN II	Exocervix	(-)	2.5x2.5x1.8	Recurrence
2011								
LV	36	G6P5	CIN II	CIN II	Exocervix	(-)	2.5x1.5x1.6	NED
AB	41	G2P2	CIN III	CIN I	Exocervix	(-)	3.2x1.4x0.6	NED
PV	76	G5P5	CIN III	CIN III	Endocervix	(-)	4x2.6x1	Lost to ffup
RB	26	G1P1	Abnormal pap smear (LSIL) CIN III	CIN I	Exocervix	(-)	2.5x1.3x1.3	NED
RP	39	G3P3	Suspicious cervix				2x1.5x1	NED
MS	34	G2P2	Suspicious cervix CIN II	CIN II	Exocervix	(-)	2.2	NED
2012								
AD	54	G6P5	CIN II	CIN II	Exocervix	(-)	3.5x2.5x1.5	NED
JC	44	G2P2	CIN III	CIN I	Exocervix	(-)	2x1.1x1	NED
JG	45	G8P6	Abnormal Pap smear ASCUS CIN II	CIN I	Exocervix	(-)	3.5x2.5x1.6	NED
LB	62	G3P3	Abnormal Pap smear HSIL CIN I	Cervicitis			3.6x2.3x2	Lost to ffup
OD	40	G2P2	CIN II	CIN II	Endocervix	(-)	3.5x3.5x2	NED
MP	43	G3P3	CIN II	CIN II	Exocervix	(-)	2.5x2.5x1.2	NED
LA	43	G6P4	CIN III	CIN I	Exocervix	(-)	3.4x2.2x1.4	NED
MC	34	G1P1	CIN II	CIN I	Endocervix	(-)	3x2.5x2.1	NED
RN	30	G1P1	CIN II	CIN II	Endocervix	(-)	2.5x1x1	NED

SCCA = Squamous cell carcinoma
HSIL= High-grade squamous intraepithelial lesion
LSIL = Low-grade squamous intraepithelial lesion
ASCUS = Atypical squamous cells of undetermined significance
NED = No evidence of disease

Table 2. Age distribution of patients.

Age (in years)	Number	Percent
20-29	3	8
30-39	15	40
40-49	10	27
50-59	7	20
60-69	1	2.5
70-79	1	2.5
Total	37	100

Diagnosis of patients prior to loop electrosurgical excision procedure (LEEP).

Diagnosis	Number	Percent
Suspicious cervix	2	5.4
LSIL	1	2.5
HSIL	8	21.6
ASCUS	1	2.5
CIN I	2	5.4
CIN II	17	46.0
CIN III	6	16.2
TOTAL	37	100

Table 3. Histologic diagnosis of LEEP specimen.

Histologic Diagnosis of the LEEP Specimens	Number	Percent
Negative for neoplasia		
chronic cervicitis	5	13.5
Positive for neoplasia		
CIN I	13	35.1
CIN II	14	37.8
CIN III	4	10.8
Squamous cell carcinoma	1	2.7
Total	37	100

underlying cervical cancer was 1 out of 32 (3%). The patient had a pre-LEEP diagnosis of CIN III (Table 3). The post-LEEP histology was squamous cell carcinoma. After LEEP, she underwent exploratory laparotomy, radical hysterectomy with bilateral salpingooophorectomy and pelvic lymphadenectomy. Final diagnosis was squamous cell carcinoma, cervix stage IB1.

Twenty six out of 32 (81%) had lesions located in the exocervix. Six out of 32 (19%) had endocervical lesions.

Among the patients who had neoplasia, the largest LEEP specimen measured 4.5cm x 2.7cm x 1.5cm. The specimen came from a 36 year old, G1P1 patient with a pre-LEEP diagnosis of CIN II. The smallest specimen removed measured 1.3cm x 0.8cm x 0.5cm. The specimen came from a 58 year old, G6P5 patient with a pre-LEEP diagnosis of LSIL on cytology.

The surgical margins of the LEEP specimens were negative for tumor except for one patient with squamous cell carcinoma.

