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Daftar Isi

Korelasi *Hypoxia Inducible Factor-1A* (HIF-1A) dan *Vascular Endothelial Growth Factor* (VEGF) Dengan Hasil Operasi pada Kanker Ovarium Jenis Epitel

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ABSTRACT

Hypoxia inducible factor 1α (HIF-1α) *regulates gene involved in response to hypoxia and promotes angiogenesis. HIF-1α is a transcriptional factor to induce* vascular endothelial growth factor (VEGF). *The objective of this study was to examine the correlation of HIF-1α and VEGF expression with surgical outcome in epithelial ovarian cancer, therefore could predict optimality of debulking in ovarian cancer.*

Thirty patients with epithelial ovarian cancer who underwent primary surgery were included in this study. Tumor tissues were obtained from surgery and examined with q reverse transcriptase polymerase chain reaction (qRT-PCR) *for HIF-1α and VEGF expression analysis. Evaluation of surgical outcome was based on volume of residual tumor. Correlation between HIF-1α and VEGF was analyzed by using Spearman correlation test while the correlation between HIF-1α and VEGF and surgical outcome was analyzed by ANOVA.*

Results: The mean age of the study subjects was 47.53±10.41 years. Eleven patients (36.7%) were diagnosed with stage I ovarian cancer, 9 patients (30%) with stage II, 8 patients (26.7%) stage III and 2 patients (6.7%) with stage IV. Out of 30 patients, 22 patients (73.3%) successfully underwent optimal debulking and 8 patients (26.7%) with suboptimal debulking. There was a correlation between HIF-1α and VEGF expression (r=0.582) but no correlation between HIF-1α and VEGF expression with surgical outcome in patients with epithelial ovarian cancer.

Conclusion: There was a significant correlation between HIF-1α and VEGF expression but no significant correlation between HIF-1α and VEGF expression with surgical outcomes.

Keyword: *HIF-1α, VEGF, surgical outcome*

ABSTRAK

Tujuan penelitian ini adalah untuk melihat korelasi antara HIF-1α dan VEGF dengan hasil operasi pada kanker ovarium jenis epitel sehingga dapat diprediksi tercapainya sitoreduksi optimal tumor ovarium.

Tiga puluh pasien dengan kanker ovarium jenis epitel yang menjalani operasi primer diikutsertakan dalam penelitian. Jaringan tumor yang diambil melalui prosedur operasi kemudian diperiksa menggunakan *q reverse transcriptase polymerase chain reaction* (qRT-PCR) untuk menganalisis ekspresi HIF-1α dan VEGF. Evaluasi hasil operasi berdasarkan volume tumor residu. Korelasi antara HIF-1α dan VEGF dianalisis menggunakan tes korelasi Spearman, sedangkan korelasi antara HIF-1α dan VEGF dengan luaran operasi dianalisis menggunakan Anova.

Hasil penelitian menunjukkan usia rata-rata objek penelitian adalah 47,53 tahun. Sebelas pasien (36,7%) didiagnosis kanker ovarium stadium I; 9 pasien (30%) dengan kanker ovarium stadium II; 8 pasien (26,7%) dengan kanker ovarium stadium III; dan 2 pasien (6,7%) dengan kanker ovarium stadium IV. Dari 30 orang pasien, 22 di antaranya (73,3%) berhasil dilakukan sitoreduksi optimal dan 8 pasien (26,7%) dilakukan sitoreduksi suboptimal.

Dari hasil penelitian didapat adanya korelasi antara ekspresi HIF-1α dengan VEGF (r=0,582), namun tidak terdapat korelasi yang signifikan antara ekspresi HIF-1α dan VEGF dengan hasil operasi pada pasien dengan kanker ovarium jenis epitel.

Kesimpulan: Terdapat korelasi yang signifikan antara ekspresi HIF-1α dan VEGF, namun tidak terdapat korelasi yang bermakna antara ekspresi HIF-1α dan VEGF dengan hasil operasi pada kanker ovarium jenis epitel.

Kata Kunci: HIF-1α, VEGF, hasil operasi

Hubungan antara Ekspresi p63 dengan Jenis Histopatologis Penderita Kanker Serviks Stadium IB2 dan IIA

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ABSTRACT

HPV is known the main etiology of cervical cancer, through its E6 and E7 oncogenes that inactivate p53 and retinoblastoma protein, thus suggested as the mechanism of phenotype changes. As the p53 homologs was found, p73 and p63, study focusing on p53 is more complex. Analysis of p63 expression by immunohistochemistry has prognostic and predictive value on several tumor types. p63 has main role on stratified epithelial growth by maintaining proliferation and differentiation.

This study was analytic observational with cross sectional design. All subjects underwent cervical biopsy and were analyzed for p63 expression by immunohistochemistry. Statistical analyze used in this study were chi square and Mann Whitney. This study has been approved by the institution ethical committee.

We found no significant correlation between subjects characteristic (age, marital age, parity) and clinical stage of cervical cancer (p>0.05).

