

Tumor Markers in Cervical Cancer

BACKGROUND

Cancer of the uterine cervix is the major cause of death from gynecologic cancer worldwide. Reported incidence rates in developing countries are much higher than those in developed countries, ranging from 83.2 per 100,000 women in Recife, Brazil, to 3 per 100,000 for non-Jews in Israel (358,359). In 2008, cervical cancer was diagnosed in an estimated 11,070 women within the US, with 3,870 estimated deaths (360). The mean age for cervical cancer is 51 years (358). Cervical cancer progresses slowly from preinvasive cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ to squamous cell carcinoma or adenocarcinoma, respectively. Screening asymptomatic women with regular Papanicolaou smears allows diagnosis of treatable preinvasive lesions (361). However, in developed countries, most cases of cervical cancer occur in women who have not had regular Papanicolaou smear screening. In developing countries, screening facilities are not readily available and most women present with advanced stage disease that may have already spread into the bladder, rectum, pelvic nerves, or bone (358).

Abnormal vaginal bleeding, including postcoital, intermenstrual, and postmenopausal bleeding, is the most common symptom of cervical cancer. In women who are not sexually active, however, cervical cancer is often asymptomatic until relatively advanced (358). Large tumors may present with vaginal discharge. In advanced cases, pelvic pain, pressure symptoms pertaining to the bowel or bladder, and occasionally vaginal loss of urine or feces may occur (358).

Cervical cytology screening is the current method for early detection of premalignant cervical lesions and cancer. It has been shown to reduce both the incidence and mortality of this malignancy in Western countries (361,362). Screening techniques include conventional Papanicolaou smears or liquid-based cytology, and national screening programs have been established in a number of countries. Women with abnormal cytology are referred for colposcopy and directed biopsy for histological diagnosis (361). Premalignant cervical lesions can be treated by loop electrosurgical excision, cold-knife conization, cryosurgery, CO₂ laser, or hysterectomy (361,363).

It is generally accepted that specific high-risk human papilloma virus (HPV) types are causally involved in the pathogenesis of cervical cancer. The HPV types HPV-16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-68, HPV-73, and HPV-82 are considered oncogenic HPV types (364). Oncogenic types can cause cervical cancers and other anogenital cancers.

Nononcogenic types HPV-6 and HPV-11 can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis (364). It has been demonstrated that 99% of cervical cancers worldwide are associated with high-risk HPV (364-366). Most cervical cancers (70%) are caused by two high-risk HPV types, HPV-16 and HPV-18 (364,366,367). Persistent infection with high-risk HPV has been recognized as necessary for the development of cervical cancer and its precursor lesions (368-370). It has been suggested that HPV testing can improve the efficacy of cervical cancer screening. Recent follow-up data on longitudinal population-based randomized controlled trials have indicated that HPV testing leads to earlier detection of high-grade CIN lesions or cervical cancer compared with cytological screening (371).

Because persistent infection with high-risk HPV is the most important risk-factor for the development of cervical cancer precursor lesions and cervical cancer, primary prevention of (pre)malignant cervical disease is feasible. The currently available prophylactic HPV vaccines are based on virus-like particles (VLPs) and are composed of HPV L1 proteins (372,373). Three prophylactic HPV-VLP vaccines have been clinically evaluated to date, including a monovalent HPV16 L1 VLP vaccine, a bivalent HPV16/18 L1 VLP vaccine, and a quadrivalent HPV6/11/16/18 L1 VLP vaccine (373). Efficacy data of the bivalent and quadrivalent vaccines demonstrate protection against persistent HPV-16 and/or HPV-18 infections (lasting 6 months or longer) for more than 90% of those vaccinated for up to at least 5 years after vaccination (372,373). The efficacy against high-grade CIN and adenocarcinoma in situ is documented as an intermediate end point because these lesions are the obligate precursors to invasive cancer. Estimation of the efficacy against cervical cancer will require long-term follow-up in clinical trials (372,373). It is expected that the maximum effect of current HPV vaccines in the long term (15-20 years) will be a reduction of 75%-80% of cervical cancers (372,373).