After the loop electrosurgical excision procedure, patients were advised to have a repeat cytology after 6 months (Table 4). Patients who were diagnosed with chronic cervicitis and negative for neoplasia were lost to follow up. Among the 13 patients with CIN I, 11 had normal cytology; 1 had abnormal cytology and 1 was lost to follow-up. Among the 14 patients with CIN II, 12 had normal cytology, 1 had abnormal cytology and 1 was lost to follow up. Among the 4 patients diagnosed with CIN III, 1 had nromal cytology, 1 had abnromal cytology and 2 were lost to follow up. The patient who was diagnosed to have squamous cell carcinoma had normal cytology with no evidence of disease after surgery.

Recurrence was noted in 3 patients (9%). The first patient was a 35 years old, G3P3, who was diagnosed with CIN II after LEEP. The recurrence was noted 6 months after the procedure when a high grade lesion was noted on colposcopy. Cervical punch biopsy showed acute chronic cervicitis with squamous metaplasia and focal koilocytic atypia. A repeat LEEP was done.

The second patient was a 39 years old, nulligravid who was diagnosed with CIN III after LEEP. Recurrence was noted 21 months post LEEP when patient had unsatisfactory colposcopy. Endocervical curettage was done and revealed chronic ectocervicitis with koilocytic changes. Patient underwent cryotherapy and had normal cytology on follow up.

The third patient was a 56 year old, G2P2 who was diagnosed with CIN II after LEEP. Recurrence was noted 22 months post LEEP when a colposcopy guided cervical biopsy and endocervical curettage

Table 4. LEEP histology and post-LEEP cytology.

LEEP Histology	Number	Normal cytology	Abnormal Cytology	No cytology
Negative for neoplasia	5	0	0	5
CIN I	13	11	1	1
CIN II	14	12	1	1
CIN III	4	1	1	2
Squamous cell carcinoma	1	1	0	0
TOTAL	37	25	3	9

showed chronic endocervicitis with squamous metaplasia and focal koilocytic changes consistent with HPV related effects. Repeat LEEP was done and histopathology result was chronic ectocervicitis, chronic endocervicitis, and no dysplasia was seen along the margins.

There are no data regarding obstetrical complication post-LEEP because none of the patients got pregnant during follow up. There was no report of post-LEEP cervical stenosis.

Discussion

There has been no long-term study on the treatment outcome of patients who underwent LEEP for pre-malignant cervical lesions. The result of this 5 year review was comparable with international literature. The indications for LEEP were due to abnormal cytology (HSIL, LSIL, ASCUS) and presence of pre-malignant cervical lesions CIN I, CIN II and CIN III.

The recommended methods for surveillance in patients who underwent LEEP for pre-malignant lesions includes cytology and colposcopy. HPV DNA testing was not included because of the high cost.

Despite the effectiveness of LEEP, recurrent dysplasia occurs in 5% to 64% of patients. Several factors such as margin status, endocervical and glandular involvement and disease in multiple colposcopic quadrants have been associated with an increased risk of recurrence.[8] In this review series, the surgical margins of the LEEP specimens were negative for tumor except for one patient with squamous cell carcinoma. However, in patients (99%) recurrence was noted; the earliest occurred 6 months post-LEEP, while the latest occurred 22 months post-LEEP.

Conclusion

This five year retrospective descriptive study included 37 patients who underwent LEEP for pre-malignant cervical lesions from January 2008 to December 2012 in the Philippine General Hospital Colposcopy Clinic. The study was approved by the technical and review board of the institution. Data collection was done by medical chart review and data obtained were analyzed using descriptive statistics.

The study was conducted to determine the incidence of persistence, recurrence and progression of the pre-malignant cervical lesions, incidence of underlying carcinoma after LEEP.

Based on this review series, the cure rate after LEEP was 91% (34 out of 37), the CIN recurrence rate was 9%, the incidence of underlying carcinoma

ML	35	G3P3	Abnormal Pap smear (HSIL)	CIN III	Endocervix	(-)	3.4x1.5x0.6	Recurrence
MS	39	G0	CIN II	CIN III	Exocervix	(-)	2.5x1.5x0.5	Recurrence
EN	56	G2P2	CIN II	CIN II	Exocervix	(-)	2.5x2.5x1.8	Recurrence

was 2.7%. There were no data regarding obstetrical complication post-LEEP because none of the patients got pregnant during follow up. There was no report of post-LEEP cervical stenosis.

Limitations and Recommendations

The five year treatment outcome in this review series was limited due to the small number of patients who underwent LEEP. The results of this review should be confirmed in a larger group of patients with a longer post-LEEP follow up interval. A study comparing outcomes with cold knife conization for pre-malignant cervical lesions is also recommended.

