Squamous Cell Carcinoma of Head and Neck

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Abstract

Head and neck cancers are a major heath problem and common malignancies in Thailand. Up to 80 per cent of cases are caused by smoking and alcohol consumption. Epithelial mucosa of the aerodigestive tract exposed to carcinogens results in cellular mutations at different areas by a process called field cancerization and causes multistep carcinogenesis. Over 90 per cent of cases are squamous cell carcinoma. Prognostic factors depend on the patients, diseases and treatment. Currently, several molecular pathogenesis have been discovered such as abnormalities of c-myc, c-ras, c-erbB-1, bcl, int-2, hstl oncogenes, p53 and p16 tumor suppressor genes. Common chromosomal abnormalities are 3p, 9p, 11q, 13q, 17p. Diagnosis requires symptoms and signs, radioimaging, and pathology. Stage I and II can be treated by surgery or radiotherapy. However, stage II requires and combination of surgery and radiotherapy, and studies of chemotherapy and local treatment to increase therapeutic efficacy by several approaches such as combination chemotherapy, new drugs, and biologic therapy.

Head and neck cancer is a public health problem worldwide. Despite two decades of advance in surgery, radiotherapy, and chemotherapy, the long term survival rate has only marginally improved. Recently, considerable progress has been made in the understanding of head and neck tumorigenesis, prevention, and treatment. Since nasopharyngeal carcinoma has a different clinical course and treatment, only squamous cell carcinomas of the head and neck excluding nasopharyngeal carcinoma were included is this review.

Biology and Epidemiology

The incidence of head and neck cancer varies throughout the world. Fifteen per cent of all malignancies in Thai patients are head and neck

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cancer[1]. It accounts for 4-5 per cent of all invasive cancer in United States[2]. Worldwide, more than 500,000 new upper aerodigestive tract cancer (10% of all cancer) occur each year[3]. The male to female ratio is approximately 4:1. Ninety five per cent of the cases is squamous cell type. It consists of a heterogenous group of cancers in multiple anatomic sites with independent natural history, treatments, and therapeutic results. The usual time of diagnosis is past 40, except for salivary gland tumor and nasopharyngeal tumors, which may occur in younger age groups. The frequency of occurrence from the most common to the least is as follows : larynx (20% of all head and neck cancer), tongue, lip, oropharynx and buccal mucosa, floor of mouth, hypopharynx, and nasopharynx (2-3%)[4]. In contrast, the most common head and neck cancers in Chulalongkorn Hospital are nasopharynx (28% of all head and neck cancer) followed by larynx (13.9%), tongue (11.9%), oropharynx (7.4%), hypopharynx (7%), lip (4.9%), nasal cavity (4.3%), gum (4.1%), salivary gland (3%), and floor of mouth (2.8%)[1].

Tobacco and alcohol use account for approximately 80 per cent of head and neck cancer (Table 1). The effect of tobacco and alcohol on the development of head and neck cancer appears to be synergistic[5]. Besides smoking cigarettes, differing patterns of tobacco abuse are associated with variations in head and neck cancer sites. For example, smokeless tobacco mixture produces a high incidence of oral cancer, whereas, smoking cigarettes produces high rates of laryngeal cancer. The habit of reverse smoking in India is associated with cancer of the hard palate. In addition, the use of oral snuff is associated with oral cancer. The practice of betel squid chewing in Asia is associated with a high incidence of cancer of buccal mucosa[6].

The mechanism of carcinogenesis for tobacco and alcohol is not yet well defined. The development of head and neck cancer has been proposed as a multistep process of tumorigenesis. The whole epithelial field exposed to carcinogen (i.e. tobacco and alcohol) is at risk of cancer development by a process called field cancerization[7]. The entire epithelium at risk accumulates genetic damage leading to dysregulation of proliferation and differentiation proceeding cancer development. There is substantial clinical and laboratory evidence to support these notions with head and neck cancer[8]. Second, premalignant lesions (i.e. oral leukoplakia/oral cancer) develop during head and neck tumorigenesis[9]. Third, animal models such as hamster cheek pouch model of oral carcinogenesis demonstrated the multistep progression through cancer[10]. Fourth, numerical chromosomal alterations occur in adjacent normal appearing epithelium and increased polysomies of chromosome 7 and 17 accompany multistep tumorigenesis[11]. Lastly, proliferative dysregulation progressively increased as tissue histology progressed through cancer[12]. Besides EBV, human papilloma virus has been found in laryngeal papillomatosis, oral, and laryngeal cancer[13].

