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Response to External Radiation and Mupit Brachytherapy in Bulky Vulvar Cancer

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Abstract

Vulvar cancer is a gynaecologic malignancy with an incidence of 3-5% of all gynaecologic malignancies. In Indonesia, number of new cases of vulvar cancer reaches 1153 cases with a mortality rate of 420. To establish diagnosis and exclude differential diagnosis for vulvar mass, a histopathological examination is needed. Multimodal therapy is the main therapy of vulvar cancer at advanced stage which consists of surgery, radiotherapy, and chemotherapy. The role of brachytherapy as adjuvant therapy combined with external beam radiotherapy (EBRT) is widely studied, there is still no guideline however it can be considered for tumour near critical organ such as bladder, rectum, urethra, or vagina. Interstitial brachytherapy can be used as adjuvant post EBRT. A boost vary from 2 Gy equivalent dose (EQD2) 16 – 24 Gy_{10} can be considered to be given after EBRT. The purpose of writing this case report is to assess the response of radiotherapy in the form of EBRT and brachytherapy use the MUPIT applicator in patients with vulvar cancer. Here is a case report of a patient with diagnosis of grade IIIC vulvar cancer. From the relevant studies, brachytherapy did not improved overall survival (OS) and disease specific survival (DSS) however in post hoc analysis, brachytherapy as consolidation therapy can improve DSS in patient with FIGO stage IVA, node positive disease, or tumor size > 4 cm. It can be concluded that the combination of EBRT and brachytherapy can be one of the therapeutic modality of choice in vulvar cancer.

Keywords: vulvar cancer, radiotherapy, brachytherapy, MUPIT, response therapy

Introduction

Vulvar cancer is one of gynaecologic malignancy comprising 3-5% of all gynaecologic malignancies and 1% of all malignancies in women.[1,2] In Indonesia, based on GLOBOCAN 2018 data, the incidence of vulvar cancer was 1153 cases with 420 deaths.[3] The most common type of vulvar cancer is squamous cell carcinoma which comprises 95% cases of vulvar cancer. *Human papillomavirus* (HPV) infection is thought to be the cause of more than 50% vulvar cancer cases.[4,5]

The main symptomps of vulvar cancer are itchiness and mass in vulvar area.[6] However, these symptomps are often neglected due to lack of knowledge.[7] Meanwhile, based on SEER database, the 5-*year survival rate* is related to the cancer stage, being 86% in stage I dan II, 53% in stage III and IVA, and 19% in stage IVB.[8]

The treatment of locally advance stage vulvar cancer incorporates multiple modalities. Besides improving survival rate, treatment also aims to improve quality of life and reduce postoperative complications. This multimodal treatment includes surgery, radiotherapy, and chemotherapy. Based on previous studies, radiotherapy could reduce tumour size preoperatively, while chemotherapy acts as radiosensitizer in patients who will undergo radiotherapy.[9,10] Occasionally, brachytherapy could be used as adjuvant therapy.[7,9]

Indications for brachytherapy is not establish yet but can be considered for tumour near critical structures

such as bladder, rectum,urethra, or vagina because if only using EBRT, the dose might exceed dose tolerance to critical structure. This case report aims to assess the response to external beam radiotherapy (EBRT) and brachytherapy in vulvar cancer patient with a discussion based on previous studies.

Definition and Epidemiology

Vulvar cancer is a rare type of *cancer*. It forms in a woman's external genitals, called the vulva. It is the fourth most common gynaecologic malignancy among women after endometrial, ovarian, and cervical cancer.[6] The incidence is 2-3 per 100.000 and it has continually been increasing during the last 10 years.[12] Based on GLOBOCAN 2018 data, there are 1153 new cases in Indonesia with up to 420 deaths.[3]

This disease progresses slowly, with a peak incidence in the 7th and 8th decade of life. More than 50% cases are associated with HPV infection.[4,5] It is commonly diagnosed during early stages (I dan II). Late stage cases are commonly found in the elderly.[7]

The most common type of vulvar cancer is squamous cell carcinoma (95%). Other types include melanoma, sarcoma, extramammary paget's disease, Bartholin gland adenocarcinoma, verrucous carcinoma, sarcoma, and basalioma.[1,2,6] The most common location is the major labia.[14]

There are two routes of extension, which are local and regional (lymphatic). Hematogenous spread is rarely reported, but the risk is up to 66% when ≥3 lymph nodes are involved.[13]