Our samples consisted of 25 squamous cell carcinoma (64%), 11 adenocarcinoma (28%), and 3 adenosquamous carcinoma (8%). Expression of p63 had no correlation with clinical stage, however its nuclear expression was significantly higher on squamous carcinoma type (72%) compared to adenocarcinoma (11%), with p < 0.001.
Conclusion: expression of p63 on squamous cell carcinoma cervix is significantly higher compared to adenocarcinoma or adenosquamous.

***Keyword**: p63, cervical cancer, histopathology*

ABSTRAK

HPV diketahui sebagai penyebab utama keganasan serviks melalui dua protein virus, yaitu E6 dan E7, yang bekerja menginaktivasi tumor supresor utama p53 dan protein retinoblastoma (pRb), dan dipertimbangkan bertanggung jawab terhadap terjadinya asal usul serta penegakan perubahan fenotipe. Akhir-akhir ini ditemukan p53 homologs, yaitu p73 dan p63, yang menyebabkan penelitian tentang p53 menjadi lebih kompleks. Analisis ekspresi p63 secara imunohistokimia banyak dipergunakan untuk diagosis diferensial dan memiliki kamampuan berupa informasi prognostik serta prediktif pada tipe tumor tertentu. p63 memegang peran penting pada perkembangan epitel bertingkat, serta membuktikan pentingnya p63 dalam mempertahankan potensi proliferasi, memengaruhi diferensiasi.

Penelitian ini merupakan penelitian observasional analitik dengan rancangan *crosssectional*. Seluruh subjek yang memenuhi kriteria inklusi penelitian akan dilakukan biopsi serviks dan diperiksa ekspresi p63 dengan imunohistokimia. Analisis statistik yang digunakan adalah uji chi kuadrat dan Mann Whitney. Penelitian ini telah mendapat persetujuan dari komite etik institusi.

Hasil penelitian menunjukkan tidak ditemukan hubungan bermakna antara karakteristik pasien dilihat dari usia, usia menikah, dan paritas dengan stadium klinik kanker serviks (p>0,05). Sampel penelitian ini terdiri dari karsinoma sel skuamosa sebanyak 25 (64%), adenokarsinoma sebanyak 11 (28%), dan adenoskuamosa 3 (8%). Ekspresi p63 tidak berhubungan dengan stadium kanker serviks, tetapi ekspresinya di inti ditemukan lebih banyak pada jenis sel skuamosa, yaitu 72% untuk ekspresi > 80%, sedangkan pada jenis histopatologi adenokarsinoma didapatkan semua sampel mempunyai ekspresi <20% 11 (100%) dengan nilai p<0,001. Ekspresi p63, baik pada sitoplasma maupun inti, tidak berhubungan secara bermakna dengan stadium kanker serviks (p>0,05).

Kesimpulannya, ekspresi p63 pada jenis karsinoma sel skuamosa lebih tinggi dibandingkan dengan adenokarsimoa atau adenoskuamosa pada kanker serviks.

Kata Kunci: p63, kanker serviks, histopatologi

Gambaran Status Metilasi Gen Promoter *Methylguanine-deoksiribonucleic Acid Methyltransferase* pada Astrositoma dan Faktor yang Memengaruhinya

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ABSTRACT

Astrocytoma is the most common primary central nervous system tumor with difficult management as it requires a combination of surgery, chemotherapy and radiotherapy. This multimodalities approach increases patients survival rate significantly, however chemotherapy resistance is now commonly seen. One of the potential causes of chemotherapy resistance is the epigenetic factors from O^6 methylguanine-DNA-methyltransferase (MGMT) gene. MGMT gene has a role in DNA repair and also have a protective effect against exogenous and endogenous alkylation agents. The methylation of MGMT gene promoter leads to the decrease of MGMT protein, attenuating its function. Therefore, the methylation status of MGMT gene promoter can act as an indicator for astrocytomas progressivity and treatment progressivity.

The aim of this study to determine the frequency of MGMT gene promoter methylation among patients with astrocytomas using methylation specific polymerase chain reaction (MS-PCR) and methylation sensitive high resolution melting (MS-HRM).

Clinical data, imaging and parafin blocks from astrocytoma patients were collected in RSCM from 2008-2012. The methylation status of MGMT gene promoter was confirmed using MS-PCR and MS-HRM. This is cross-sectional study.

The total of 13 samples collected including 7 low-grade and 6 high-grade astrocytomas. The MGMT gene promoter was methylated in 1/13 cases using MS-PCR and 4/13 cases using MS-HRM. All methylated cases were low-grade astrocytoma. There was significant association between the methylation status of MGMT gene promoter with the degree of malignancy which is 4/7 samples hypermethylated in low-grade with no hypermethylation in high-grade astrocytomas (p=0.049). While other factors like age, sex, karnofsky performance scale (KPS) and astrocytomas location have no significant association (p= 1,000; p= 0,657; p= 0,354; p= 0,538).

The present study showed difference of methylation of MGMT gene promoter in astrocytomas with others studies which is hypermethylated MGMT only found in low grade astrocytomas. Our study was the first to report the frequency of MGMT promoter methylation among Indonesian astrocytoma patients.

