CHAPTER I

RATIONALE AND BACKGROUND

Cervical cancer is the most common cancer and a significant health problem in Thailand. Approximately 5,500 Thai women develop invasive cervical cancer per year.[1] Among these, 15-25% are in the early stage of disease (stage Ib or IIa)[2], which can be treated with either radical hysterectomy with pelvic lymphadenectomy or pelvic radiation with equal survival benefit.[3-5] However, most patients favor surgery because of the opportunity to preserve ovarian and vaginal functions, less long term complications, and better tolerable.

In patients with early stage cervical cancer treated by radical hysterectomy with pelvic lymphadenectomy, the overall 5- year survival rate is 80-90%.[3-6] The presence of lymph node metastases is the most significant prognostic factor in these patients.[7-13] Patients who had retroperitoneal node metastases or positive surgical margin or parametrial involvement should receive postoperative adjuvant therapy. Despite the adjuvant treatment, recurrence occurred in 33-42% of patients with pelvic node metastases.[7,9,10] However, recurrence was still seen in 7-11% of those without pelvic node metastases.[7,9,10]

Although recurrent rate in patients with negative node is low, more than one-half of cervical cancer patients whose tumors recur after radical hysterectomy have negative node and clear resection margin.[7,9,10]

Tumor-related variables linked with an increased risk of recurrence in node negative patients include close surgical margin involvement,[14] parametrial invasion,[15] tumor size,[16] depth of invasion,[17,18] lymph-vascular space invasion (LVSI),[17] adenocarcinoma cell type,[16,18] and histologic grade.[17] However, these clinicopathologic prognostic factors do not always correspond with the recurrence of disease. In node negative patients, it has been suggested that the presence of only a single tumor risk

factor (with the exception of surgical margin involvement and parametrial invasion) does not confer sufficient adverse prognosis to routinely justify adjuvant therapy.[19] To date, there is no consensus on the criteria to select the patients with negative node and free surgical margin but with other risk factors for adjuvant postoperative treatment. An investigation to search for a new biomolecular prognostic factor is important to identify the risk of recurrence in this group of patients.

The bcl-2 oncogene (B-cell lymphoma/leukemia-2 gene) is located on chromosome 18 and encodes for cytoplasmic protein, which was found to be localized mainly in the mitochondria,[20,21] endoplasmic reticulum, [21] and the nuclear envelope. [21] The bcl-2 protein can be immunohistochemically demonstrated in different tissues,[22,23] which can be grouped as (i) precursors of all hematopoietic elements (ii) glandular epithelium in which hormones or growth factors regulate hyperplasia and involution such as breast duct epithelium, thyroid gland epithelium, endometrial gland, pancreatic acinar cell and islet cell (iii) cell populations with proliferative activity such as basal cells of skin and other squamous epithelium, and cells at the bottom of colon crypts (iv) long-lived postmitotic cells such as neurons. In normal cervical tissue, bcl-2 expression is high (95%) in the basal cells of the ectocervix.[23-26] and in the reserve cells of the endocervix.[24-26]

Concerning cancer; bcl-2 expression is suggested to be of prognostic relevance in many types of cancer such as lung, [27-31] colorectal,[32-33] laryngeal,[34] endometrial,[35,36] breast, [37,38] and ovarian cancer.[39] Most studies associated bcl-2 positive malignancies with a favorable prognosis.[28-32,35-39]

In cervical cancer, prognostic significance of bcl-2 is still controversial, some reported bcl-2 expression with good prognosis, [25,40-44] some associated bcl-2 expression with poor prognosis,[45,46] while some could not demonstrate the association.[47-52] The objective of this study was to examine the association between bcl-2 expression and tumor recurrence in cervical cancer patients who underwent radical hysterectomy with pelvic lymphadenectomy and had negative pelvic node and free surgical margin.