# Radiation Treatment for Primary Adenocarcinoma of Bartholin's Gland

## — A Case Report and Review of Literature —

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A patient with primary adenocarcinoma of Bartholin's gland is reported and the literatures relevant to this disease reviewed. Not only this disease is very rare but also primary carcinomas of Bartholin's gland are misdiagnosed as cysts or abscesses in half of the cases, leading to considerable delay in diagnosis. And so, It was wasted long time before definitive therapy. However, because of a different clinical behavior, cancer of the Bartholin's gland should be distinguished from other vulvar carcinomas. Histologically, squamous cell carcinoma and adenocarcinoma are the most common. Virtually all histologic types of Bartholin's gland carcinoma metastasize to lymph node, bone, lung and liver in distant sites. The authors data and a review of the literature support the concept that radical vulvectomy with or without bilateral inguinal-femoral lymphadenectomy is required. On the other hand, except primary radiation treatment for small or medium sized cancers, the results obtained by radiation therapy in carcinoma of the vulva including Bartholin's gland are generally discouraging. A role for postoperative adjuvant radiation therapy suggests because of high incidence of positive inguinal-femoral lymph nodes. In the near time, natural history and biological behavior of Bartholin's gland cancer must be disclosed in detail. And also optimal treatment modality and prognostic factors shall be determine.

Key Words: Radiation Treatment, Primary Adenocarcinoma of Bartholin's Gland

## INTRODUCTION

Primary cancer of the Bartholin's gland is a rare lesion accounting for between 2 and 7% of all vulvar neoplasms and 0.001% of all female genital malignancy[1,2]. Malignancy of the Bartholin's gland was first reported by Klob in 1864[3]. In 1944, Aquinaga[4] reported on 77 cases, and Masterson and Goss[5] added 40 more cases in 1954. Thirty five cases were reported by Barclay et al in 1964, and since then additional cases reported in the literature have brought the total number to more than 200[6].

The Criteria of pathology for the diagnosis of Bartholin's gland carcinoma which established by the Armed Forces Institute[7] is used in recent. These are: 1) areas of apparent transition from normal to neoplastic elements; 2) involvement areas of the Bartholin's gland and origin histologically compatible from the gland; and 3) no evidence of a concurrent primary tumor else-where.

Despite above reports, carcinoma of the Bartholin's gland remains an enigma and agreement on the optimal treatment of this disease has yet not to be defined. Various modalities of treatment have been used in the past, ranging from local excision to radiation alone[2,5]. In the near future, natural history, biological behavior and optimal treatment modality for carcinoma of the Bartholin's gland shall be determine.

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## CASE REPORT

A 63 year old female complained of walnut sized palpable mass in left inguinal area since about 20 years ago. The overlying skin was intact and not ulcerated. Since 3 months ago from the admission (Sept-86), it was markedly enlarged, 1.5×1.5×2.0 cm in size, and so she was admitted for further evaluation and management with impression of left inguinal lymphadenitis. After admission, in the result of excisional biopsy of left inguinal mass, it was confirmed as metastatic mucinous adenocarcinoma. On admission, she has not suffered from dyspareunia and other specific symptoms and signs on examination. There was not past history except ectopic pregnancy.

Routine studies of X-ray and laboratory examination, barium enema, pelvic sonogram and gal-

lium bone scann were done for the evaluation of metastatic lesion and primary site. And then tumor marker studies such as CEA and AFP were done. But its were all within normal limits. At last in the abdomino-pelvic CT scan, it was showed left distal external lymph node enlargement without the discovery of primary site. After 2 weeks from admission date, she was discharged without the confirmation of primary site and the plan of further adequate management. After 6 months from discharge, she was readmitted because of the recurrence of left inguinal lymph node and the occurrence of relatively hard mass (2×2×1 cm in size) at left labium major, i. e.; the Bartholin's gland. As soon as admission it was confirmed of mucinous adenocarcinoma in the result of pathologic report after excisional biopsy of left Bartholin's gland mass. Left inguinal regrowing mass was diagnosed of metastatic mucinous adenocarcinoma.