***Keyword**: astrocytoma, MGMT gene promoter, methylation status, MS-PCR, MS-HRM*

ABSTRAK

Metilasi gen promoter *O⁶-methylguanine-DNA methyltransferase* (MGMT) adalah salah satu faktor yang berperan pada karsinogenesis dan berkembang menjadi marker dalam menilai progresivisitas dan respons terapi astrositoma.

Penelitian ini bertujuan untuk mendapatkan gambaran frekuensi status metilasi gen promoter MGMT pada pasien astrositoma menggunakan *methylation specific polymerase chain reaction* (MS-PCR) dan *methylation specific high resolution melting* (MS-HRM).

Untuk mencapai tujuan tersebut, dilakukan pengumpulan data klinis, imajing, dan blok parafin jaringan astrositoma di Rumah Sakit Ciptomangunkusumo (RSCM) dalam kurun waktu 2008-2012. Status metilasi gen promoter MGMT dianalisis menggunakan MS-PCR dan MS-HRM serta dihubungkan dengan berbagai faktor prognostik klinis. Penelitian ini merupakan penelitian potong-lintang.

Dari penelitian ini didapatkan 13 sampel, terdiri dari 7 astrositoma derajat rendah dan 6 astrositoma derajat tinggi. Metilasi gen promoter MGMT didapatkan pada 1/13 sampel astrositoma dengan MS-PCR dan 4/13 sampel dengan MS-HRM yang seluruhnya merupakan astrositoma derajat rendah. Terdapat perbedaan yang bermakna antara status metilasi gen promoter MGMT dengan derajat keganasan astrositoma, yaitu astrositoma derajat rendah 4/7 sampel dan tanpa ditemukan pada astrositoma derajat tinggi (p=0,049). Sedangkan faktor lain seperti usia, jenis kelamin, *karnofsky performance scale* (KPS), lokasi astrositoma, dan derajat WHO tidak terdapat perbedaan yang bermakna (p= 1,000; p= 0,657; p= 0,354; p= 0,538).

Penelitian ini menunjukkan bahwa frekuensi status metilasi gen promoter MGMT pada astrositoma sedikit berbeda dengan berbagai penelitian lain sebelumnya, yaitu hipermetilasi hanya terjadi pada astrositoma derajat rendah. Penelitian ini merupakan penelitian pertama di Indonesia yang melaporkan gambaran status metilasi gen promoter MGMT pada pasien astrositoma.

Kata Kunci: *astrositoma, gen promoter MGMT, status metilasi, MS-PCR, MS-HRM*

Kesesuaian Sistem TIRADS Dengan Hasil Pemeriksaan Patologi Anatomi Nodul Tiroid

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ABSTRACT

Thyroid ultrasonography is the modality of choice to detect, and to evaluate the morphology of thyroid nodule. Thyroid Imaging Reporting and Data System (TIRADS) *is a system to evaluate risk of malignancy of thyroid nodule, that first proposed by Horvath et al. There are various* TIRADS *proposed by other authors. To the author knowledge, until the writing of this study there is not yet found a study to evaluate implementation and diagnostic value of* TIRADS *in Indonesian.*

Methods: Diagnostic study with cross sectional approach using retrospective evaluation of thyroid ultrasonography data and post operative histopathology data to evaluate conformity relationship between TIRADS *and post operative histopathological result of thyroid nodule.*

There is comparable result (p=0.065) between TIRADS *result and post operative histopathological result of thyroid nodule.* TIRADS *resulted in 96.4% sensitivity; 83.0% specificity; 85.7% positive predictive value; dan 95.7% negative predictive value.*

Conclusion: TIRADS *can be implemented in evaluation, and reporting of thyroid ultrasonography result with good diagnostic value.*

***Keywords:** Thyroid ultrasonography, Thyroid Imaging Reporting and Data System* (TIRADS), *Post operativehistopathological result.*

ABSTRAK

Ultrasonografi (USG) tiroid adalah modalitas radiologis terpilih untuk mendeteksi dan mengevaluasi gambaran morfologis nodul tiroid. *Thyroid Imaging Reporting and Data System* (TIRADS) adalah sistem evaluasi risiko keganasan nodul tiroid yang diajukan pertama kali oleh Horvath *et al*. Terdapat berbagai variasi TIRADS yang diajukan oleh peneliti-peneliti lain. Sepengetahuan penulis, sampai penelitian ini ditulis, belum ditemukan penelitian yang mengevaluasi penerapan atau nilai diagnostik sistem TIRADS di Indonesia.

Penelitian ini adalah penelitian diagnostik dengan pendekatan potong lintang menggunakan evaluasi retrospektif data USG tiroid dan histopatologis pascaoperasi untuk mengetahui kesesuaian sistem TIRADS dengan hasil histopatologis pascaoperasi nodul tiroid.

Hasil penelitian menunjukkan adanya hubungan kesesuaian (p=0,065) antara hasil TIRADS dengan hasil histopatologis pasca operasi nodul tiroid. Sistem TIRADS memberikan nilai sensitivitas 96,4%; spesifisitas 83,0%; nilai prediksi positif 85,7%; dan nilai prediksi negatif 95,7%.
Penelitian ini menyimpulkan bahwa sistem TIRADS dapat diterapkan pada evaluasi dan pelaporan hasil USG tiroid dengan nilai diagnostik yang baik.