Approximately 85% of cervical cancers are of the squamous cell type. Other histological types less frequently found include adenocarcinoma (approximately 10%-15%) and adenosquamous carcinoma (approximately 3%). Treatment planning of patients with cervical cancer is primarily determined by the clinical stage of disease, usually according to the International Federation of Gynecology and Obstetrics (FIGO) staging criteria (358).

Early-stage cervical cancer (stage IB1, IIA, tumor \leq 4 cm diameter) is primarily treated with either radical hysterectomy and pelvic lymphadenectomy or radiotherapy, which are equally effective (358,374). However, with radical surgery,

ovarian function can be preserved and vaginal stenosis secondary to radiation avoided, which is of great advantage for younger patients (374). Therefore, most patients with early-stage cancer will be treated by radical hysterectomy and pelvic lymphadenectomy. For cases in which preservation of fertility is desired, radical vaginal trachelectomy and laparoscopic pelvic lymphadenectomy or abdominal trachelectomy and pelvic lymphadenectomy may be an option in patients with small tumors (< 2 cm in diameter; 374). If there are pelvic lymph node metastases, parametrial involvement, or positive surgical margins, adjuvant radiation therapy to the pelvis is given to increase local control (374). In these cases, it has been reported that concomitant chemoradiation with platinum-based chemotherapy significantly improved disease-free survival and survival compared with radiotherapy alone (375,376). For lymph node-negative patients with unfavorable prognostic factors such as large tumor volume, deep stromal invasion, or lymphovascular invasion, adjuvant radiation therapy reduces the risk of recurrence and prolongs progression-free survival (374,377).

Bulky stage IB2 or IIA (tumor > 4 cm) cancer can be treated by radical surgery, concomitant chemoradiation, or neoadjuvant chemotherapy followed by radical surgery (358,374,378-380). For locally advanced cervical cancer (stage IIB, III, IVA), concomitant chemoradiation, with weekly single-agent cisplatin, has been the standard treatment since 2000 (374,378,379). A review including 24 randomized controlled trials comparing concomitant chemotherapy and radiation therapy with radiotherapy alone for locally advanced cervical cancer strongly suggested that chemoradiation improves overall survival and progression-free survival with absolute benefits of 10% and 13%, respectively (378). Neoadjuvant chemotherapy followed by radiotherapy versus radiotherapy alone in locally advanced cervical cancer has shown disappointing results in terms of survival. However, a metaanalysis suggested that both dose intensity of cisplatin and interval duration between the chemotherapy cycles might be of critical importance, but further study is required (380). A comparison of neoadjuvant chemotherapy followed by surgery versus chemoradiation is presently ongoing within the European Organisation for the Research and Treatment of Cancer Gynecologic Cancer Group (protocol 55994), in patients with stage IB2, stage IIA > 4 cm, or stage IIB cervical cancer. The role of chemotherapy in patients with recurrent or metastatic disease is merely palliative, although response rates up to 34% have been reported. Agents with the greatest activity include paclitaxel, ifosfamide, bleomycin, and topotecan (381). Median survival after treatment with chemotherapy for recurrent or metastatic cervical cancer is 4 to 17 months (381).

Patients with stage IB or IIA disease (early-stage disease) have an overall 5-year survival rate of between 66% and 95% (358). Patients with more advanced stage disease (stage IIB and higher) have a 5-year survival rate between 9% and 64% (358). The FIGO staging procedure fails to detect lymph node metastases in approximately 15%-20% of patients with early-stage cervical cancer (358). However, the presence of lymph node metastases is the most important prognostic factor associated

with recurrent disease and poor survival (358,374,382-384). The 5-year survival rate of patients with stage IB or IIA cervical cancer declines dramatically from approximately 80%-95% in patients without lymph node metastases to approximately 50%-65% in patients with positive lymph nodes (358).