Diagnosis and Staging

The main clinical manifestation of vulvar cancer is itchiness and mass in vulvar area.[6] Other symptomps include pain, bleeding, and mass in inguinal area. Invasion of adjacent organs could result in bladder and bowel dysfunction. Other rarely reported symptoms include limb edema, dysuria, and discharge.[7, 13]

To establish diagnosis and exclude differential diagnosis for vulvar mass, a histopathological examination is needed. It could also determine the type and degree of the cancer. Vulvoscopy could help in determining biopsy location.[7]

After histopathological examination, patient would be staged based on the size of the primary tumour, invasion of adjacent genitourinary organs, anus, pelvic bone, and inguinal lymph nodes. The stage of vulvar cancer is based on T-N-M classification system proposed by the International Federation of Gynecology and Obstetric (FIGO) and American Joint Coint Commision on Cancer (AJCC).[15]

X-ray is the initial radiological examination. If an abnormality is found, CT-scan without contrast should be performed. Pelvic MRI with/without radiation could help in surgery planning. Whole body PET/CT or thorax/abdominal/pelvic CT should be considered for T2 or bigger tumours if metastasis is suspected.[7,9]

Treatment

Vulvar cancer Treatment is based on clinical staging. For microinvasive vulvar cancer (stage IA) which lesion is 2 cm or less in diameter with depth of invasion of 1 mm or less, the main treatment is wide local excision. The groin node dissection is not indicated.[14,15]

For early stage vulvar cancer which is stage IB and II, the gold standard treatment is radical wide local excision. It decreases psychosexual morbidity compared to radical vulvectomy and effective treatment in preventing local reccurence. In management of the groin lymph node, the current standard is inguinofemoral lymphadenectomy because inguinal node dissection alone is associated with a higher incidence of recurrence in groin area. Sentinel node procedure is being used increasingly in management of early stage vulvar cancer which indication is unifocal tumors confined to the vulva, tumor less than 4 cm in diameter, stromal invasion more than 1 mm, and clinically negative groin nodes. When ipsilateral sentinel node is negative, complete ipsilateral inguinofemoral lymphadenectomy must be done but if its positive, bilateral inguinal lymphadenectomy is recommended. In early stage vulvar cancer, radiation has a role as an adjuvant.[15] The Gynecologic Oncology Group data showed that improvement in outcome is observed in adjuvant pelvic radiation for those who had more than one or grossly positive nodes at inguinal lymph node dissection. Several studies also showed that the presence of extracapsular extension after lymphadenectomy alone has worse prognosis compared to negative presence of extracapsular extension. Therefore, indication for pelvic and groin irradiation is two or more positive groin nodes and presence of extracapsular spread. Radiation field area should include inguinofemoral , external iliac dan internal iliac lymph node. Radiation should be performed after surgery within 6-8 weeks. If microscopic inguinal metastases are found, 50 Gy in 1,8-2 Gy fraction is sufficient. In the case of multiple positive nodes and extracapsular extension, radiation can be given up to 60 Gy and for gross residual disease, 60-70 gy is needed. In locally advanced vulvar cancer, bilateral inguinofemoral lymphadenectomy can be performed in the case when there are no

suspicious nodes either clinically or on imaging. If after lymphadenectomy the nodes are negative, radiation is not needed in the groin and pelvic area however if nodes positive, radiation is indicated as early stage vulvar cancer. Surgical excision with clear surgical margin and without sphincter damage is the standard in locally advanced vulvar cancer. In case when surgery is not possible because the resection would damage central structures like anus and uretra, concurrent chemoradiation is an alternative. Chemoradiation has better overall survival compared to radiation alone. The preferred regimen for chemoradiation is cisplatin and the radiation dose can be given up to 70 Gy. The alternative recommended regimen includes carboplatin monotherapy, cisplatin/ paclitaxel, carboplatin/paclitaxel, or cisplatin/ paclitaxel/bevacizumab. For locally advance, Radiation can also be given preoperative.[14] According to GOG 279 study, the dose that is utilized are 45 to 50 Gy to the elective nodal volume and 64 gy to the vulva and gross nodal disease with a combination of weekly cisplatin and gemcitabine. Dissection is performed upfront in patients with resectable nodal disease and then 6-8 weeks post preoperative chemoradiation, surgery can be performed.[4]

