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Report

Intra-arterial plus i.v. chemotherapy for advanced bulky squamous cell carcinoma of the buccal mucosa

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From July 1994 to December 1996, 41 patients with previously untreated, advanced bulky squamous cell carcinoma arising from the buccal mucosa (BSCC) were enrolled. All patients were males with a median age of 47 years (range 29–72). The tumor extent was stage III/IV: three of 38, T4: 85%, N2–3: 20%. Patients were initially scheduled to receive intra-arterial (i.a.) chemotherapy, followed by i.v. chemotherapy and regional therapy. The i.a. chemotherapy catheter was properly placed by external carotid artery angiography via the femoral artery. The i.a. chemotherapy consisted of cisplatin (P) 100 mg/m^2 day 1 plus 5-fluorouracil (F) 1000 mg/m^2 day 1–4, and the i.v. chemotherapy consisted of PF (10 patients) or PF plus methotrexate 200 mg/m^2 day 15 and 22 (31 patients). All chemotherapy regimens were administered at 4-week intervals. The response rate of i.a. plus i.v. chemotherapy for the primary site was 85% (35 of 41) with 29% complete remission (CR) (12 of 41). The response and CR rates of neck nodes were 82% (14 of 17) and 41% (seven of 17), respectively. The combined overall response rate was 80% (33 of 41) with a 29% CR (12 of 41). Major toxicity from i.a. chemotherapy of WHO grade $\geqslant$3 included: mucositis of infusion area (76%), hemialopecia (56%) and leukopenia (5%). Three neurologic complications of i.a. chemotherapy including one hemiparesis occurred. The median follow-up time was 47 months (range 36–66 months), and the overall survival and disease-free survival were both 34% (14 of 41). Four patients were cured with chemotherapy alone and eight patients (19.5%) were cured without surgical intervention. Using i.a. chemotherapy as a cytoreductive therapy followed by subsequent i.v. chemotherapy produces a high response rate and an encouraging degree of complete response rate in advanced bulky BSCC. However, toxicity management and catheter placement will need to be improved in order to better define the role of this therapy in advanced BSCC. [© 2001 Lippincott Williams & Wilkins.]

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Introduction

Oral cancer accounts for 4% of the cancer incidence in Taiwan.[1] Betel quid chewing is a part of traditional culture in Taiwan and is an important factor causing oral cancer in the Taiwanese.[2–4] Distinct from the picture of the Western population, squamous cell carcinoma arising from the buccal mucosa, retromolar area and soft palate (International Classification of Disease 145) constitutes 45–50% of oral cancers in Taiwan, with squamous cell carcinoma arising from the buccal mucosa (BSCC) being the representative oral cancer in betel quid chewing prevalent areas.

Despite advances in reconstructive techniques, the significant cosmetic deformity and functional impairment after surgical resection leaves many Taiwanese patients with BSCC reluctant to accept surgery. In addition, many patients present with advanced inoperable or unresectable disease. In patients with advanced inoperable or unresectable head and neck squamous cell carcinoma (HNSCC), neoadjuvant chemotherapy and definite radiotherapy improved survival compared with controls treated with radiotherapy alone.[5] However, in our previous study, patients with bulky advanced disease responded quite poorly to neoadjuvant chemotherapy.[6] The inversive relationship between local control and primary tumor volume has also been reported for radiotherapy in patients with HNSCC.[7,8] This may be due to the probability of a given tumor containing resistant

clones being a function of the mutation rate and the size of the tumor.[9,10]

The localized nature of HNSCC means that the entire local-regional tumor can usually be perfused with a single catheter into the external carotid artery and the possible regional advantage from high drug concentration for this chemosensitive tumor makes it an attractive candidate for intra-arterial (i.a.) chemotherapy. However, despite decades of clinical trials, i.a. chemotherapy still lacks an established role in the treatment of HNSCC.[11–14] The chief reasons cited for its abandonment are a high catheter complication rate and lack of evidence demonstrating its therapeutic superiority to systemic i.v. cisplatin plus infusional 5-fluorouracil (5-FU). Nevertheless, with improvements in procedural accuracy and the availability of combinations of more agents with different cell kinetic effects, i.a. chemotherapy is currently undergoing a renaissance.

The therapeutic advantage of i.a. chemotherapy in HNSCC is partly due to a tumor/normal tissue blood flow ratio that favors drug delivery to a tumor contained within the infused external carotid arteries.[15] A more bulky HNSCC has a higher tumor/normal tissue blood flow ratio and is thus more suitable for i.a. chemotherapy.[15] Since advanced bulky HNSCC responded poorly to i.v. chemotherapy and the natural course of BSCC was more localized than other HNSCC,[16] incorporation of i.a. chemotherapy into the therapeutic schedule seems an appealing approach for the treatment of advanced bulky BSCC.