Pathology and Prognosis

Histological typing of tumors of the upper aerodigestive tract has been revised recently by the World Health Organization[14]. More than 90 per

Table 1. Etiology of head and neck cancer.

1.	Tobacco	
2.	Alcohol	
3.	Viral	- Ebstein-Barr Virus
		- Human Papilloma Virus
4.	Environmental factors	
	Nickel, chromium, wood dust, Shoe industry	- nasal cavity/paranasal sinuses
	Iron deficiency (Plummer-Vinsor)	- tongue
	Syphilis	- tongue
	Immunosupressive therapy	- skin, lip
	Prior radiation	- skin, thyroid, salivary gland
	Asbestos, metal processing	- larynx
5.	Diet (deficiency in vitamin A, carotene)	- all sites

cent of head and neck cancer are squamous cell carcinoma. There has not been a consistent association between histologic differentiation and response to chemotherapy reported in most studies of induction chemotherapy[15-17]. Although tumor grade may not predict the response to chemotherapy, it may predict the relapse after initial response to chemotherapy. A significant risk of relapse was noted in patients with moderately or poorly differentiated squamous cell carcinoma who had a complete response to initial therapy[18].

Prognostic factors in head and neck cancer can be classified as patient-related, disease related, and treatment-related prognostic factors[19]. Patient-related prognostic factors include age, sex, tobacco and alcohol consumption, performance and nutritional status, and immunologic competence. The male gender appears to be a poor prognostic factor in one study which included 152 patients treated with induction chemotherapy[20]. Continued alcohol and tobacco consumption may increase the risk of a second primary tumor. Several studies showed that perfomance status and/or nutritional status correlated with response to chemotherapy and survival[21-23]. Although attempts have been made to evaluate the prognostic value of available immunologic parameters in head and neck cancer, clinical implication remains unclear and warrants further investigation[24].

Disease-related prognostic factors are site, TNM stage, lymphatic invasion, perineural invasion, DNA aneuploidy, lymph node metastasis, the presence of extracapsular spread, histologic pattern of invasion, blood group antigens, and major histocompatibility complex (MHC) antigens. The presence of regional lymph node metastasis is the single most important prognostic factor in head and neck cancer. In 76 patients with primary resectable squamous cell carcinoma of head and neck, aneuploidy was associated with poor prognosis (significantly decreased relapse-free survival and overall survival) independent of all evaluated clinical and pathologic features[25]. However, aneuploid tumors seem to more responsive to cytotoxic chemotherapy than diploid malignant cells[26,27]. The penetration of the tumor through the capsule of involved lymph nodes is associated with a high incidence of distant metastasis[32]. Tumors which invade with thin finger-like projections or single associated cells behave more aggressively regardless of histologic grade and tends to have neural and vascular invasion[29]. The loss of ABH blood group antigen was associated with early metastasis in 82 consecutive, previously untreated patients with squamous cell carcinoma of the larynx correlated with a worse differentiation and greater tumor aggressiveness[32].

The most important treatment-related prognostic factor is having a complete response to therapy. In the induction chemotherapy trials, only patients with a complete response to induction chemotherapy will have a significant prolonged survival after completion of treatment compared to the non-chemotherapy arm[33].

Molecular Abnormalities

Chromosome deletions in 3p, 9p, 17p and 13q are the most frequent chromosome aberrations[34]. The cell cycle gene p16 is located on chromosome 9p and is an inhibitor of the cyclin-CDK complex which regulates the transition to the synthetic or the mitotic phase of cell cycle[35]. Abnormal expression of oncogenes has been implicated in the development of cancer of the head and neck region. Amplification and elevated c-myc mRNA expression was correlated with advanced stage of disease[36], and increased expression of the c-myc oncoprotein correlated with poor prognosis in head and neck squamous cell carcinoma[37]. It was shown that there was a correlation between increased expression of ras oncoprotein and poor prognosis in 212 squamous cell carcinoma of head and neck[38]. In the multistep carcinogenesis of hamster cheek pouch model, c-erbB-1 gene was amplified and may correspond to an early event in tumorigenesis[39]. Interestingly, there are several genes located on chromosome 11q13, a constitutively fragile site, including bcl-1, cyclin D, int-2 and hst-1 genes[40]. It has been found that many squamous cell carcinoma cell lines from head and neck region demonstrated amplification of these genes. Bcl-1 gene is a breakpoint locus of chromosome translocation, t(14:18) (q13;q32), originally found in B-cell neoplasms[41]. Cyclin D1 plays roles in cell cycle regulation[42]. Overexpression of epidermal growth factor receptor is another frequent abnormality and associated with poor prognosis[43].