For tumour near critical structures such as bladder,rectum,urethra, or vagina, external beam radiotherapy dose may exceed dose tolerance to critical structure. In this case, interstitial brachytherapy can be a consolidation after EBRT that allows safe dose escalation.[16] It can be useful for residual disease or for those who develop early progression. However, there is still no guideline of the role brachytherapy in vulvar cancer. Rao et al reported that brachytherapy did not improved overall survival (OS) and disease specific survival (DSS) however in post hoc analysis, brachytherapy as consolidation t herapy can improve DSS in patient with FIGO stage IVA, node positive disease, or tumor size > 4 cm . The proposed mechanism for potentially improved survival with addition of brachytherapy is due to improved local control.[4] There is no standard reccomendation for fractination dose of interstitial brachytherapy. Based on available evidence, a boost vary from EQD2 16 – 24 Gy_{10} can be given after EBRT.[17]

Prognosis

The recurrency rate of vulvar cancer after therapy is up to 40% in 10 years.[1,18] Aside from staging, several factors that affect the prognosis in vulvar cancer are tumour diameter, depth of invasion, lymph and blood vessels involvement, and age.[7]

Case Illustration

A 43-year-old woman was referred to the Radiotherapy clinic at Cipto Mangunkusumo Nasional General Hospital (RSCM) on August 7, 2019 with a diagnosis of grade IIIC vulvar cancer. A year before, the patient started to notice a firm, marble-sized-mass on her vagina that itched and grew in size. After 8 months, the mass ruptured, produced blood, and left an open wound. However, the patient did not seek medical treatment. One month afterwards, the mass grew bigger, causing significant walking problems that prompted the patient to seek medical help. She was initially referred to the gynecology oncology clinic at RSCM where she underwent gynaecologic examination as well as biopsy, chest x-ray, and blood test before referred to the radiotherapy clinic. The patient has no past illness and general physical examination showed normal results.

Upon gynaecologic examination, an exophytic, irregular 6x6 cm (LLxAP) mass was found on the right vulva (7-11 o'clock region) which was prone to bleeding. The left vulva and vagina was normal. Upon inspeculo examination, no mass was detected on portio and vaginal mucosa. Rectovaginal toucher revealed good anal sphincter tone and intact rectovaginal wall. There was no blood or vaginal discharge. No inguinal or supraclavicular lymph node enlagerment was found.

Histopathological examination showed moderately-differentiated nonkeratinizing vulvar squamous cell

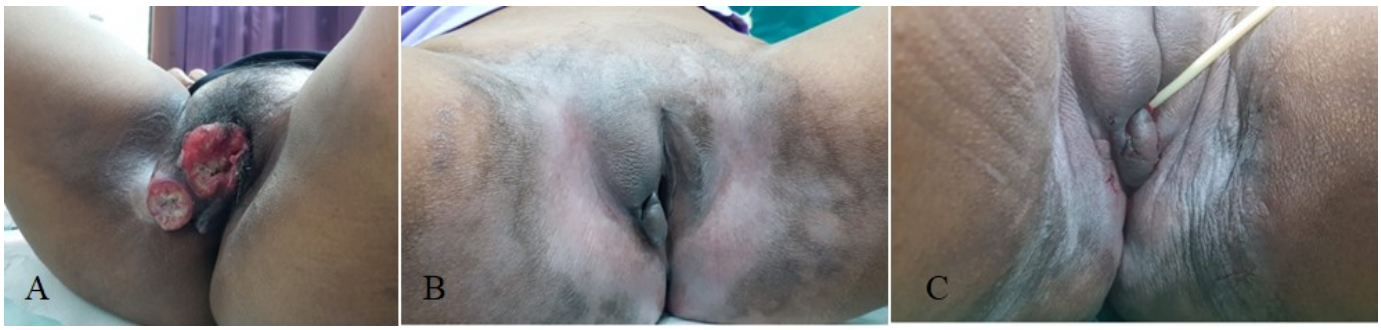

Figure 1. Clinical picture on first visit to the radiotherapy clinic (A), after external radiation (B), and after MUPIT implant brachytherapy (C)

carcinoma with no lymphovascular invasion. MRI showed a malignant mass on the anterior right vulva with multiple inguinal and bilateral paraobturator lymph enlargement. Chest x-ray showed no pulmonary metastasis. FNAB of the right inguinal lymph enlargement was positive of malignancy spread.

Simulator CT with frog leg position was performed at the radiotherapy department using intravenous contrast, showing a contrast-enhancing, irregular, protruding mass with bilateral extension that seemed to have involved the minor labia as well as right perineal subcutaneous area. There were multiple bilateral inguinal and obturator lymph node metastases.