However, the greatest limitation of i.a. chemotherapy for patients with advanced bulky HNSCC is that the tumor blood supply is widespread and the tumor (clinical or subclinical) usually extends beyond the territory of arteries that can be infused. These considerations suggest that using i.a. chemotherapy as an initial cytoreductive therapy followed by systemic i.v. chemotherapy may be a more beneficial approach to treat advanced bulky HNSCC. This study evaluated the therapeutic outcome of this method in the treatment of advanced BSCC.

Materials and methods

Patient characteristics

Inclusion criteria for this study were patients having histologic confirmation of squamous cell carcinoma arising from the buccal mucosa, a measurable or evaluable locoregional disease that had not crossed the midline, no distant metastasis and no prior treatment for the disease. They had an advanced bulky primary tumor (Figure 1A) and/or upper cervical lesion, which were not considered suitable for resection by surgery, or they refused surgery, and the dominant blood supply was judged by clinical examination to be derived from branches of the external carotid system. They had a WHO performance status (PS) of 0–2,

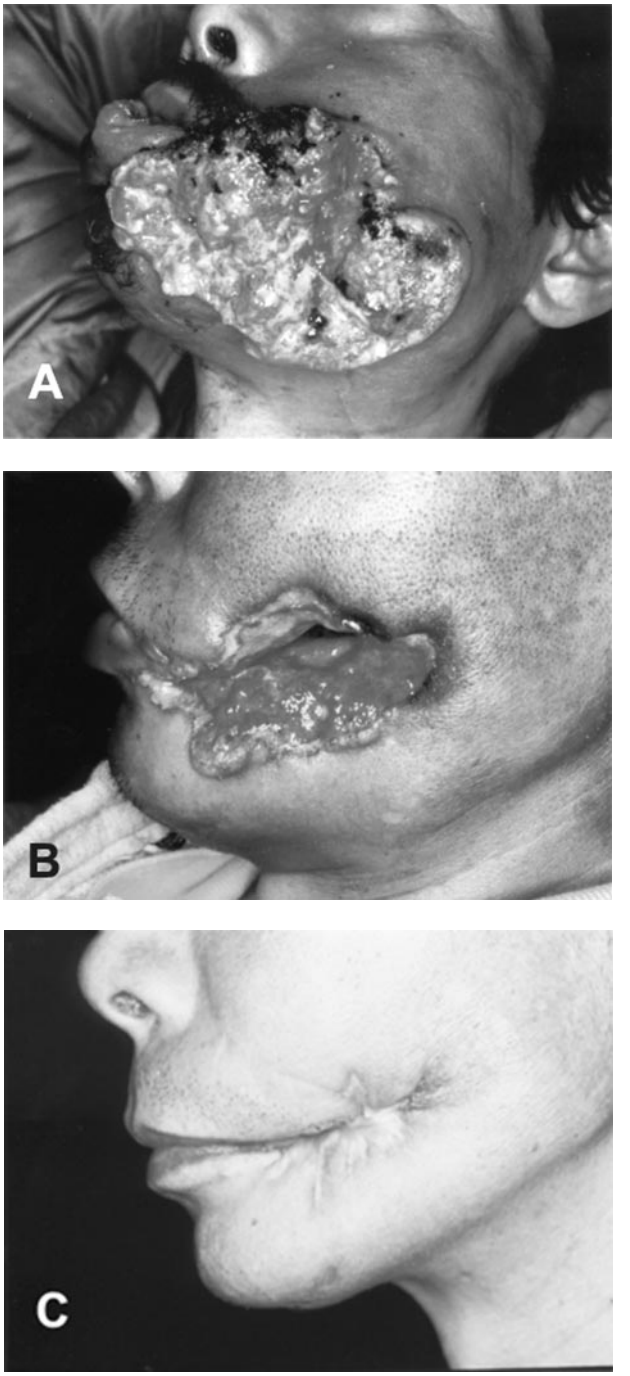

Figure 1. A patient with advanced BSCC before chemotherapy (A), which partially responded after i.a. chemotherapy (B) and disappeared completely after i.a. plus i.v. chemotherapy (C).

adequate renal function (serum creatinine <1.5 mg/dl), leukocyte count $>4000/\mu$l, platelet count $>100\,000/\mu$l, normal plasma thromboplastin and normal partial thromboplastin time. The pretreatment staging procedures consisted of history taking and physical examination, a complete blood count, and biochemistry. Routine imaging studies included chest radiography, bone scan, liver echography, and computed tomographic scan of the head and neck. The clinical stage of the tumor was determined according to the American Joint Committee for Cancer Staging as revised in 1992.[17] Patients whose tumors were not stage III or IV or who had concurrent malignancy were excluded. All patients were carefully instructed on thrombotic events and they needed to refrain from walking or moving the insertion site of the catheter during the i.a. therapy. Informed consent was obtained prior to entry into trial.