The presence of mutant p53 genes in a premalignant lesion of squamous cell carcinoma of upper aerodigestive tract suggests that this genetic alteration may be an early event in the progression

toward malignancy. The p53 protein was indentified in dysplastic epithelium, undifferentiated tumor cells, and was progressively lost as the cell keratinized[43]. Evidence is accumulating that p53 expression gradually increases as tissue progresses from adjacent normal epithelium to hyperplastic and dysplastic lesion toward squamous cell carcinoma as well as a topological change in p53 expression[45]. Molecular analysis of p53 gene mutation may be used to assess risk of local recurrence of histologically negative surgical margins and cervical lymph node metastasis of patients with squamous cell carcinoma of the head and neck[46].

Diagnosis

Head and neck cancer is a heterogenous group of cancer with variable presentations, natural history, staging, management, and expected outcome. Clinical suspicions of symptoms and signs suggesting head and neck cancer depend on the sites of the tumors[47]. Clinical evaluation of head and neck patients should include a complete history and a thorough physical examination. The examination should include head and neck examination including an indirect mirror examination, which may be supplemented with direct flexible or rigid fiberoptic examination for primary lesion, evaluation of disease extent both regional and distant metastasis, evidence of multiple primary and/or second primary tumors. Panendoscopy including laryngoscopy, bronchoscopy, and esophagoscopy, is essential before planning radiotherapy to evaluate multiple primary lesions[48]. Investigations include complete blood count, urinalysis, electrolytes, liver function test, chest X-ray and CT or MRI of head and neck. Individuals with suspicion of bone involvement such as cancer of the floor of the mouth, should have reongenographic evaluation of adjacent bone at risk. Evaluation by dental oncologists should be obtained prior to definitive therapy. It is important to have adequate biopsy for precise histological diagnosis. Fine needle aspiration is frequently used to evaluate neck mass. Open biopsy of the lesion is contraindicated unless all diagnostic attemps fail to reveal any diagnosis. The procedure may increase in distant or local and regional disease after primary therapy due to violated neck and alter definitive therapeutic approach[49].

Occasionally, patients present with unknown primary cancer. Usually, ultimate primary sites are nasopharyngeal carcinoma, base of tongue, pyriform sinus, and tonsil. Eighty per cent of primary tumors are found on examination and 10 per cent after radiographic evaluation. In less than 10 per cent of cases, the primary tumor cannot be detected even after extensive investigation. Thirty per cent of cases was found by autopsy. Evaluation of patients with cervical lymphadenopathy of no obvious primary origin should include a history, physical examination including evaluation of the head and neck region by otolaryngologists. If no cancer is found, a fine needle aspiration of the neck mass should be performed. Radiographic evaluation should include chest X-ray, sinus X-ray if there is symptomatology, and a thyroid scan if there is a low anterior neck mass or thyroid scan if there is a low anterior neck mass or thyromegaly. The roles of CT-scan and MRI are currently under evaluation. Extensive evaluation of other organ systems is not indicated except for Virchow's node enlargement which may arise from intraabdominal neoplasms. If the primay lesion is still obscure, panendoscopic examination (laryngoscopy, bronchoscopy, esophagoscopy and nasopharyngoscopy) should be performed. At the time of the panendoscopy, incisional biopy from all suspicious sites should be performed including blind biopsy of nasopharynx, tonsil, base of tongue, and pyriform sinus. In addition, an examination under general anesthesia with palpitation of the oropharynx should be considered. Only if the primary tomor is not found after all these tests should an open or excisional biopsy of the neck mass to obtain fresh tissue be performed to rule out lymphoreticular or mesenchymal tumors. Open biopsy is not performed intitially because a histologic diagnosis rarely indicates the primary site. Moreover, it may interfere with anatomical and surgical planes which may complicate the definite plan. Local biopsy may predispose the spread of tumor. Among 714 patients who had a radical neck dissection, the incidence of distant metastasis was higher (42%) in the group that had initial biopsy compared to those who had a biopsy at the time of neck dissection (12%). However, others showed no influence of excisional or incisional biopsy of metastatic neck nodes on distant metastasis[47].