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The Utility of Performing Appendectomy in Patients Who Underwent Laparotomy for a Mucinous Tumor of the Ovary*

Ana Bella S. Juan-Cristobal, MD; Rene V. Sotto, MD, FSGOP, FPOGS and Elsie I. Callos, MD

Department of Obstetrics and Gynecology, Quezon City General Hospital

Forty eight patients with mucinous tumors of the ovary were studied. Concomitant appendectomy was done during the exploratory laparotomy. Most of the subjects belong to ages 21 to 30 years old. The majority had either a pelvic mass or abdominal pelvic pain and 22% underwent an emergency procedure. There was a high frequency of unilateral ovarian tumors and right sided predominance. Most of the cases are multigravid and multiparous. Three of the 48 cases (6.2%) were discovered to have mucinous cystadenoma of the ovary and appendix. This shows the importance of performing appendectomy for cases of mucinous ovarian tumors. With the procedure, a dreadful and fatal complication may be prevented, and this is pseudomyxoma peritonei (PMP).

Key words: laparotomy, appendectomy, mucinous tumor

Pseudomyxoma peritonei is a consequence of rupture of mucinous cyst within the peritoneal cavity, thus transforming the peritoneal mesothelium into a mucin secreting epithelium. With continuous accumulation, this would eventually transform into a gelatinous material constituting pseudomyxoma peritonei (PMP).[1]

The rupture of mucinous cyst may not only originate from the mucinous tumor of the ovary. It may also start from rupture of the appendix, plugged by an appendiceal mucocoele. This would repeatedly throw mucin producing cells into the peritoneal cavity. Appendiceal mucocoele is a rare pathologic entity and diagnosed definitively by histopathologic studies,[2] particularly in cases that would appear grossly normal intraoperatively. Appendiceal mucocoeles may be found in 0.2%-0.3% appendectomy specimen.[3]

A study by Djorjeric showed that 75% of cases of PMP are secondary to gross or microscopic rupture of appendiceal tumor. Our study would like to observe the incidence of synchronous mucinous tumors of the appendix and ovary in our institution since both would be associated with the development of PMP in the future.

Although, treatment of PMP is a tedious process and would require several surgical procedures, performance of appendectomy in addition to salpingo-oophorectomy may lessen the chance of developing PMP, particularly those with unruptured

* Third Place, 12th SGOP Research Paper Contest.

appendiceal mucocoele. In addition, it would provide identification of the patients who may require the repeat laparotomy in the future.

General Objective:

To determine the utility of appendectomy in patients who underwent laparotomy for a mucinous tumor of the ovary at the Quezon City General Hospital.

Specific Objectives:

1. To compare the histopathologic results of specimens signed out as mucinous tumor of the ovary and mucinous tumor of the appendix.
2. To determine the clinical profile of patients operated with mucinous cystadenoma of the ovary according to: age, contraceptive use and OB score.

Inclusion Criteria:

The study included all cases with histopathological results of patients diagnosed with ovarian new growth and intra-operative findings consistent with mucinous tumor, and underwent appendectomy. The patients' profiles were recorded.

Exclusion Criteria

Histopathological results of patients diagnosed with ovarian new growth, non-mucinous type, and did not undergo appendectomy were not included in this study.

Study Setting and Time Period

All patients diagnosed with ovarian new growth and intra-operative findings consistent with mucinous tumor, and underwent appendectomy at the Department of Obstetrics and Gynecology of Quezon City General Hospital from 2006 to 2012.

Materials and Methods

All patients admitted with diagnosis of ovarian new growth probably mucinous tumor since 2006 to 2012 were included in the study. Intraoperative, gross morphologic findings such as 1) size > 10cm ovarian tumor, 2) multiloculated mass, 3) On cut section, would contain mucin and 4) on exploratory laparotomy, particularly those with pre operative rupture of the cyst, mucinous fluid would be admixed with peritoneal fluid were taken into consideration.

After performing the definitive procedure for the ovarian pathology, the case would be referred to general surgery service for performance of appendectomy. Histopathologic results of the appendix were collected to compare if the specimen would also exhibit mucinous pathology particularly appendiceal mucocoele.

Analysis of Data

Data were encoded and tallied in SPSS version 10 for windows. Descriptive statistics were generated for all variables. For nominal data frequencies and percentages were computed. For numerical data, mean ± SD were generated. McNemar test was used to compare the proportion of subjects with mucinous ovary and mucinous appendix.