The patient was diagnosed with FIGO stage IVB vulvar cancer (Paraobturator Lymph Node) and underwent radiotherapy. Locoregional external radiation was targeted on pelvic with IMRT technique (25x2 Gy) starting from August 21, 2019 until September 30, 2019. Radiation was performed 5 times/ week alongside Cisplatin chemotherapy (3 times/ week). Blood examination was performed weekly and the patient was followed up every 5 fractions. After completion of external radiation, the patient showed good clinical response with no progressive lesion. She had acute side effects on the skin (moderate hyperpigmentation, skin RTOG grade 2) and mucous (dysuria, genitourinary RTOG grade 2).

Afterward, the patient underwent implant brachy-therapy with MUPIT applicator from November 12, 2019 until November 13, 2019 with a dose of 4 x 3 Gy (2 radiations/day). After therapy, no mass was found on the vulva. She had grade 1 side effect but did not come back to policlinic for evaluation.

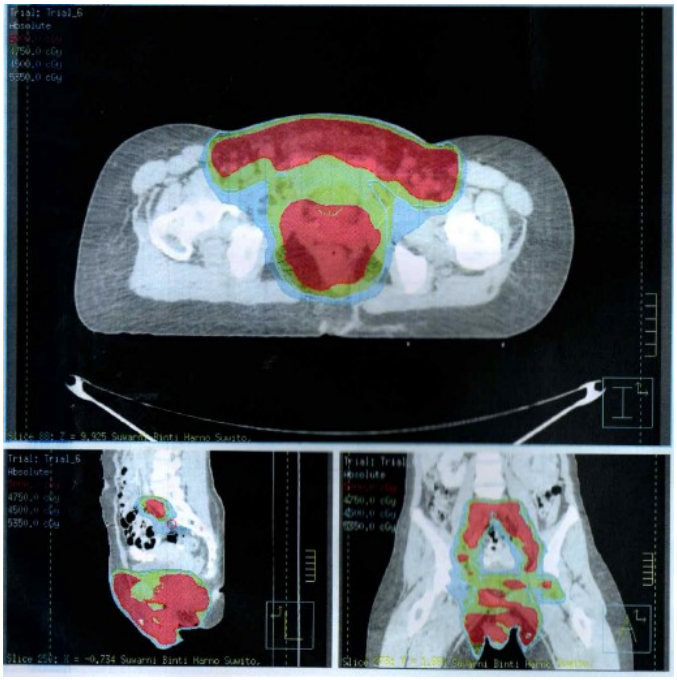

Figure 2. IMRT dose distribution for locoregional tumour on TPS precise plan

Discussion

Vulvar cancer is uncommon gynecological cancer. It account for about 2-5 % malignancy.[14] In Indonesia based on GLOBOCAN 2018 data, the number of new cases of vulvar cancer in Indonesia reached 1153 cases with a death rate of 420. Patient usually admitted at advance stage.[19] in this case, our patient also being referred to our department as stage IIIC vulvar cancer. before deciding to seek medical treatment, our patient has had a growing mass on her vagina for over a year. The mass even ruptured and left an open wound. It was not until the mass caused significant walking problems that she decided to go to the doctor and was referred to the gynecology oncology clinic at RSCM where she underwent a series of examinations and was diagnosed with FIGO stage IVB vulvar cancer (Paraobturator Lymph Node). Based on this diagnosis she was referred to the radiotherapy department.

Radiation has a curative goal. In locally advanced stage, multimodal treatment is chosen to increase cure rate, improve quality of life, and decrease postoperative complications. Based on a study by Koh WJ et al., postoperative radiotherapy could reduce tumour size and make it resectable. Chemotherapy could also be added as radiosensitizer in patients undergoing radiotherapy.[9]

Several small size cohorts on stage III/IVA patients showed a high response towards chemoradiation therapy (CRT). CRT is reported to have a superior survival rate compared to radiotherapy among 54 patients in locally advanced stage. Similar result was reported by Rao et al. Based on a review from National Cancer Database, CRT has a higher survival rate (49.9% vs. 27.4%, $p<0.001$) compared to radiotherapy among patients who do not undergo surgery. The agents used for CRT are cisplatin, 5-FU/cisplatin, or 5-FU/mitomycin-C.[4]