Kata Kunci: USG tiroid, TIRADS, histopatologis pascaoperasi

VEGF-C Serum Level as Predictor Lymph Node Metastasis in Advanced Stage Cervical Cancer

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ABSTRACT

The aim of this study to identify correlation between VEGF-C and lymph node metastasis in advanced stage cervical cancer in Dr. Hasan Sadikin General Hospital Bandung from April to August 2013. Cross sectional study from 30 patients diagnosed with advanced stage Cervical Cancer (IIB – IVA). We performed transperitoneal lymphadenectomy pelvic and para-aortic and measuring VEGF-C serum with ELISA prior chemoradiation.

Results : 17/30 patients (56.7%) metastasis to pelvic lymph nodes and 4/30 pastients (13.3%) metastases to para-aortic lymph nodes. VEGF-C > 5333 pg/mL has a metastasis risk to pelvic lymph node 21.6 times with 94% sensitivity; 84.6% specificity; 88.9% positive predictive value; and 84.6% negative predictive value. Meanwhile VEGF-C > 8915.5 pg/mL has a metastasis risk to para-aortic lymph node 15 times with 75% sensitivity, 100% specificity, 100% positive predictive value and 96.3% negative predictive value in advanced stage cervical cancer.

Conclusion: a significant correlation between VEGF-C serum level with lymph node metastasis (pelvic and para-aortic) (p < 0.05)

Key words: *Advanced stage Cervical cancer, Lymph Node metastasis pelvic and para-aortic, VEGF-C serum level*

ABSTRAK

Penelitian ini bertujuan mencari hubungan antara kadar serum VEGF-C dengan terjadinya metastasis kelenjar getah bening pelvis dan para-aorta pada penderita kanker serviks stadium lanjut di rumah sakit Dr. Hasan Sadikin, Bandung, periode April 2013–Agustus 2013. Penelitian potong silang dilakukan terhadap 30 pasien kanker serviks stadium lanjut (IIB –IVA) yang dilakukan laparotomi limfadenektomi pelvis bilateral dan para-aorta serta pemeriksaan serum VEGF-C dengan metode ELISA. Didapatkan 17/30 pasien (56,7%) metastasis KGB pelvis dan 4/30 pasien (13,3%) metastasis kelenjar getah bening (KGB) para-aorta. Kadar serum VEGF-C > 5333 pg/mL memiliki risiko metastasis ke KGB pelvis 21,6 kali dengan sensitivitas 94%; spesifisitas 84,6%, nilai duga positif 88,9%; dan nilai duga negatif 84,6%. Sementara, pada kadar serum VEGF-C > 8915,5 pg/mL memiliki risiko metastasis ke kelenjar getah bening (KGB) para-aorta 15 kali dengan sensitivitas 75%, spesifisitas 100%, nilai duga positif 100%, dan nilai duga negatif 96,3% pada penderita kanker serviks stadium lanjut.

Kata Kunci: kanker serviks stadium lanjut, metastasis KGB pelvis dan para-aorta, kadar serum VEGF-C

Peran Faktor Nutrisi pada Pencegahan Kanker Prostat

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ABSTRACT

Prostate cancer is a malignancy disease which originates in prostate organ that only can be found in men. This cancer is the second most common in men after lung cancer and the fifth in the entire world. The incidence will be increasing in the fifth decade of life with the peak in the eight decade. Several factors which are thought to be the etiology are: genetic, hormonal, diet, environment, and infection. Diet factor has great influence for both, the development and the prevention of this disease. Man who consumes high fat diet will have not only the risk to get that disease but also will increase the progresiveness of the disease. Several nutrients that are thought for decreasing the incidence of the prostate cancer are cruciferous vegetables and fruits which contain carotenoid. Furthermore, soya which contains much of isoflavon or phytoestrogen can also acts as the prevention of development of cancer cell. Green tea, lycopene (carotenoid group that can be found in tomato products) can also act as the source of the antioxidant. This paper will discuss the role of nutrition factors of lycopene and soya in prostate cancer.

Keyword: *Prostate cancer, diet factor, soya, lycopene*

ABSTRAK

Kanker prostat merupakan penyakit keganasan yang terjadi pada organ prostat yang hanya ditemui pada pria. Penyakit keganasan pria ini merupakan nomor dua tersering pada pria setelah kanker paru

dan nomor lima tersering secara keseluruhan di dunia. Insidennya meningkat pada usia lebih dari 50 tahun dengan puncak pada usia dekade kedelapan. Beberapa faktor yang diduga sebagai penyebab timbulnya penyakit ini adalah predisposisi genetik, pengaruh hormonal, diet, pengaruh lingkungan, dan infeksi. Faktor diet dapat berperan pada perkembangan ataupun pencegahan penyakit ini. Pria yang mengonsumsi tinggi lemak berisiko tidak hanya akan menderita kanker prostat, namun juga membuatnya berkembang lebih agresif. Beberapa nutrisi juga diduga dapat menurunkan insiden kanker prostat, di antaranya sayur-sayuran *cruciferous* dan buah-buahan yang banyak mengandung karotenoid. Golongan isoflavon atau fitoesterogen yang banyak terdapat di kedelai juga berperan dalam mencegah perkembangan sel kanker. Sumber antioksidan yang berasal dari teh hijau, likopen (golongan karotenoid yang banyak terdapat dalam tomat) juga berperan sama, yakni mencegah perkembangan sel kanker. Makalah ini akan membahas peran faktor nutrisi likopen dan kedelai pada kanker prostat yang dapat memicu atau mencegah perkembangan penyakit.