On gross findings of excisional Bartholin's gland mass, it was measuring 2.3×1.8×2.0 cm in size. The skin is diffusely elevated and nodular with myxoid hemorrhagic surface. On section with nodular tissue measures 1.4×1.1×1.0 cm in size and shows diffuse grayish white myxoid appearance which have noted fibrotic tissue within the mass.

On microscopic finding, it discloses the tumor within fibroadipose tissue, showing many variable sized tubular structures lined by abundantly mucin secreting tall columnar epithelium. The cells have rather hyperchromatic nuclei with nucleoli. Some peripheral portion show multifocal lymphoid cell aggregation similar to follicular architecture but identified structure of Bartholin's gland is not found (Fig. 1).

Radiation treatment was administered by Cobalt-60 (Theratron-780) teletherapy unit, externally. Radiation field was whole pelvis including the perineum and both groin areas (Fig. 2). Radiation dose was 5,000 cGy, delivered in 25 fractions in 5 weeks and then 1,000 cGy boost irradiation at the main primary site and left inguinal area for 1 week. Not only she was well tolerable during the time of radiation treatment but also at that time of the finishment of irradiation, moist or dry desquamation of the perineum was not showed.

After radiation finishment, on 3 month FU, left inguinal area which was excisional site and left Bartholin's gland area of the vulva were more soft and were disappeared the hardness. But disappointingly, a slightly hard mass, 3×3×3 cm in size, at left supraclavicular area was newly appeared. And so aspiration biopsy was done, it was diagnosed of metastatic carcinoma which consistented with mucoepidermoid carcinomatous. Thereafter, local irradiation at left supraclavicular

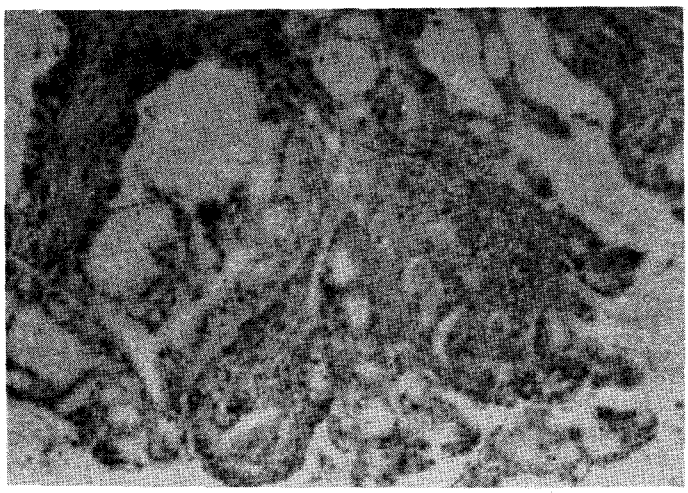

**Fig. 1.** Frozen section discloses tumors fibroadipose tissue, showing many variable sized tubular structures lined by abundantly mucin producing tall columnar epithelium. The cells have rather hyperchromatic nuclei with nucleoli. Some peripheral portion show multifocal lymphoid cell aggregation similar to follicular architecture and identified stricture of Bartholin's gland is not found.