Treatment

Radiation treatment is an effective treatment for local and regional diseases. For early

lesions, it provides results comparable to those achieved with surgery with local and regional control rates for stage I and II of 75-90 per cent. It is preferred over surgery in certain sites that functional result is better with radiotherapy such as larynx and the tip of the tongue. Nasopharyngeal carcinoma is treated with radiotherapy since surgery is not feasible for this site. In larger primary tumors, it was fused adjuvantly after surgery to improve local and regional control. Recently, many clinical trials have been designed to optimize tumor control while reducing normal tissue damage. Phase III randomization studies have been conducted to compare hyperfractionated radiotherapy with conventional radiotherapy. By giving a smaller dose of radiation per fraction that allows normal tissue to repair more effectively than tumor between fractions, this will allow the delivery of a higher tumor dose and improve the therapeutic ratio. Increased local and regional tumor control has been recently reported from a randomized control trial[51] and a better survival in the hyperfractionated radiotherapy may be achieved by improving local and regional control. Alternative approach is the use of accelerated fractionation refers to giving multiple daily doses of such size that the overall treatment time is shortened relative to that conventional radiotherapy to reduce the effect of tumor cell proliferation during treatment[52]. Although early results from a number of phase II study is promising, acute toxicity especially acute mucosal reaction remains a problem.

Early stage squamous cell carcinoma of the head and neck can be successfully treated with surgery. Advanced stage diseases have poor prognosis and require a multimodality approach. Surgery plays no role in the management of nasopharyngeal carcinoma except to obtain the biopsy. Surgery in the irradiated field continues to be of concern for potential complications. Conservative and endoscopic surgery for early stage larangeal cancer have recently received increased attention to decrease surgical morbidity, improve functional results, and shorter hospitalizations. New techniques of free flap reconstruction of soft tissue and bone defect following extensive surgery for head and neck cancer have provided better functional and cosmetic results[53].

In general, surgery or radiation can be used effectively for early stage (T_1, T_2, or favarable T_3). Larger tumors (T_3 and T_4) and/or with nodal involvement (N_{1-3}) need sequential surgery and radiation. Exceptions include nasopharyngeal carcinoma and some glottic laryngeal carcinoma, which are best treated with radiation. Coventional therapy of limited disease (T_{1-2} N_{0-1}) has the equivalent outcome of surgery or radiotherapy. However, radiotherapy is cosmetically more acceptable with preservation of function. In infiltrative lesion, hypoxia may exist leading to inferior radiotherapy results. Early tonsillar, largyngeal and hypopharyngeal cancers can be treated successfully with radiotherapy. Oral tongue tumor should be treated successfully with radiotherapy. Tumor of the base of the tongue can be treated with surgery and brachytherapy. In advanced disease (T_{3-4} N_{2-3}), combined surgery and radiation improve local control. Post-operative radiation is superior to pro-operative treatment because of the obscured margins and complication rate in pre-operative radiotherapy. A new modality of treating recurrent head and neck cancer currently being investigated is intraoperative radiotherapy. In a series of 47 patients with previously irradiated recurrent cancer of the head and neck treated with salvage surgery and intraoperative radiotherapy, operative mortality was low and survival rates were impressive for these advanced recurrent tumors[54].

If the primary tumor cannot be identified, treatment should include neck dissection with or without radiotherapy-6,000 cGy to a field encompassing almost all head and neck sites as well as bilateral neck. Over half of the patients can be cured with this therapeutic plan. Other approaches include neck dissection or radiotherapy as single modalities. Five-year survival is worse in patients whose primary site was not found (60%)[55].

The role of chemotherapy in the management of squamous cell carcinoma of head and neck is yet to be defined and is currently under active investigation. Chemotherapy in head and neck cancer falls into four main catagories: 1) palliative treatment in recurrent disease or metastatic disease 2) neoadjuvant chemotherapy to reduce tumor burden prior to definite treatment 3) adjuvant chemotherapy to maintain, or prevent recurrence in patients after definite local control 4) concurrent chemoradiation for controlling locally advanced disease.