Results

Table 1 shows the distribution of subjects according to age, gravidity, parity and contraceptive use. Their ages ranged from 15 to 68 years with a mean age of 35.23 years. Majority of the cases were 21 to 30 years of age.

There were 15(31.2%) nulligravid and 33(68.8%) multigravid, nulliparous 12(25%) and multiparous 36(75%). Four patients used contraception. Table 2 shows the descriptive statistics for the size intraoperatively and according to histopath as well as laterality of ovarian mass. There was a slight difference on the intraoperative and histopathologic measurements. The intraoperative range of length was 7cm-35cm and width was 5cm-30cm. The histopathologic length range was 5.8cm-26cm and width 3cm-24cm. Mucinous cystadenoma occurred most on the right [27(66.7%)] compared to left [16(33.3%)]. There were 5(10.4%) affecting both ovaries and 43(89.6%) cases affecting either the left or the right ovary only.

In 48 cases, 11(22.9%) were operated at the time of consultation, 37(77.1%) cases were elective cases. Intraoperatively 26 (54.2%) cases showed mucin admixed with peritoneal fluid. On cut section of the specimen, 36 (75%) were multiloculated and 12 (25%) uniloculated. (Table 3)

Table 1. Demographic characteristics of subjects.

Characteristics	Frequency (n=48)	Percentage
Age in years		
15 - 20	4	8.3
21 - 30	17	35.4
31 - 40	10	20.8
41 - 50	10	20.8
51 - 60	5	10.4
61 - 70	2	4.2
Mean ± SD = 35.23±13.38		
Gravidity		
Nulligravida	15	31.2
Multigravida	33	68.8
Parity		
Nulliparous	12	25.0
Multiparous	36	75.0
Contraceptive Use		
Yes	4	8.3
No	44	91.7

Table 2. Descriptive statistics for size and laterality.

Size		Mean ± SD	Range
Intraoperative	Length	15.70 ± 7.39	7 - 35
	Width	12.62 ± 6.14	5 - 30
	Length x Width	232.94 ± 226.08	35 - 1050
Histopath	Length	15.26 ± 4.96	5.8 - 26
	Width	11.69 ± 4.52	3 - 24
	Length x Width	196.01 ± 124.93	23.2 - 50

	Frequency (n=48)	Percentage
Laterality		
Left	16	33.3
Right	27	66.7
Side		
Uni	43	89.6
Bilateral	5	10.4

Table 3. Distribution of subjects according to urgency to do the operation and characteristics of the ovary intra-operatively.

Characteristics	Frequency (n=48)	Percentage
Emergency		
Emergency	11	22.9
Scheduled	37	77.1
Multiloculated		
(+)	36	75.0
(-)	12	25.0
Peritoneal Fluid		
(+)	26	54.2
(-)	22	45.8

Of 48 subjects with mucinous cystadenoma of the ovary, 3 (6.2%) were found to have mucinous cystadenoma of the appendix. (Table 4)

Table 4. Comparison of the results of the histopath.

	Appendix		Total
	Mucinous	Non Mucinous	
Ovary			
Mucinous	3 (6.2%)	45 (93.8%)	48

P value <0.05 (S)

90% level of confidence

Discussion

Mucinous cystadenoma of the ovary is an epithelial ovarian tumor. Bilaterality is rare at 2%-10% of cases. The estimated peak incidence is around 30-50 years of age.[5] Mucinous cystadenoma tends to be larger than serous cystadenoma at presentation, and is more likely to remain clinically silent[4] but can at times compromise breathing because they may present as large abdominal mass.

Grossly they may attain large sizes, weighing 200 to 300 pounds. They are generally multiloculated with firm solid areas particularly the malignant tumors. The fluid content is usually mucoid but may be watery in 25% of cases. Microscopically they resemble the lining

of the endocervix (tall columnar cells with basal nuclei) which is indistinguishable from the appendix. These epithelial cells contain mucin. Carcinoembryonic antigen (CEA) has been demonstrated in cyst fluid and tissue sections stained with immunoperoxidase.[11]

The gross appearance describing mucinous tumors of the ovary has been our basis in judging if an ovarian mass, after performing salpingo-oophorectomy (SO), would also require appendectomy. Our results with regards to size were consistent with mucinous tumor found in the general population.