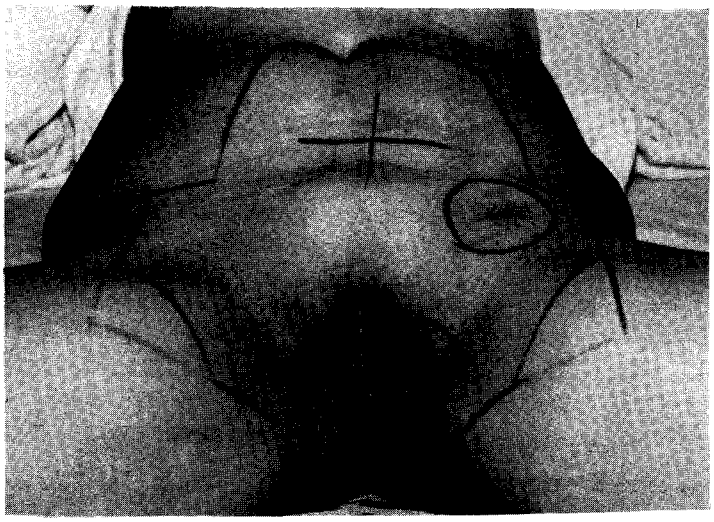

**Fig. 2.** Portal for external beam irradiation of the pelvis, including Bartholin's gland and both groin nodes.

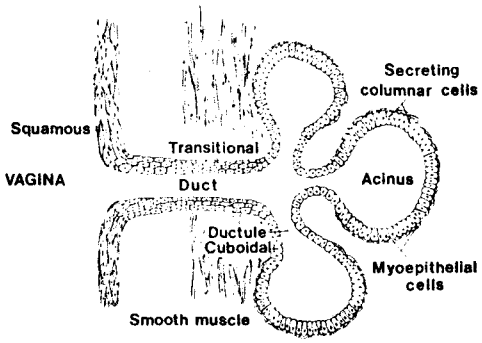


**Fig. 3.** Schematic diagram of the Bartholin gland revealing various cell types.

area and systemic chemotherapy were began. Total 6,000 cGy of tumor dose was irradiated in 30 fractions in 6 weeks for the metastatic left supraclavicular area. In recent follow-up, metastatic left supraclavicular hard mass is completely disappeared. There is showed only slight diffuse hardness and swelling of irradiated area including left Bartholin's gland and the perineum.

## DISCUSSION

According to the latest review of the literatures, about 200 cases of Bartholin's gland carcinoma have been reported[8]. It has been estimated that there is about one case of Bartholin's gland carcinoma to every 1,000 female genital cancers[9]. Although the median age of the patient with this neoplasm is 57 years, the range is wide. Thirty-eight percent of the patients in this review were below the age of 50, the youngest patient being reported as 14 years of age. Clinically these tumors usually produce pain, bleeding, swelling, and a palpable vulvar tumor mass which may be hard, tender, and indurated. But it is more commonly cystic. The mass may be fixed or movable, and dyspareunia is common and vulvar pruritus may be present. Ulceration of the skin occurs later[9].

The etiology of the tumor is unknown but in the result of the review of many literatures, the pertinent current factors as followings were to discovered[10]. 1) Bartholin's cyst or abscess and Bartholinitis 2) other benign disease of Bartholin's gland. And so, it is initially misdiagnosed as cysts or inflammatory processes of Bartholin's gland, and that considerable time was wasted before establishing the diagnosis and instituting definitive therapy. In the other author's series[8], of the 90 cases reviewed, only 7.8 % of the patients had a history of previous inflammation or infection of the Bartholin's gland. Thus, infection is not a common antecedent of Bartholin's gland carcinoma, and the genesis of squamous cell cancers of Bartholin's gland remains unclear.

Although still now, natural history and biological behavior is not disclosed, cancer of the Bartholin's gland should be distinguished from other vulvar carcinomas. Honan's criteria[11] for establishing the clinical diagnosis of a primary carcinoma of the

Bartholin's gland, as given by Barclay are met. These are; 1) correct anatomic position of the tumor 2) location of the tumor deep in the labium 3) overlying skin intact 4) presence of some elements of glandular epithelium. Histologically the Bartholin's duct[12] lies between the superficial and deep perineal compartments with a 3 cm duct passing obliquely to open just external to the hymen near the middle of the vaginal orifice. The duct is lined by a stratified squamous epithelium which gradually becomes a transitional epithelium as the gland is approached. This transitional epithelium is ultimately replaced by columnar epithelium (Fig. 3). Adenocarcinoma and squamous cell carcinoma are the most common, representing 85.6% of histologic types of Bartholin's gland carcinoma. The other types of Bartholin's gland carcinomas such as mixed, transitional cell, and anaplastic do occur but are in the minority[8].