This patient received EBRT to treat locoregional using IMRT technique 25x2 Gy concurrently with chemotherapy Cisplatin , followed by implant brachytherapy using MUPIT 4x3 Gy (2 fraction per day) with EQD2 13 Gy for 2 days . The sum of total dose with EBRT is equivalent to 63 Gy. the dose in our institution is lower compared with previous study conducted by mahantshetty et al with 3,4-4 Gy per fraction (2 fraction per day). in mahantshetty et al study, it is reported that 30 of 38 patients achieved clinically complete response.[17] In our patient, after being followed up for 3 months, patient clinically

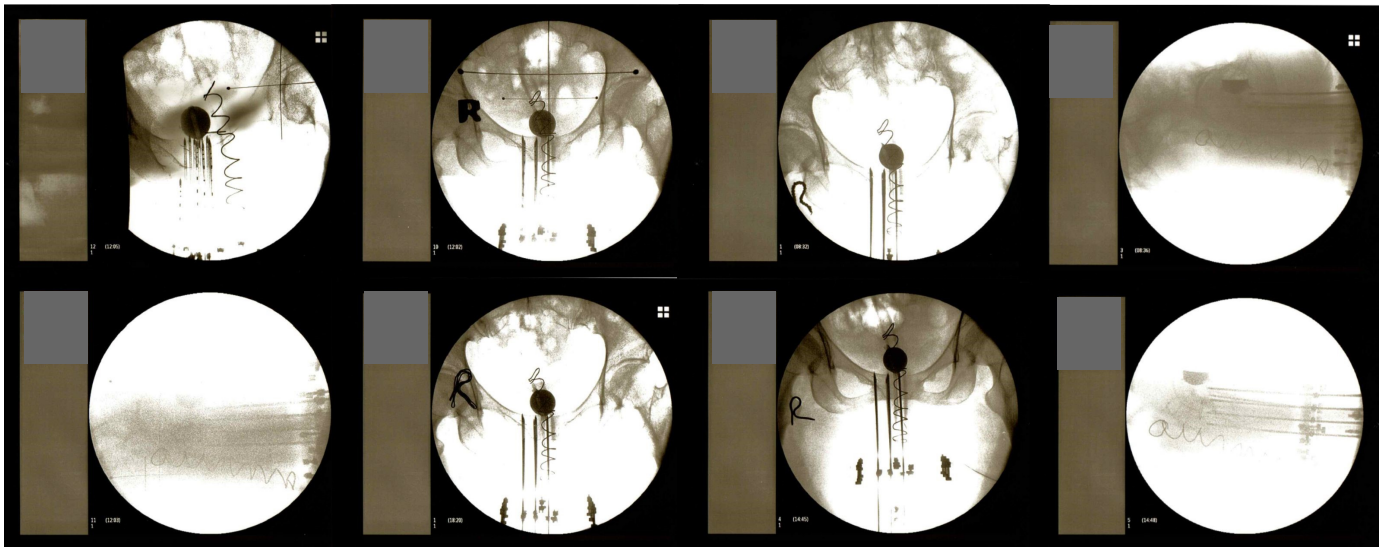

Figure 4. C-Arm pictures of MUPIT implant

partial response. In comparison of toxicity, we observed acute toxicities grade two on skin based on RTOG which is moderate hyperpigmentation and grade 2 on mucous which is dysuria that tend to resolve after being follow up 3 month post chemoradiation. It showed similar acute toxicities with mahantshetty et al study. However late reaction unable to be observed because patient did not appear on follow up after that. It also made it difficult to estimate the prognosis of the treatment. Rao et al. reported that in group analysis, EBRT combined with brachytherapy has a significantly higher disease-specific survival (DSS) compared to EBRT (52% vs 27%, p=0.02). The referred group is stage IVA patients with tumour size of >4cm and positive lymph node involvement, which has a high recurrency and mortality rate. Therefore, brachytherapy is suggested as an adjunctive therapy in this group even though further studies are still required.[4] However, based on SEER database, the 5-year survival rate is up to 19% among stage IVB patients. According to Thaker et al, 20 patients with lymph node involvement showed a high 5-year survival rate (43%) and DSS (48%) despite being categorized into stage IVB.[18]

Conclusions

In accordance with the current literature, platinum based chemoradiation and MUPIT brachytherapy resulted in good response in our patient who had stage IVB vulvar cancer however the prognosis in these patients is inconclusive. Prognosis factors apart from stage, several factors that affect the prognosis of patients with vulvar cancer are tumor diameter, depth of invasion, lymph and vascular involvement, and age. Tumor diameter, depth of invasion, and lymph and vascular involvement were associated with the risk of lymph node metastasis. It was stated that tumor diameter was related to the survival rate where the 5-year survival rate for tumors measuring ≥5cm was 44%. However, this is presumably due to a positive correlation with the rate of lymph nodes involvement. The depth of invasion was associated with the risk of lymph node metastasis, whereas the invasion depth ≥5mm had the risk of lymph node metastasis up to 48%.