Chemotherapy was used exclusively in recurrent disease. Tumor response rate was 20-25 per cent. However, the duration of response was

Table 2. Single agent chemotherapy in recurrent and metastasis head and neck cancer.

Agent	No. of patients	Response (%)
Bleomycin	374	21
Carboplatin	169	22
Cisplatin	288	28
Cyclophosphamide	86	36
5-FU	118	15
Hydroxyurea	38	32
Methotrexate	988	31
Taxol	23	26

4-6 months and survival rate has not yet been improved significantly by chemotherapy[56]. Single agent activity is shown in Table 2. Although, multiagent therapy is more effective than single-agent therapy in recurrent or metastatic disease, no survival benefit was observed among different combination regimens. Therefore, for patients with metastatic or locally recurrent squamous cell carcinoma following maximal surgery and/or radiotherapy, methotrexate nonetheless remains the standard therapy[57].

Randomized trials of neoadjuvant chemotherapy have been conducted. Thirteen randomized trials compared chemotherapy and surgery with or without radiotherapy with surgery with or without radiotherapy only and 12 randomized trials compared chemotherapy and radiotherapy with radiotherapy only[57-76]. The former were patients with resectable disease, whereas, the latter included both resectable and unresectable patients. Induction chemotherapy can result in significant tumor regression in 60-90 per cent and 20-50 per cent complete remission in patients with locally advanced squamous cell carcinoma of head and neck. Pathologic complete remission has been documented in 30-70 per cent of clinical complete responders. Distant metastases decreased when chemotherapy was included in combined modality treatment. Despite these promising results of tumor response, only two of the trials showed a significant survival benefit. Moreover, patients who had a complete response to induction chemotherapy had a better survival rate. Although many studies did not show survival benefit, induction chemotherapy has been shown to be an effective approach for organ preservation. In one study, the larynx was preserved in two thirds of patients with laryngeal carcinoma. The study included 332 patients with stage III or IV laryngeal cancer and were randomized to receive either three cycles of chemotherapy (cisplatin and 5-FU) and radiation or surgery plus radiation. Patients who failed chemotherapy and radiotherapy underwent salvage laryngectomy. The clinical response was 31 per cent CR and 54 per cent PR after two cycles of chemotherapy. The larynx was preserved in 64 per cent of the chemotherapy group[77].

Adjuvant chemotherapy may have a role in eradicating micrometastases and controling subclinical persistent disease after surgery or radiation which may lead to decreased local-regional and distant failure after definite therapy. Results from six randomized trials were conflicting: five trials showed no survival benefit in the adjuvant arm [78-83] and on a small trial demonstrated a significant survival benefit in the chemotherapy group[82].

Concomittant chemoradiotherapy has shown to improve local-regional control and increase survival in randomized trials for both locally advanced resectable and unresectable patients. Concommittant single-agent chemoradiotherapy consisting of bleomycin, 5-fluorouracil, methotrexate, hydroxyurea, mitomycin C, and cisplatin have been tested which revealed encouraging but inconclusive results in many phase II trials[56,84,85]. Among these chemotherapy, cisplatin seems to be ideal as a single agent for chemoradiotherapy based on its establised activity, synergistic activity *in vitro* and non-overlapping toxicity (no mucositis) with radiotherapy. Many randomized trials are currently in progress. Concomittant multi-agent chemoradiotherapy greatly increases acute toxicity, especially mucositis, and thus requires dose reduction of radiotherapy or chemotherapy which may compromise treatment results. Six randomized trials that showed significant increased disease-free survival and overall survall[86-91] are shown in Table 3.

Eventhough the response rate is better with concomittant chemoradiotherapy, toxicity is also enhanced. Therefore, another approach to minimize normal tissue toxicity is to give chemotherapy followed by radiation therapy (sequential approach) or give chemotherapy, and radiation therapy one after the other (alternating modes will allow for recovery of the normal tissue. In addition,

Table 3. Randomized trials of concomittant chemoradiotherapy *versus* radiation therapy.