By Chamlian DL et al[7], all adenocarcinomas are mucin producing as like in this case but the histologic patterns ranged from papillary to mucoepidermoid to mucinous (←gelatinous). The ultrastructural features of Bartholin's gland adenocarcinoma are described by K. Kuzuya et al[13]. There was a suggestion that the tumor composed of three cell populations, e. g., 1) principal cells with small, electron-dense granules 2) goblet-like cells with small, electron-dense granules, and 3) eccrine sweat gland-like cells with large, variable-shaped granules with moderate electron density. It was diagnosed that these secretory granules were exocrine in nature because they were mainly located in the apical region.

Virtually all histologic types of Bartholin's gland carcinoma metastasize to lymph nodes[8]. According to the report of Leuchter RS et al, 37.3% of inguinal-femoral nodes were involved with all histologic types of Bartholin's gland carcinoma. And no patient had metastatic involvement of the pelvic lymph nodes when the groin nodes were negative, but when the inguinal femoral nodes were positive for tumor, 18% demonstrated pelvic lymph node metastases.

Although until now, the ideal mode of therapy for carcinoma of Bartholin's gland remains unsettled but most authors recommend a radical vulvectomy and bilateral inguinal-femoral node dissection[2,8,9,11,14,15]. On the other hand, the results obtained by radiation therapy in carcinoma of the vulva including Bartholin's gland cancer are generally discouraging[16]. In the past, there has been applied radium implant, surface radium applicator and external high voltage irradiation, its were ordinarily not satisfactory results except small or medium sized cancers of epitheliomas of the vulva. Vulvar cancer including Bartholin's gland cancer is not generally considered a radio-curable neoplasm because 1) it often metastasizes to the regional lymph nodes and a monobloc surgical dissection of the cancer and its metastases is preferable 2) it not infrequently arises from multicentric foci, which makes localization of the radiation portals difficult 3) it frequently arises in pre-existent disease (leukoplakia) which interferes with the effects of radiation. Moreover, the fatty moist, infected, and atropic vulva with ischemic changes results in a tumor bed that is not suited for radiation therapy. And also, because of the anatomic location of Bartholin's gland[12],deep extension of a neoplasm arising in this area into the lateral wall of the vagina and ultimately into the ischiorectal fossa can make it surgically difficult to remove the entire lesion. The attempt to attain tumor-free surgical margins may necessitate extending the dissection to the levator ani muscles in order to remove the deep fascial plane of the urogenital diaphragm. Because of above described two reasons; 1)surgically incomplete resection 2) radio-resistant tumor, radiation treatment of vulvar cancer including Bartholin's gland cancer have often been combined with surgery with extirpation of the vulva or excision of the regional lymph nodes, or both. The results which achieved combined with radiation and surgery shall be much favorable than those obtained with radiation or surgery alone[8,12,15,16,17]. In the radiation treatment[18], the perineum will tolerate fairly high megavoltage doses much better than orthovoltage doses. Total doses of 5,000~7,000 rads in 6~9 weeks at the primary site, sometimes employing multiple portals, have been tolerated well and have effected prolonged local control. A tumor dose of 5,000 rads to the node-bearing areas is indicated. Although information concerning chemotherapy in vulvar cancer including Bartholin's gland carcinoma is sparse. By Masterson et al[5], systemic chemotherapy with Methotrexate, Chlorambucil and Actinomycin-D to the point of toxicity has not been beneficial. And also, by the report of Leuchter et al[8], one patient who had negative lymph nodes developed metastases to the liver and the lungs 36 months postoperatively. She was treated with Cyclohexylchloroethyl nitrosourea (CCNU) chemotherapy and survived and additional 28 months, or 64 months after primary diagnosis.