Follow-up of patients after primary treatment consists of gynecological investigation. Depending on clinical symptoms and physical findings, additional cytological or histological investigations, CT scan, MRI, or ultrasound can be performed. The aim of follow-up after initial treatment is to detect recurrent disease in an early phase to improve prognosis. It has been suggested that tumor markers may be helpful in the management of patients with cervical cancer (eg, in predicting prognosis, in selecting high-risk patients who need adjuvant treatment, and in monitoring after primary treatment). The aim of this report is to present guidelines on the possible clinical utility of tumor markers in cervical cancer, especially squamous cell cervical cancer.

To prepare these guidelines, the literature relevant to the use of tumor markers in cervical cancer was reviewed. Particular attention was given to reviews, including systematic reviews, prospective randomized trials that included the use of markers, and guidelines issued by expert panels. Where possible, the consensus recommendations of the NACB panel were based on available evidence (ie, were evidence based).

CURRENTLY AVAILABLE MARKERS FOR CERVICAL CANCER

Tumor markers that may be helpful in the management of patients with cervical cancer are listed in Table 4, together with the phase of development for each marker as well as the LOE for its clinical use. Only tumor markers for which possible clinical usefulness has been demonstrated in several studies are listed. For squamous cell cervical cancer, squamous cell carcinoma antigen (SCC) is the marker of choice. Serum concentrations of SCC have been found to correlate with tumor stage, tumor size, residual tumor after treatment, recurrent or progressive disease, and survival in patients with squamous cell cervical cancer (385-415). Carcinoembryonic antigen (CEA) and CA125 have demonstrated possible utility in patients with cervical adenocarcinoma (414-419). These guidelines focus on the use of SCC in squamous cell cervical cancer, the most prevalent histologic type of cervical cancer.

TUMOR MARKERS IN CERVICAL CANCER: NACB RECOMMENDATIONS

Table 5 summarizes the NACB guidelines for the use of SCC in squamous cell cervical cancer. Although other markers have been investigated (Table 4), based on currently available evidence, SCC seems the most useful marker in squamous cell cervical cancer (420). Detailed discussion of its use is presented here.

Table 4. Currently Available and Potentially Useful Serum Markers for Cervical Cancer

Cancer Marker	Proposed Use	Phase of Development	LOE	Reference
SCC	Pretreatment identification of high-risk group with lymph node metastases in squamous cell cervical cancer	Needs further evaluation for clinical usefulness	III	385, 391, 393, 395, 399, 408, 410, 430-434
	Pretreatment prediction of prognosis in squamous cell cervical cancer	Independent prognostic value in several studies, not validated for individualizing treatment	III	385, 389, 393, 399, 408
	Prediction of response to treatment in squamous cell cervical cancer	Needs further evaluation	IV	389, 399, 404, 405, 408, 412, 430
	Monitoring disease and detecting recurrent disease in squamous cell cervical cancer	Strong correlation with course of disease, in clinical use in some centers	III	386-388, 392, 396-398, 400-403, 405-407
CA125	Pretreatment prediction of prognosis, in particular in cervical adenocarcinoma	Needs further evaluation	III-IV	385, 417
	Preoperative prediction of the presence of lymph node metastases, in particular in cervical adenocarcinoma	Needs further evaluation	III-IV	385, 417, 433
	Monitoring disease, in particular in cervical adenocarcinoma	Needs further evaluation	IV	415, 416, 418, 419
CEA	Pretreatment prediction of prognosis	Results conflicting, needs further evaluation	III-IV	385, 407, 415, 417, 430, 567
	Preoperative prediction of the presence of lymph node metastases, in particular in cervical adenocarcinoma	Needs further evaluation	III-IV	385, 417, 433
	Pretreatment prediction of clinical response to neoadjuvant chemotherapy	Needs further evaluation	IV	430
Cytokeratins (TPA, TPS, cyfra 21-1)	Pretreatment prediction of prognosis	Needs further evaluation, results conflicting	III-IV	385, 395, 406, 568, 569
	Monitoring disease after primary treatment	Needs further evaluation, results conflicting	III-IV	419, 567, 570-574