Arterial catheterization technique

All catheterizations were performed by the Seldinger technique via a transfemoral approach. The diagnostic angiographic procedure was accomplished with a 4-French angiocatheter using a digital subtraction technique. At first the common carotid artery was injected to assess the bifurcation of the carotid artery and origin of the feeding vessel. We next gently entered the proximal external carotid artery and selective external carotid images were then obtained. If the tumor was nourished by multiple feeding arteries, we positioned the catheter in the external carotid artery just proximal to the orifice of the facial artery. In cases where the lesion was nourished primarily by the facial artery, we advanced the tip of the catheter delicately into the facial artery. Thereafter, the catheter was well fixed on the groin and was connected to the vascular pump for i.a. chemotherapy.

Study protocol

Patients were treated with i.a. chemotherapy as the initial cytoreductive therapy, followed by i.v. chemotherapy and then regional therapy. The i.a. chemotherapy consisted of cisplatin plus daily $\times 4$ infusion of 5-FU. Before cisplatin administration, patients received i.v. hydration with 1000 ml of 0.9% normal saline (NS) or 5% dextrose 0.9% normal saline (D5S) at a rate of 250 ml/h for 4 h. Cisplatin 100 mg/m^2 was administered in 500 ml of NS i.a. infused over 3 h. During i.a. cisplatin therapy, mannitol 30 g was administered concurrently through i.v. infusion for 3 h to ensure an adequate urine output. After the end of cisplatin administration, patients were hydrated with another 1000 ml fluid, followed by 5-FU at 1000 mg/m^2/day continuous i.a. infusion for 4 days. All patients received antiemetic therapy with dexamethasone 20 mg i.v. bolus prior to cisplatin and metochlopramide 3 mg/kg plus diphenhydramine (Benadryl) 30 mg i.v. infusion given 30 min before and 30 min post cisplatin. Aspirin (100 mg/day) was administered during i.a. therapy to decrease the tendency toward adverse thrombotic events. The i.v. chemotherapy also consisted of cisplatin plus 5-FU (PF) or PF plus methotrexate (MTX) 200 mg/m^2/day i.v. days 15 and 22 with oral calcium folinate 15 mg q 6 h rescue for 3 days (starting at 24 h post MTX). Each cycle was repeated every 28 days.

Following chemotherapy, patients received radiotherapy and/or surgery according to the following algorithm: unresectable disease—radiotherapy alone; partial responders with resectable disease—radiotherapy and salvage surgery for residual disease or recurrent disease; non-responders with resectable disease—surgery and postoperative radiotherapy.

Criteria for response and toxicity

Toxicity was assessed according to WHO criteria. The criteria for delay in the chemotherapy cycle consisted of residual mucositis or persistent myelosuppression of grade 2 or higher on the scheduled day of chemotherapy administration.

The responses to i.a. chemotherapy and i.v. chemotherapy were evaluated separately. Clinical examination and computed tomographic scan were used to classify tumor response according to the WHO criteria.[18] A response was considered to be complete (CR) if there was no evidence of visible or palpable tumor on gross inspection and computed tomographic scan. A partial response (PR) was defined as 50% or greater decrease in the product of the longest tumor dimension and its greatest perpendicular diameter and no increase in the size of any other known disease. Stable disease (SD) was defined when 50% decrease in total tumor area could not be established nor a 25% increase in the product of the two diameters. Progressive disease (PD) was defined as the product of the two diameters showing a greater than 25% increase or the finding of a newly developed lesion. These response criteria were applied separately to the primary tumor and the clinically involved regional lymph nodes. To obtain an overall response for each patient, the responses at the primary tumor and regional nodes were combined, the worst of the two responses was taken as the combined tumor/node response.

Results

From July 1994 through December 1996, 41 patients with locally advanced bulky BSCC were enrolled in the study. Thirteen patients refused surgery for their resectable lesions and 28 patients had unresectable disease. All patients were males with a median age of 47 years (range 29–72). The classification of tumor extent was T3N0 in three patients, T3N2 in three patients, T4N0 in 21 patients, T4N1 in nine patients, T4N2 in four patients and T4N3 in one patient. Tumors were stage III in three patients and stage IV in 38 patients.