Survival rate after the treatment of Bartholin's

gland carcinoma is poor prognosis which reported in only about 9% of 5 years[19,20]. By Sackett[21], 5 year survivals after radical surgery for primary carcinoma of Bartholin's gland is only 3 of 4 patients. These three patients are living 7,5 and 6 years respectively. But by the report of Chamlian et al[7], 6 of 24 patients that was radical surgery were survived above 5 years longer. And also by Leuchter et al[8], it is more favorable prognosis which 20 of 51 patients that was radical vulvectomy with bilateral inguinal-femoral lymph nodes dissection were lived above 5 year free of disease. The main determinant of survival of patients with this tumor is the status of the inguinal-femoral lymph nodes. The presence of multiple positive groin nodes forecasts a poor prognosis, with only 18% patients surviving 5 years. When only 1 inguinal node has microscopic metastases, prognosis for survival is excellent with 71% surviving 5 or more years. Local recurrences[15] are most commonly primary site, vaginal area and also in the pelvis, suggesting the presence of pelvic node involvement, distant metastasis in the skull, hip, lung and liver demonstrates the systemic nature of this disease.

Primary carcinoma of the Bartholin's gland is a rare tumor for which the optimal treatment plan is unconfirmed. Recognition of the increased risk of cancer in any woman over the age of 40 years who develops a Bartholin gland mass will help to identify these tumors earlier if appropriate biopsy specimens are taken. Clinical staging is unreliable in estimating the extent of surgery necessary for clear margins. At the present time, radical vulvectomy and bilateral inguinal-femoral node dissection is recommended. As noted by Masterson and Goss[5], early diagnosis and aggressive surgical therapy offer the best chance for improved survival. The high incidence of positive inguinal-femoral nodes and subsequent failure in pelvic nodes in the study suggests a role for postoperative adjuvant radiation therapy. In the near time, natural history and biological behavior of Bartholin's gland carcinoma must be disclosed in detail and need to be determine optimal treatment modality. Especially, the methods and techniques of radiation treatment shall be develop.

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## ═국문초록═

# Bartholin 氏腺에서 발생한 腺癌의 방사선치료

국립의료원 치료방사선과

오 원 용·황 인 순

외음부의 Bartholin씨선에서 발생하는 악성종양은 지금까지 세계적으로 약 200예가 보고되고 있지만 아주 희귀한 종양이다. 일반적으로 처음 내원 당시에는 낭종이나 또는 염증성 농양으로 오진하기 쉬우며 조직병리학적으로 확진이 이루어져서 근치적치료가 시도되기 까지는 상당한 기간이 소모되는 경우가 많다. 아직까지는 이 악성종양에 대한 원인과 적절한 치료방침에 대하여 결정된 바 없이 논란이 많으나 다른 외음부악성종양과는 엄격히 다르게 구별지어야 할 것으로 생각된다. 이 악성종양에 대한 치료방법으로써 방사선치료는 라듐삽입 또는 전자선을 이용한 치료등이 다양하게 적용되여 왔지만 그 효과는 기대에 훨씬 못 미치고 치료성적과 생존율도 불량한 것으로 보고되고 있다. 최근에는 외과적으로 근치적 외음부절제술과 양측 서혜부 및 대퇴부 임파절절제술이 많이 시도되고 있으며 치료성적과 생존율도 괄목할 만큼 향상되었으나 수술후 잔존하는 병변으로 인하여 재발이 문제시되고 있다. 본 저자들은 본원에서 경험한 1예와 다른 저자들의 문헌고찰을 통하여 분석하여 본 결과 앞으로 이 악성종양에 대하여 보다 세심한 임상적 관찰과 생물학적 특성에 대한 분석이 시급히 요청되며, 아울러 적절한 치료방침의 결정과 함께 예후인자에 대한 분석을 통하여 생존율을 향상시키기 위한 다각적인 노력이 요망된다고 하겠다.