Table 5. NACB Recommendations for the Clinical Use of SCC in Squamous Cell Cervical Cancer

Marker	Application	NACB Recommendations (2009)	LOE	Strength of Recommendation
SCC	Screening and diagnosis	No	III	A
	Pretreatment identification of patients at high risk of having lymph node metastases	Possibly useful, further study required	IV/V	C
	Predicting prognosis	Possibly useful, further study required	III	C
	Monitoring disease and detecting recurrent disease	Possibly useful, further study required	III	C

Squamous Cell Carcinoma Antigen

Biochemistry of SCC

SCC is a subfraction of TA-4, a tumor-associated antigen first described in 1977 (421). SCC belongs to the family of serine protease inhibitors (422). In most studies evaluating clinical utility, total SCC has been measured.

Molecular cloning of the SCC genomic region has revealed the presence of two genes, SCC1 and SCC2, which are both located on chromosome 18q21.3 and arrayed in tandem. SCC1 codes for the neutral isoform of SCC and SCC2 codes for the acidic isoform (423). The neutral isoform is detected in both normal epithelial cells and malignant tissues, whereas the acidic isoform is found only in tumor cells, especially those located at the periphery of the tumor. The acidic form may also be found in the sera of cancer patients with well-differentiated squamous cell carcinomas (424). It has been suggested that SCC1 and SCC2 are capable of regulating proteolytic events involved in both normal (eg, tissue remodelling, protein processing) and pathologic processes (eg, tumor progression; 425). Structurally, SCC1 and SCC2 are almost identical, differing only in their reactive site loops. The two forms, however, may have different biological functions (423,425,426).

Reference Intervals for SCC

In apparently healthy women, the 99th percentile of circulating SCC is found at a concentration of 1.9 $\mu\text{g/L}$. Most studies have adopted a cutoff point between 2.0 and 2.5 $\mu\text{g/L}$. SCC is not organ specific (for cervix) or malignancy specific. Elevated concentrations have been found in patients with squamous cell carcinomas of the vulva, vagina, head and neck, esophagus, and lung (390,427,428), as well as in patients with benign diseases of the skin (eg, psoriasis, eczema), lung (eg, sarcoidosis), liver, and kidney. Very high values (up to 18 $\mu\text{g/L}$) have been found in patients with renal failure, lung disease, and head and neck tumors (427). There is no cutoff point that is specific for cervical malignancy.

Clinical Utility of SCC in Squamous Cell Cervical Cancer: Screening and Diagnosis

SCC is not sufficiently sensitive (particularly in early-stage disease) or specific for cervical cancer for use in screening. Diagnosis in all cases is based on histopathological findings. Elevated concentrations of serum SCC are found at initial diagnosis in approximately 60% of patients with cervical cancer, when all stages are included (429). More specifically, serum SCC is elevated in approximately 24%-53% of patients with stage IB or IIA squamous cell cervical cancer, and in approximately 75%-90% of patients with advanced-stage (FIGO IIB and higher) disease (390,393-395,399,409,413,414). Pretreatment serum SCC concentrations correlate significantly with tumor stage (388,391-395,398,409,412-414) and tumor size (393-395,408,410,413,414).

NACB Cervical Cancer Panel Recommendation 1 Use of Tumor Markers for Screening and Diagnosis of Cervical Cancer

Currently available serum tumor markers, including SCC, are not recommended for use in screening or diagnosis of cervical cancer (LOE, III; SOR, A).

Prediction of Lymph Node Metastases and Treatment Planning

A number of studies have examined the utility of elevated pretreatment SCC as a marker for the presence of lymph node metastases (385,391,393-395,399,408,410,413,430-434). In patients with stage IB or IIA squamous cell cervical cancer, sensitivity of an elevated pretreatment concentration of SCC to detect lymph node metastases ranged from 60% to 87%, with specificity ranging from 41% to 91% (385,391,393,395,408,434). In a large series of 414 patients with early-stage cervical cancer, elevated pretreatment SCC, large tumor size, and lymphovascular space involvement were independent risk factors for the presence of lymph node metastases (393). In another study ($n = 401$), after controlling for stage, only high concentrations of SCC (ie, $> 10 \mu\text{g/L}$) were associated with enlarged lymph nodes shown on CT scan (399). On combining SCC (cutoff value 2.5 $\mu\text{g/L}$) with CA125 in 81 women with stage IB/IIA cervical cancer that included all histological types, a positive predictive value of 76% was found for detecting lymph node metastases or lymphovascular space involvement (433).