Forty-five cycles of i.a. chemotherapy and 78 cycles of i.v. chemotherapy were performed. One patient died of pneumonia 2 days after the completion of i.a. chemotherapy. One patient refused further i.v. chemotherapy after i.a. chemotherapy and another patient died of pneumonia before completing the i.v. chemotherapy schedule. Based on intent-to-treat analysis, the response rate of i.a. chemotherapy for the primary site was 93% (38 of 41) (Figure 1B) with 2% CR (one of 41). While the response and CR rates of neck lymph nodes were 94% (16 of 17) and 12% (two of 17), respectively. The combined overall response to i.a. chemotherapy was 93% with a 2% CR. The response rate after completion of i.a. plus i.v. chemotherapy for the primary site was 85% (35 of 41) with 29% CR (12 of 41) (Figure 1C), while the response and CR rates of neck lymph nodes were 82% (14 of 17) and 41% (seven of 17), respectively. The combined overall response rate was 80% (33 of 41) with a 29% CR (12 of 41).

The toxicity of i.a. chemotherapy was assessed in 40 patients. The most common drug-related toxicity (Table 1) was stomatitis limited to the infused area. Of patients, 78% experienced stomatitis of WHO grade $\geqslant 3$. Alopecia limited to the infused region occurred in 35 (87.5%) patients. Local swelling in the upper neck and parapharyngeal area with dyspnea occurred in five patients within 24–48 h of receiving therapy. This was probably due to regional irritation from the catheter or high concentration of chemotherapy drugs. This symptom was resolved by using corticosteroid and diuretics in four cases, but one patient had to terminate i.a. chemotherapy prematurely due to persistent dyspnea. Dermatitis of WHO grade 2–3 on the injection side was observed in 22 (55%) patients and regressed over the ensuing 2 weeks after topical therapy.

Table 1. Toxicity of chemotherapy (% of patients)

		WHO grading				
		0	1	2	3	4
Leukopenia	i.a.	79	5	11	5	
	i.v.	70	11	16	3	
Thrombocytopenia	i.a.	97		3		
	i.v.	81	3	13	3	
Nausea and vomiting	i.a.	61	17	20	2	
	i.v.	33	26	31	10	
Stomatitis	i.a.	10	2	15	27	46
	i.v.	18	26	18	33	5
Dermatitis	i.a.	16	28	41	15	
	i.v.	100				
Renal	i.a.	100				
	i.v.	82	11	7		

There were three catheter-related complications. One patient experienced unilateral reversible seventh cranial nerve palsy. One patient developed numbness of the arm contralateral to the infusion side on the first day of i.a. chemotherapy that resolved within 24 h. The third patient suffered a seizure on the first day of i.a. chemotherapy, which left the sequel of permanent hemiparesis despite immediately stopping i.a. chemotherapy. Brain computed tomographic scan revealed infarction of the territory of the middle cerebral artery.

The i.a. chemotherapy was terminated prematurely in another two cycles due to catheter occlusion. The unfinished i.a. chemotherapy drugs were reinstated by i.v. infusion.

The toxicity related to the i.v. chemotherapy is listed in Table 1. There were more episodes of vomiting, renal insufficiency and thrombocytopenia than during i.a. chemotherapy.

Of the 38 patients who completed the i.a. plus i.v. chemotherapy schedule, five complete responders to chemotherapy refused radiotherapy and one non-responder received herbal medicine therapy only. The regional therapies for the remaining 32 patients were radiotherapy in 23 and radiotherapy followed by surgery for residual or recurrence disease in nine.

The median follow-up time of the entire group was 47 months (range 36–66 months) and the median survival was 13.3 months. The overall survival (also the disease-free survival) for the resectable and unresectable diseases was 46% (six of 13) and 29% (eight of 28), respectively. The entire group had a survival rate of 34% (14 of 41) (Figure 2; by the Kaplan–Meier method). Four patients were cured by chemotherapy alone, and had follow-up durations of 76, 64, 57 and 53 months till now. Twenty-seven patients died. Death was due to pneumonia with premature death in two patients, local and metastatic disease in 22 (54%) patients, second malignancy in one patient, and other conditions with unknown cancer status in two patients.