Studies have demonstrated the occurrence of synchronous existence of ovarian mucinous tumor and appendiceal mucinous tumor. A study by Young. et al showed > 90% co existence rate. Locally it is not yet seen how much of our ovarian mucinous tumor co exist with an appendiceal tumor. It has been advocated by the Society of Gynecologic Oncologists of the Philippines Foundation Inc,(SGOP) to perform appendectomy in cases of mucinous tumor of the ovary as part of complete staging procedure for malignant cases. Performance of appendectomy for benign mucinous ovarian masses has not been thoroughly studied and advocated.

Pseudomyxoma peritonei (PMP) is a syndrome first described by Karl F. Rokitansky in 1842, it is an enigmatic, often fatal intra-abdominal disease characterized by dissecting mucinous ascites and multifocal peritoneal epithelial implants secreting copious globules of extracellular mucin (i.e., MUC2 and MUC5AC) because these two mucins possess the physicochemical property of being gel forming. This is the property exhibited by pseudomyxoma peritonei grossly.[8]

It also causes accumulation of gelatinous material in the peritoneal cavity. It is associated with benign and malignant mucinous tumors. Some believe that the pathogenesis of PMP is secondary to an inflammatory foreign body reaction from the extravasated mucinous fluid that induces metaplasia of the peritoneal mesothelial cells to neoplastic mucinous epithelium. Patients suffering from PMP deteriorate and succumb to inanition and infection secondary to repeated surgeries for evacuation of mucin as well as secondary to intestinal obstruction.

Our study has shown the occurrence of right sided laterality of co-existing ovarian and appendiceal mucinous tumor. A study by Ronneth showed that an ovarian mucinous tumor associated with PMP is almost always metastatic rather than primary. This showed further that appendiceal or other intestinal sites of origin should be ruled out primarily prior to concluding that PMP is secondary to ovarian origin. The primary appendiceal tumor maybe small relative to the ovarian tumor and may not be appreciated macroscopically. Thus, removal and thorough histologic examination of the appendix is indicated in all cases of ovarian mucinous cystadenoma. This may also be a good avenue to explore further, that appendectomy be done only in cases of right ovarian mucinous cyst in the future.

Majority of our cases had their operation on an elective basis. There were 11 cases (22.9%) who underwent emergency laparotomy due to acute abdomen. The 3 cases with appendiceal mucocoele had their appendectomy, in addition to salpingo-oophorectomy, performed on an elective operative procedure.

Our study has shown a 6.2% rate of co existence of ovarian and appendiceal mucinous tumor. The 3 cases that were positive for both ovarian and appendix were all benign cases. Grossly the appendix appeared normal, but pathological sectioning of the 3 cases which showed positive for occurrence of mucocoele strengthened our belief that appendectomy should be performed for cases of ovarian mucinous cyst, be it benign or malignant.

Conclusion

Mucinous tumor consists of epithelial cells filled with mucin. The cells resemble the lining of the endocervix or may mimic intestinal cells. This poses a problem in the differential diagnosis of tumors that appear to originate from the ovary or intestines.

The appendix has been claimed to be a preferential site of metastasis in ovarian cancer and it is generally accepted that routine appendectomy should be performed in advanced disease, specifically those with appendix affected by cancer tissue. However, it remains unresolved whether appendectomy aids in

better staging or has therapeutic value by being a part of debulking occult disease in early stage epithelial ovarian cancer.

The performance of appendectomy is an aggressive treatment which provides sufficient benefit to outweigh the cost in patients operated with mucinous tumor of the ovary. In this study, there were appendices which were positive for mucinous cystadenoma. This is a very good prophylaxis for the development of PMP because this is a neoplastic process that is progressive and fatal.

Recommendation

The researcher focused on epithelial ovarian tumor, mucinous type. Some readings stated that cases with other types of epithelial ovarian tumor also underwent appendectomy with a significant findings. It is recommended that a broader study to include appendectomy procedure in all the types of epithelial ovarian tumor undergoing salpingo- oophorectomy be done. Further follow up to this study is recommended, by investigating and following up all the subjects regularly every 5years after the SO and appendectomy procedure, particularly those who showed mucinous cystadenoma in both ovary and appendix. Lastly, immunohistochemical analysis should be done to distinguish if the tumor is primary (ovary or appendix) or metastatic.

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