Study	Chemotheapy	No. of patients	Response	Survival
Gupta[86]	Methotrexate	313	benefit	benefit
Shanta[87]	Bleomycin	157	benefit	benefit
Fu[88]	Bleomycin	104	benefit	benefit*
Shigematsu[89]	5-Fluorouracil	63	NR	benefit*
Lo[90]	5-Fluorouracil	163	benefit	benefit
Weissberg[91]	Mitomycin-c	117	benefit	benefit

heterogenous tumor cell population with drug resistance may be eradicated by the two alternating modalities of treatment. Alternating chemotherapy and radiotherapy compared with radiotherapy alone improved progression-free and overall survival in patients with advanced, unresectable head and neck cancer in one recent report[92].

Combination of chemotherapy and radiotherapy in the management of head and neck cancer patients will need further evaluation preferably using a randomized trial comparing the standard treatment and yet cannot be recommended as a standard practice outside of clinical trials.

Biological Therapy for Head and Neck Cancer

Retinoid has a significant activity to reverse premalignant lesion (oral-leukoplakia)[93] and prevent the development of second primary tumors of head and neck[94]. A 15 per cent response rate was reported of 13-cis-retinoic acid in heavily previously treated recurrent head and neck cancer[95]. Interferon-alpha had limited activity in squamous cell carcinoma of head and neck[96]. Combination of interferon-alpha and 13 cis-retinoic acid showed only minimal activity in 21 evaluable patients with recurrent head and neck cancer[97]. Based on the high expression of interleukin-2 receptors in human squamous carcinoma cell lines and growth inhibited by interleukin 2 *in vivo* and *in vitro*, a clinical trial using systemic interleukin-2 alone or with interferon-alpha has been conducted and showed transient antitumor activity, however, with substantial toxicity[98]. The integration of biologic therapy into cytotoxic regimen have been studied. However, the results of treatment were not better than for chemotherapy alone.

SUMMARY

The majority of cancers of the head and neck are of the squamous cell carcinoma. The standard therapy for local stages is surgery or radiotherapy or both. Systemic chemotherapy has been used for metastatic disease and combined with local treatment to increase therapeutic efficacy for locally advanced disease. Biologic therapy is under active investigation in the treatment of head and neck cancer. Recent research focusing on molecular carcinogenesis of head and neck cancer development offers great promise for the future. It appears clear that major breakthroughs in the treatment of cancer can occur only by developing a better understanding of the molecular regulatory mechanisms that control cell growth and cancer development.

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โรคมะเร็งของศีรษะและคอ

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โรคมะเร็งของศีรษะและคอเป็นปัญหาที่ทางสาธารณสุขและเป็นโรคมะเร็งที่พบมากในประเทศไทย การสูบบุหรี่และการดื่มเหล้าเป็นสาเหตุของการเกิดโรคถึง 80% ของผู้ป่วยทั้งหมด สารก่อมะเร็งเมื่อสัมผัสกับเยื่อบุของช่องปากและคอทำให้เกิดการกลายพันธุ์ของเซลล์ที่ตำแหน่งต่าง ๆ โดยขบวนการณ์ "field cancerization" และมีการเปลี่ยนแปลงเป็นโรคมะเร็งอย่างเป็นขั้นตอน "multistep carcinogenesis" พยาธิสภาพของโรคมากกว่า 90% เป็น squamous cell carcinoma การพยากรณ์โรคขึ้นอยู่กับผู้ป่วย ตัวโรค และการรักษา ในปัจจุบันพบสาเหตุของการเกิดโรคในระดับชีววิทยาอณูหลายชนิด เช่น การผิดปกติของยีนส์มะเร็ง c-myc c-ras c-erbB-1 bcl-1 int-2 hst-1 ยีนส์ต้านมะเร็ง P53 และ P16 โครโมโซมผิดปกติที่พบบ่อยคือ 3p 9p 11q 13q 17p การวินิจฉัยโรคอาศัยอาการและอาการแสดงของโรค การตรวจทางพยาธิสภาพและรังสีวินิจฉัย โรคระยะที่ I และ II สามารถรักษาได้ด้วยการผ่าตัดหรือการฉายรังสี ส่วนระยะที่ III รักษาด้วยการผ่าตัดร่วมกับการฉายแสง และมีการศึกษาวิธีการใช้ยาเคมีบำบัดร่วมกับวิธีการรักษาเฉพาะที่ เพื่อเพิ่มประสิทธิภาพในการรักษาด้วยวิธีต่าง ๆ กัน เช่น การใช้ยาหลายอย่างร่วมกัน การนำยาใหม่มาใช้รักษา และการรักษาด้วยยาทางชีวภาพ

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