Kata Kunci: Kanker prostat, faktor nutrisi, kedelai, likopen

VEGF-C Serum Level as Predictor Lymph Node Metastasis in Advanced Stage Cervical Cancer

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ABSTRACT

The aim of this study to identify correlation between VEGF-C and lymph node metastasis in advanced stage cervical cancer in Dr. Hasan Sadikin General Hospital Bandung from April to August 2013.

Cross sectional study from 30 patients diagnosed with advanced stage Cervical Cancer (IIB – IVA). We performed transperitoneal lymphadenectomy pelvic and para-aortic and measuring VEGF-C serum with ELISA prior chemoradiation.

Results : 17/30 patients (56.7%) metastasis to pelvic lymph nodes and 4/30 pastients (13.3%) metastases to para-aortic lymph nodes. VEGF-C > 5333 pg/mL has a metastasis risk to pelvic lymph node 21.6 times with 94% sensitivity; 84.6% specificity; 88.9% positive predictive value; and 84.6% negative predictive value. Meanwhile VEGF-C > 8915.5 pg/mL has a metastasis risk to para-aortic lymph node 15 times with 75% sensitivity, 100% specificity, 100% positive predictive value and 96.3% negative predictive value in advanced stage cervical cancer.

Conclusion: a significant correlation between VEGF-C serum level with lymph node metastasis (pelvic and para-aortic) ($p < 0.05$)

Key words: *Advanced stage Cervical cancer, Lymph Node metastasis pelvic and para-aortic, VEGF-C serum level*

ABSTRAK

Penelitian ini bertujuan mencari hubungan antara kadar serum VEGF-C dengan terjadinya metastasis kelenjar getah bening pelvis dan para-aorta pada penderita kanker serviks stadium lanjut di rumah sakit Dr. Hasan Sadikin, Bandung, periode April 2013– Agustus 2013. Penelitian potong silang dilakukan terhadap 30 pasien kanker serviks stadium lanjut (IIB –IVA) yang dilakukan laparotomi limfadenektomi pelvis bilateral dan para-aorta serta pemeriksaan serum VEGF-C dengan metode ELISA. Didapatkan 17/30 pasien (56,7%) metastasis KGB pelvis dan 4/30 pasien (13,3%) metastasis kelenjar getah bening (KGB) para-aorta. Kadar serum VEGF-C > 5333 pg/mL memiliki risiko metastasis ke KGB pelvis 21,6 kali dengan sensitivitas 94%; spesifisitas 84,6%, nilai duga positif 88,9%; dan nilai duga negatif 84,6%. Sementara, pada kadar serum VEGF-C > 8915,5 pg/mL memiliki risiko metastasis ke KGB para-aorta 15 kali dengan sensitivitas 75%, spesifisitas 100%, nilai duga positif 100%, dan nilai duga negatif 96,3% pada penderita kanker serviks stadium lanjut.

Kata Kunci: kanker serviks stadium lanjut, metastasis KGB pelvis dan para-aorta, kadar serum VEGFC

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INTRODUCTION

Advanced cervical carcinoma typically managed with definitive chemo-radiation therapy, a combination of external and intra cavitary radiotherapy with concurrent

chemotherapy that has shown to significantly improve disease free and overall survival over radiotherapy alone.[1]

Primary radiotherapy (RT) fails to control locoregional involvement in 20% to 85% of woman with advanced cervical carcinoma, depending on disease stage, tumor bulk, and lymph node status. One reason for the high failure rate may be that cervical cancer represents the only remaining gynecology malignancy that is staged clinically. Compared with surgical staging, clinical staging is only 60% accurate. In many instances, errors in clinical staging are related to undiagnosed lymph node metastases. It is accepted commonly that patients with para-aortic lymph node (PALN) metastases have lower progression-free survival (PFS), survival after recurrence, and overall survival (OS).[2,3]

Several imaging modalities have been used to determine the extent of disease before initiating therapy. Contemporary literature demonstrates that CT or magnetic resonance imaging (MRI) fails to detect macroscopic lymph node metastases in 20% to 50% of patients and fails to detect most, if not all, patients with microscopic disease.[4-8]