Several authors have suggested using higher cutoff values for SCC to identify patients with squamous cell cervical carcinoma that has spread to lymph nodes. Sensitivity of 59% and specificity of 94% with the use of a cutoff value of 4 $\mu\text{g/L}$ have been reported in 148 patients with stage IB squamous cell cervical carcinoma (410). The corresponding positive and negative predictive values were 65% and 92%, respectively. Sensitivities for lymph node metastases of 58%, 45%, and 23% using cutoff values of 2, 4, and 8.6 $\mu\text{g/L}$, respectively, have been reported in a study of 171 patients with squamous or adenocarcinoma of the cervix (431). The corresponding positive predictive values were 51%, 70%, and 100%. Negative predictive values varied between 84% and 89% (431). About 86% of the patients in a large series of 284 patients with stage IB and IIA squamous cell cervical carcinoma with SCC concentrations below 8 $\mu\text{g/L}$ showed no lymph node metastases, whereas about 65% of the patients with serum concentrations above 8 $\mu\text{g/L}$ exhibited nodal metastases (432).

The clinical performance of SCC over a range of decision levels has been found to be poor in identifying lymph node metastases, as reflected by the diagonal appearance of ROC curve (395). The authors concluded that a normal pretreatment SCC concentration cannot exclude the presence of lymph node metastases and extracervical spread, and hence is of limited use in treatment planning. Nevertheless, these studies confirm that a high pretreatment serum SCC concentration ($> 4 \mu\text{g/L}$)

significantly increases the likelihood of lymph node metastases or extracervical spread in patients with squamous cell cervical cancer (399,430-432).

It has been suggested that the pretreatment concentration of SCC can identify patients who require intensive or additional treatment and hence may be of value in treatment planning in the individual patient (393,399,433). To prevent morbidity associated with double modality treatment, for example, surgery should be offered only when there is a low likelihood of the need for adjuvant radiotherapy. Pretreatment SCC concentration, along with tumor size, was shown to be useful in predicting recurrence and the need for postoperative adjuvant therapy in a series of 99 patients with stage IB and IIA squamous cell cervical cancer (389). The value of pretreatment SCC in clinical decision-making in 337 surgically treated stage IB/IIA cervical cancer patients has also been investigated (435). The frequency of postoperative adjuvant radiotherapy was related to FIGO stage, tumor size, and preoperative SCC concentrations. In patients with normal preoperative SCC concentrations, 16% of IB1 and 29% of IB2/IIA patients had postoperative indications for adjuvant radiotherapy, in contrast with 57% of IB1 and 74% of IB2/IIA patients with elevated SCC concentrations. Serum SCC was the only independent predictor for a postoperative indication for radiotherapy. The authors suggested that SCC allows a more refined preoperative estimation of the likelihood for adjuvant radiotherapy than current clinical parameters (435).

It is not surprising that an elevated pretreatment SCC concentration is associated with the need for postoperative adjuvant therapy because elevated concentrations are strongly correlated with tumor stage, tumor size, and the presence of lymph node metastases. Therefore, pretreatment SCC concentrations might be used to individualize treatment planning, in particular in patients with low-stage squamous cell cervical cancer, but no randomized trials have yet been conducted to confirm this hypothesis.

***NACB Cervical Cancer Panel Recommendation 2
Serum SCC Concentrations in Prediction of Lymph Node
Metastases and Treatment Planning***

Pretreatment SCC concentrations may provide additional information because high SCC concentrations are associated with the presence of lymph node metastases and the need for adjuvant treatment (LOE III) and might be used to individualize treatment planning in patients with low-stage squamous cell cervical cancer, but are not recommended for routine use at this time (LOE, IV/V; SOR, C).