References

1. Chapman BV, Gill BS, Viswanathan AN, Balasubramani GK, Sukumvanich P, Beriwal S. Adjuvant Radiation Therapy for Margin-Positive Vulvar Squamous Cell Carcinoma: Defining the Ideal Dose-Response Using the National Cancer Data Base. Int J Radiat Oncol. 2017 Jan;97(1):107–17.
2. Hacker NF, Eifel PJ, van der Velden J. Cancer of the vulva. Int J Gynecol Obstet. 2015 Oct;131:S76–83.
3. Indonesia - Global Cancer Observatory. IARC; 2018.
4. Rao YJ, Hui C, Chundury A, Schwarz JK, DeWees T, Powell MA, et al. Which patients with inoperable vulvar cancer may benefit from brachytherapy in addition to external beam radiation? A Surveillance, Epidemiology, and End Results analysis. Brachytherapy. 2017 Jul;16 (4):831–40.
5. Xanthopoulos EP, Grover S, Puri PM, Corradetti MN, Heilbroner SP, Mitra N, et al. Survival Benefit of Adjuvant Radiation Therapy in Node-positive Vulvar Cancer: Am J Clin Oncol. 2018 Sep;41(9):845–50.
6. Alkatout I, Günther V, Schubert M, Weigel M, Garbrecht N, Jonat W, et al. Vulvar cancer: epidemiology, clinical presentation, and management options. Int J Womens Health. 2015 Mar;305.
7. Hoffman BL, Schorge JO, Bradshaw KD, Halvorson LM, Schaffer JI, Corton MM. Williams gynecology. 2016.
8. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018: Cancer Statistics, 2018. CA Cancer J Clin. 2018 Jan;68

(1):7–30.
9. Koh W-J, Riaz N, Bean S, Bradley K, Campos S, Cho K, et al. Vulvar cancer (squamous cell carcinoma). 2nd ed. NCCN; 2018.
10. Fuh KC, Berek JS. Current Management of Vulvar Cancer. Hematol Oncol Clin North Am. 2012 Feb;26(1):45–62.
11. Bansal I, Panda D, Rathi A, Anand A, Bansal A. Rationale, indications, techniques and applications of interstitial brachytherapy for carcinoma cervix. Asian J Oncol. 2016 Jul;02(02):069–78.
12. Hughes KE, McLaughlin CM, Fields EC. High-Dose Rate Salvage Interstitial Brachytherapy: A Case-Based Guide to the Treatment of Therapeutically Challenging Recurrent Vulvar Cancer. Front Oncol. 2017 Sep 20;7:224.
13. Lu JJ, Brady LW, editors. Decision Making in Radiation Oncology [Internet]. Berlin, Heidelberg: Springer Berlin Heidelberg; 2011 [cited 2019 Dec 9]. (Medical Radiology; vol. 0).
14. Rogers LJ, Cuello MA. Cancer of the vulva. Int J Gynecol Obstet. 2018 Oct;143:4–13.
15. Runowicz CD. Vulvar Cancer. In: The American Cancer Society, editor. The American Cancer Society's Oncology in Practice [Internet]. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 2018 [cited 2020 Dec 6]. p. 310–7.
16. Amsbaugh MJ, Bhatt N, Hunter T, Gaskins J, Parker L, Metzinger D, et al. Computed tomography–planned interstitial brachytherapy for locally advanced gynecologic cancer: Outcomes and dosimetric predictors of urinary toxicity. Brachytherapy. 2016 Jan;15(1):49–56.
17. Mahantshetty U, Naga P, Engineer R, Sastri S, Ghadi Y, Upreti U, et al. Clinical outcome of high-dose-rate interstitial brachytherapy in vulvar cancer: A single institutional experience. Brachytherapy. 2017 Jan;16(1):153–60.
18. Gaffney DK, King B, Viswanathan AN, Barkati M, Beriwal S, Eifel P, et al. Consensus Recommendations for Radiation Therapy Contouring and Treatment of Vulvar Carcinoma. Int J Radiat Oncol. 2016 Jul;95(4):1191–200.
19. Andrijono A, Aziz MF, Kampono N. Surgical management of stage I and II vulvar cancer:The role of the separated incision. Med J Indones. 2003 May 1;103.