The presence of lymph node metastasis, recognized as the most common metastatic lesion, is critical to patient prognosis in uterine cervical cancers. Recently some authors have discovered VEGF-C as biomarker for lymph node metastasis in many cancers such as breast cancer, gastric cancer, and lung cancer but few for gynecology cancer. Mathur S., et al, in their study found that VEGF-C up-regulation appears to be unique marker for an early diagnosis of cervical cancer metastasis. Vascular endothelial cell growth factor (VEGF)-C was cloned as a ligand of the Flt-4 (VEGFR-3) and KDR/flk-1 (VEGFR-2) receptor tyrosine kinases and recognized as a novel VEGF.[9] VEGF-C induces selective hyperplasia of the lymphatic vasculature, which is involved in the draining of interstitial fluid and in immune function, inflammation, and tumor metastasis. Moreover, VEGF-C-induced lymphangiogenesis mediates tumor cell dissemination and the formation of lymph node metastases in transgenic mice with VEGF-C expression. The expression of VEGF-C in prostatic carcinoma cells has been implicated in lymph node metastasis. Gastric cancer cells producing VEGF-C induce the proliferation and dilation of lymphatic vessels, resulting in the invasion of cancer cells into the lymphatic vessels and lymph node metastasis, and the lymphatic invasion was significantly increased in VEGF-C-positive early gastric carcinoma. VEGF-C is involved in the progression of human gastric carcinoma, particularly via lymphangiogenesis, and VEGF-C expression at the invading edge of a gastric carcinoma is a sensitive marker for metastasis to the lymph nodes. VEGF-C has an important role in lymph node metastasis of breast cancer even at its hormone-dependent early stage. Proliferating lymphatics can occur in head and neck cancers and may in some cases contribute to lymph node metastasis. The involvement of VEGF-C expression in the promotion of lymph node metastasis in cervical cancer has been demonstrated. Furthermore, examination of VEGF-C expression in biopsy specimens may be beneficial in the prediction of pelvic lymph node metastasis. Although lymph node metastasis has been analyzed by the manner of VEGF-C expression in primary tumors, the VEGF-C expression status in metastatic lymph nodes as a result has not been directly investigated. This status prompted us to investigate the clinical significance of VEGF-C expressed in lymph nodal metastasis of uterine cervical cancers.[10, 11]

MATERIAL AND METHODS

Design of this study was a cross sectional study. The study population was the patients who pathologically proved cervical cancer and diagnosed clinically as advanced stage cervical cancer (IIB – IVA) and underwent a laparotomy bilateral pelvic lymphadenectomy and lower para-aortic lymphadenectomy prior to concurrent chemoradiation between April and August 2013. The inclusion criteria were as follows: histologically confirmed FIGO stage IIB – IVA, never treat any modalities such as chemotherapy or radiation before, accepted to include this study. A total 30 patients being treated with pretreatment lymphadenectomy pelvic bilateral and para-aortic perlaparotomy before chemoradiation. VEGF-C level was measured by means of ELISA (examination with value unit of pg/ml before lymphadenectomy). Medical records of all subjects were reviewed for patient's characteristic, histopathologic results from lymph nodes (metastases status) and clinical parameters. Statistical analysis was performed using SPSS ver 11.0 (SPSS Inc, Chicago, USA). Independent sample t test and chi square test were used for comparison between metastases group and non metastases group with independent variable VEGF-C serum level. Differences

were considered significant when *P*-value was less than 0.05. Approval from Ethical Committee of Medical Faculty of Padjadjaran University and Dr Hasan Sadikin General Hospital, Bandung, West Java.

RESULTS

In 30 patients with stage IIB – IVA cervical cancer we performed a laparotomy bilateral pelvic lymphadenectomy and lower para-aortic lymphadenectomy. VEGF-C serum level was measured with ELISA prior to lymphadenectomy procedure. The mean age was 48.1 years (range 27–65). 70% case have normal BMI 18.5–25 kg/m^2. Squamous cell carcinoma was the most frequently found histological type (66.7%). Table 1 shows the clinical characteristic of these patients.

Table 1: Clinical characteristic of patients with advanced stage cervical cancer

Characteristic	n = 30				
	N	(%)	Range	Mean	SD
Age			27–65	48.1	9.36
BMI (kg/m2) 16–18.5 18.5–25 25–30 30–35	 3 21 3 3	 10 70 10 10	17.6 –31.4	22.7	3.77
Largest size of tumor <4 cm >4 cm	 10 20	 33.3 66.7	3–7 cm	5.0 cm	1.24 cm
Clinical stage IIB IIIA IIIB IVA	 13 3 13 1	 43.3 10.0 43.3 3.3			
Histopathology Skuamosa Adenokarsinoma	 20 10	 66.7 33.3			
Status LN pelvis Negative metastasis Positive unilateral Positive bilateral	 13 6 11	 43.3 20.0 36.7			
LN para-aortic Negative metastasis Positive metastasis	 26 4	 86.7 13.3			

BMI: Body mass Index; LN: lymph nodes; SD: standard deviation

Majority cases have bulky tumor (>4 cm 66.7%). The prevalence of lymph node positivity and negativity in pelvic nodes have equal (positive metastases 56.7%, negative metastases 43.4%). The prevalence of lymph node positivity less than negative metastases (13.3% vs 86.7%).

According to VEGF-C serum level and metastases status of pelvic lymph node we found the mean VEGF-C serum level was 3954.6 pg/mL (range 1485–8495) for negative metastases group and for metastases group mean VEGF-C 7708.5 pg/mL (range 3853–10849). Meanwhile for para-aortic lymph node; negative metastases group 5599.0 pg/mL (range 1485–8495) and for metastases group 9219.7 pg/mL (range 7300–10849). (Table 2).