Prognosis

An elevated pretreatment SCC concentration has been found to be an independent risk factor of poor survival in several studies (385,393,399,408,436-438). The pretreatment SCC concentration was the only independent risk factor of poor survival in an analysis of results for 260 patients with stage IB or IIA disease (393). However, in contrast with other reported investigations, lymph node status showed no independent prognostic value in this study (393).

Another group found that SCC and CA125, in addition to stage, were significantly related to survival in the multivariate analysis of 142 patients with cervical cancer ranging from stage IA through IVB (385). It was concluded from a multivariate analysis of 102 women with locally advanced squamous cell cancer or adenocarcinoma of the cervix that an SCC concentration greater than 5 µg/L was an independent predictor of response to neoadjuvant chemotherapy and poor survival (408). A pretreatment SCC concentration greater than 10 µg/L (but not between 2 and 10 µg/L) had a significant impact on survival in a multivariate analysis in 401 patients with stage I to IVA squamous cell cervical cancer, primarily treated with radiotherapy (399). An elevated pretreatment SCC concentration > 3 µg/L was an independent prognostic factor for both recurrence-free and overall survival in a series of 129 patients with squamous cell cervical cancer (436). Median SCC concentration > 6.0 µg/L and lymph node metastases had significant independent effects on absolute survival and disease-free survival in 352 patients with stage IIB to IVA squamous cell cervical cancer (437). Finally, an elevated pretreatment SCC concentration (> 5 µg/L) identified a subgroup of high-risk node-positive patients in early-stage cervical cancer compared with node-positive patients with normal SCC concentrations (438). Multivariate analysis showed that an elevated pretreatment SCC concentration and S-phase fraction greater than 20%, correlated significantly with a worse disease-free survival (438). However, formal trials are required to substantiate these claims and to establish that aggressive treatment triggered by elevated pretreatment SCC concentrations actually improves pelvic control and survival.

***NACB Cervical Cancer Panel Recommendation 3
Serum Scc Concentrations In Prediction of Prognosis
of Cervical Cancer***

An elevated pretreatment SCC concentration has been found to be an independent risk factor for poor prognosis in several studies, but the clinical usefulness in treatment planning is uncertain. SCC is thus not recommended for routinely determining prognosis in women with cervical cancer at this time (LOE, III; SOR, C).

Use of SCC in Monitoring Response to Treatment and Early Detection of Recurrence

Results of several studies have indicated that serum SCC is potentially useful in monitoring the course of squamous cell cervical cancer after primary therapy (386-388,391,392,397-399,403,405,407-409, 412, 428). Persistently elevated and/or increasing serum SCC concentrations after treatment suggest tumor persistence or progressive disease (387,398,399,408,412-414,428). In one study, CEA and SCC marker concentrations measured 1 month after primary treatment with chemoradiation were better than pretreatment serum concentrations in predicting clinical outcome (413). Normal CEA and SCC concentrations 1 month after treatment correlated with a complete

remission at 3 months (413). In another study, patients with residual induration and/or persistently elevated SCC concentration at 2-3 months after radiotherapy had a significantly higher incidence of treatment failure (399). The authors suggested that, together with pelvic examination, SCC concentrations can indicate a need of further work-up and management (399). A pretreatment SCC concentration $> 5 \mu\text{g/L}$ was reported to be an independent predictor of response to neoadjuvant chemotherapy in a series of 102 patients with locally advanced cervical cancer (399). Patients who were unresponsive to chemotherapy had significantly higher pretreatment SCC values than those who showed complete or partial response (408). There was a correlation between post-treatment SCC concentrations and response to chemotherapy (408). None of the patients with a complete response had post-treatment serum SCC concentrations $> 5 \mu\text{g/L}$, whereas 82% of the unresponsive patients had abnormal marker values (SCC concentrations $> 2.5 \mu\text{g/L}$; 408). The overall correlation between the clinical course of the disease and the variation of SCC concentrations was 83% (408). The authors suggested that SCC might provide useful information to improve the prognostic characterization and disease monitoring of patients with locally advanced cervical cancer undergoing neoadjuvant chemotherapy (408). It has also been reported that an elevated pretreatment SCC and/or CEA concentration was useful in predicting the clinical response to neoadjuvant chemotherapy in a series of 67 patients with squamous cell cervical cancer stage IB2, IIA, or IIB (408).