Tabel 2: VEGF-C serum level and pelvic LN status & para-aortic LN status

Pelvic LN status	Mean	Range	SD	CI 95%
(-) Metastases	3954.6	1485–8495	1986.9	2753–5155
(+)Metastases	7708.5	3853–10849	1540.3	6916–8500
Para-aortic				
(-) Metastases	5599.0	1485–8495	2343.6	4652–6545
(+) Metastases	9219.7	7300 - 10849	1458.7	6895–11540

VEGF-C: Vascular endothelial growth factor-C; LN: lymph node

From receiver operating characteristic curve (ROC) of VEGF-C serum level in pelvic lymph node metastases we found area under curve (AUC) 0.889 (CI 95% 75.4%–100%), *p*=0,00 and for ROC curve of VEGF-C serum level in para-aortic lymph node metastases AUC 0.913 (95% CI 75.5%–100%) , *p*=0.009. (Figure 1)

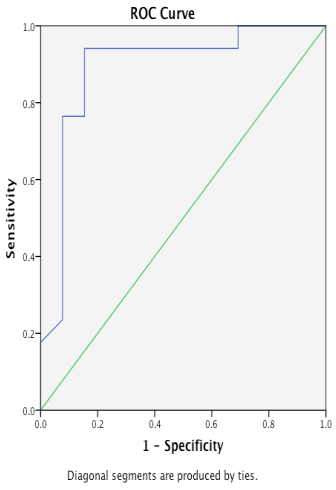

Figure1: Receiver operating characteristic (ROC) curve VEGF-C serum with positive metastases pelvic lymph node with Area Under Curve (AUC) 88.9%

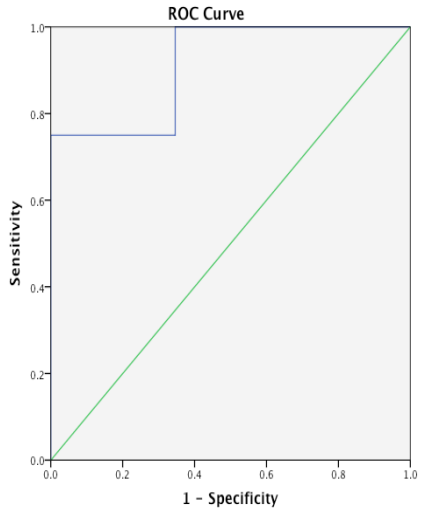

Figure 2: Receiver operating characteristic (ROC) curve VEGFC serum with positive metastases para-aortic lymph node with Area Under Curve (AUC) 91.3%

Based on the calculation of sensitivity and specificity and ROC analysis for VEGF-C, we found a cut off point of VEGF-C serum level for metastases pelvic lymph node >5333 pg/mL and for metastases para-aortic LN >8915.5 pg/mL. Patients with VEGF-C serum levels >5333 pg/mL were at risk for metastasis into pelvic lymph node (likelihood ratio 21.6) as high as that of serum VEGF-C level ≤5333 pg/mL with CI of 7.08–1093.9; and p value=0.000. Patients with VEGF-C serum levels >8915.5 pg/mL were at risk for metastasis into para-aortic lymph node (likelihood ratio 15) as high as that of serum VEGF-C level ≤8915.5 pg/mL with CI of 0.005–0.253 ; and p value=0.001. (Table 3 and 4)

The sensitivity of the examination of VEGF-C levels in relation to the risks for pelvic lymph node metastasis in this study was 94%, with specificity of 84.6%, positive predictive value (PPV) of 88.9%, and negative predictive value of 84.6%.

Table 3: Distribution of pelvic LN metastases based on VEGF-C serum

VEGF-C (pg/mL)	Pelvic LN metastases				Chi square	LR	(95% CI)	P*
	Positive		Negative					
	N	%	N	%				
>5333	16	53.3	2	6.7	19.02	21.6	7.08–1093.9	0.000
5333	1	3.3	11	36.7				

*** Chi square test**

Table 4: Distribution of para-aortic LN metastases based on VEGF-C

VEGF-C (pg/mL)	Para-aortic LN metastases				Chi square	LR	(95% CI)	P*
	Positive		Negative					
	N	%	N	%				
>8915,5	3	10.0	0	0	21.67	15	0.005–0.253	0.001
8915,5	1	3.3	26	86.7				

***Chi square test**

Table 5: Sensitivity, spesificity, positive predictive value, negative predictive value of VEGF-C serum level in pelvic lymph nodes metastases

VEGF-C (pg/mL)	Pelvic Lymp Nodes metastases				Total (%)
	Positive		Negative		
	N	%	N	%	
>5333	16	53.3	2	6.7	60.0
5333	1	3.3	11	36.7	40.0
Total	17	66.6	13	43.4	100

Table 6: Sensitivity, spesificity, positive predictive value, negative predictive value of VEGF-C serum level in para-aortic lymph nodes metastases

VEGF-C (pg/mL)	Para-aortic Lymph Nodes metastases				Total (%)
	Positive		Negative		
	N	%	N	%	
>8915,5	3	10.0	0	0	10.0
8915,5	1	3.3	26	86.7	90.0
Total	4	13.3	26	86.7	100

The sensitivity of the examination of VEGF-C levels in relation to the risks for para-aortic lymph node metastasis in this study was 75%, with specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value of 96.3%.

DISCUSSION

Concurrent radiotherapy and cisplatin-based chemotherapy are currently considered the treatment of choice for patients with advanced stage cervical cancer. Advances in radio-chemotherapy allowed for improved control of disease by adjusting radiation fields in accordance with the extension of the disease. The presence of lymph node metastasis is a major prognosis factor influencing survival of advanced stage cervical cancer patients. Therefore, assessing lymph node involvement at the para-aortic level seems appropriate to adjust radiation fields and to tailor individualized treatment for every patient.[12- 15]

Since we started pretherapeutic lymph node staging in our center, we have found 13.3% of patients with advanced stage cervical cancer with para-aortic lymph node involvement. Without para-aortic lymphadenectomy, such patients would have received radiotherapy in the conventional pelvic fields, whereas the para-aortic area would have remained untreated with the consequent risk of disease progression. Other authors reported para-aortic lymph node involvement rates of 16.3% to 27%. The influence on patient survival of treatment modifications based on para-aortic lymphadenectomy is still a controversial issue. However, Leblanc et al, in the largest published case series (184 patients), reported similar survival rates for patients with para-aortic microscopic disease treated with extended radiation fields and patients with negative para-aortic lymph nodes staging results. Holcomb et al found that the survival time of 89 patients with pretreatment lymph node staging was 29 months, whereas that of 179 patients without pretreatment staging was 19 months (P=0.01). Marnitz et al found that patients with positive results of surgical para-aortic lymph node staging, whose radio chemotherapy had been tailored according to the extension of their disease, had survival rates equivalent to those of patients with negative results.[12,14,16]

Lymph node staging prior to chemoradiation is still a controversial. Recently some authors have discovered VEGF-C as biomarker for lymph node metastasis in many cancers such as breast cancer, gastric cancer, and lung cancer but few for gynecology cancer. Mathur S., et al, in their study found that VEGF-C up-regulation appears to be unique marker for an early diagnosis of cervical cancer metastasis. They found range of VEGF-C serum for invasive cervical cancer 6021 ± 1200 pg/mL (mean ± SD) and in our study the range of VEGF-C was 6081,8 ± 2553 pg/mL (mean ± SD).[17] We found cut off point VEGF-C serum level for pelvic lymph node metastasis >5333 pg/mL. The sensitivity of the examination of VEGF-C levels in relation to the risks for pelvic lymph node metastasis in this study was 94%, with specificity of 84.6%, positive predictive value (PPV) of 88.9%, and negative predictive value of 84.6%. In another study, Andrijono, et al, found cut off point VEGF-C serum level for pelvic metastasis in early stage cervical cancer was >10066 pg/mL and Mathur S., et al, found VEGF-C serum level >4436 pg/mL is predictor for advanced stage cervical cancer. From ROC curve in our study VEGF-C serum level is good predictor for pelvic lymph node metastasis and para-aortic lymph node metastasis with p value <0.05. Especially for prediction para-aortic lymph node metastasis, VEGF-C serum level >8915.5 pg/mL could predict para-aortic lymph node metastases with sensitivity 75%, with specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value of 96.3% and likelihood ratio 15. If we compare to CT scan or MRI with sensitivity 34%

and specificity 96% with positive predictive value 60% and negative predictive value 91%.[18]

Many authors have reported that VEGF-C contributes to lymphogenous metastasis. If indeed it does, a cancer cell enriched with VEGF-C in the cancer tissue may selectively work on lymphogenous metastasis, and the expression of VEGF-C would be increased from the primary tumor to the corresponding metastatic lymph node lesions. Furthermore, such a phenomenon would be induced in a cascade manner, causing VEGF-C expression to be increased in the secondary metastatic lymph node lesions, resulting in poor clinical prognosis in such cases. On the other hand, in the cases with no change in the VEGF-C level, VEGF-C might not mainly or directly contribute to lymph node metastasis. Although lymph node metastasis appears to be regulated by additional factors besides VEGF-C, such as cascade of lymph node metastasis might be less active in these cases, resulting in comparatively better patient prognosis.[11]

CONCLUSION

Our study is the first study to correlate between VEGF-C serum level and pelvic lymph node metastasis and para-aortic lymph node metastasis in advanced stage cervical cancer. VEGF-C serum level can useful for predict para-aortic lymph node metastasis that could help tailoring radiotherapy field in advanced stage cervical cancer. This is novel, direct evidence that VEGF-C might contribute to aggressive lymphangitic metastasis, and that the increase in VEGF-C level from primary tumor to metastatic lymph nodes might be a prognostic indicator. Therefore, VEGF-C might be a key signal to evoke and maintain the cascade of lymph node metastasis, and may be useful as a tumor marker for patient prognosis and a molecular target for treatment.

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Ucapan Terimakasih Mitra Bestari

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