Serum SCC concentration has a sensitivity between 56% and 86% and specificity between 83% and 100% for detecting recurrent squamous cell cervical cancer (386,388,392,396,398,401,407,409,412). With the use of SCC, a lead time of up to 14 months for detecting recurrent disease has been reported, with a mean or median between 2 and 6 months (386,388,396-398,400,401,403,405,407). Although SCC is suitable for monitoring the course of disease and shows a strong correlation with the clinical course, it is not yet known whether earlier detection of recurrent disease influences treatment outcome and prognosis. At most, 10% of patients with recurrent disease can be cured. Furthermore, most patients (80%) with recurrent disease have clinical symptoms (439,440). Most recurrences (about 95%) are detected by the presence of clinical symptoms or clinical examination (439,440).

The role of routine follow-up after gynecological malignancy has been reviewed (441). Only two of six published reports on the role of follow-up after cervical cancer found a survival benefit. All were retrospective case series analysis. The contribution of SCC monitoring to recurrence detection and survival in the follow-up of 225 patients with early stage squamous cell cervical cancer has also been studied (441). In five (14%) of 35 patients, serum SCC elevation was the only sign of recurrent disease. Unfortunately, all of these five patients died of disease. The authors concluded that SCC analysis resulted in earlier recurrence detection in a small proportion (14%) of the patients, but did not improve survival.

Post-treatment SCC monitoring has not been found to be cost-effective in cervical cancer because SCC monitoring does not alter clinical management and has no advantage over clinical examination in detecting local recurrence (442), primarily because most recurrent disease is detected too late for curative treatment. Nevertheless, further investigation is needed to determine whether SCC monitoring is really useful or not in clinical practice. It has been reported in a small series of patients with recurrent cervical cancer that the addition of positron emission tomography to SCC monitoring significantly increased overall survival compared with a historical group of patients who had elevated SCC concentrations as a first sign of recurrent disease (443).

***NACB Cervical Cancer Panel Recommendation 4
Serum SCC Concentrations in Post-Treatment Monitoring
of Cervical Cancer Patients***

SCC monitoring after primary treatment strongly correlates with the clinical course of disease in patients with squamous cell cervical cancer but there is as yet no clear evidence that earlier detection improves outcome. Monitoring with SCC is thus not recommended for routine use at this time (LOE, III; SOR, C).

Key Points: Tumor Markers in Cervical Cancer

The NACB recommendations for the use of tumor markers in cervical cancer are presented in Table 5. SCC is not suitable for screening or diagnosis of cervical cancer; serum SCC concentrations correlate with tumor stage, tumor size, residual tumor after treatment, recurrent or progressive disease, and survival. Highly elevated pretreatment SCC concentrations may indicate the presence of lymph node metastases or extracervical spread, but a normal SCC concentration does not exclude the presence of lymph node metastases.

Pretreatment SCC concentrations may be used to individualize treatment planning, in particular, for patients with low-stage squamous cell cervical cancer, but no randomized trials have been conducted to confirm this hypothesis. An elevated pretreatment SCC concentration has been found to be an independent risk factor for poor survival in several studies. Whether pretreatment SCC concentrations are really useful in clinical practice remains uncertain. There is no evidence that more aggressive treatment improves pelvic control and survival in patients with elevated pretreatment SCC concentrations. SCC shows a strong correlation with the clinical course and is suitable for monitoring disease after primary treatment and may therefore be useful in the management of patients. However, there is as yet no evidence that earlier detection of recurrent disease using SCC monitoring influences treatment outcome or prognosis after primary treatment.