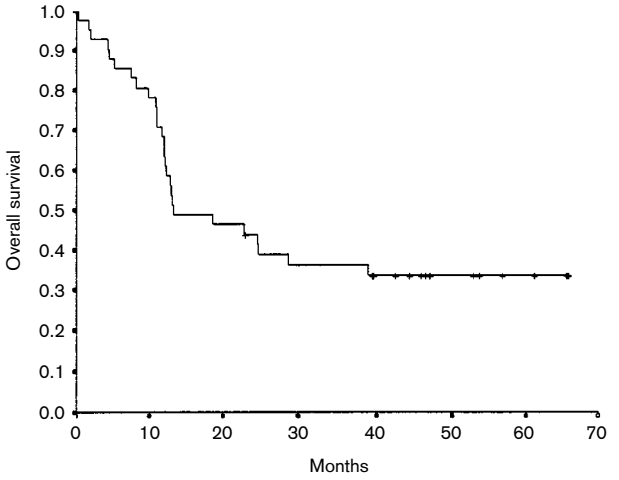

Figure 2. Overall survival for all eligible patients.

Discussion

Our study had several distinctive features. Studies of i.a. chemotherapy for HNSCC usually use single agents with short-term infusion. Because tumor cell populations are asynchronous in the phases of the cell cycle, and local vasoconstriction may result in a tumor blood flow which varies with times, prolonged arterial infusion may provide theoretical advantages.[19] Cisplatin plus daily × 5 infusion of 5-FU (FP) was an effective and the most commonly used chemotherapy for HNSCC. Theoretically, use of cisplatin plus 5-FU through i.a. infusion may enhance the therapeutic effect compared to short-term infusion of a single agent.

How much of a pharmacologic advantage if any is gained by the use of i.a. cisplatin and 5-FU is unclear. Cisplatin by the external carotid route had been shown to increase the local concentration compared with the i.v. drug.[20,21] A dose-response to cisplatin in HNSCC has also been suggested.[22] The pharmacokinetics of i.a. 5-FU have mostly been studied with hepatic arterial infusion. However, the relationship described by Collins,[23] combined with the assumption of a 100 ml/min flow rate in the external carotid artery, suggest there is a theoretical regional advantage ([drug] target region/[drug] systemic) of 40 for 5-FU and 4 for cisplatin.[24] The hemialopecia, ipsilateral dermatitis and ipsilateral stomatitis found in this study, which have not been reported in systemic cisplatin plus 5-FU, suggest the possibility of increased cytotoxic effects against local normal tissue as well as tumor.

In this trial, i.a. chemotherapy was used as initial cytoreductive therapy only and was then followed by subsequent cycles of i.v. chemotherapy. Large tumors are less well vascularized and a greater number of hypoxic cells are present which are less chemosensitive. Induction i.a. chemotherapy may convert a large tumor to a small one and may allow standard i.v. chemotherapy to be more effective. Another rationale to combine i.v. chemotherapy was that the arterial supply of advanced bulky HNSCC is usually widespread and tumor extending beyond the territory of arteries could be infused. Tumor may then have progressed outside the infused area, resulting in only a brief response duration of i.a. chemotherapy. Forastiere *et al.*[19] used cisplatin plus 5-fluorodeoxyuridine (FUDR) i.a. infusion and reported that 33% of tumors progressed outside the infused volume while local disease was controlled. A combination of cytoreductive i.a. chemotherapy followed by i.v. chemotherapy may enhance the i.v. chemotherapy effect and improve the risk of disease progression outside the infused volume. In our trial, one case of marginal failure and two cases of lung metastasis were identified during radiotherapy for a responsive primary tumor area.

Whether the use of more cycles of i.a. chemotherapy can enhance the local tumor control remains unclear. In this series, three patients had local tumor response to i.a. chemotherapy but had no further regression during subsequent i.v. chemotherapy. They received another cycle of i.a. chemotherapy but no response was observed. Forastiere *et al.*[19] also described a lack of CR to additional i.a. chemotherapy in their patients. This may due to the presence of resistant clones following initial high-dose therapy from i.a. chemotherapy limiting response to further i.v. chemotherapy or i.a. chemotherapy. These clinical observations suggest that further cycles of i.a. chemotherapy may not enhance the therapeutic outcome.

Local toxicity, specifically stomatitis, was dose-limiting with this treatment combination. BSCC is the representative oral cancer related to betel quid chewing and betel quid-related mucosal damage led to a high incidence of severe stomatitis even in conventional i.v. cisplatin plus 5-FU chemotherapy.[6,20] As was expected from the study design, 46% of patients experienced WHO grade 4 mucositis. The required recovery time for stomatitis may be up to 3–4 weeks in some patients and these patients may also need more intensive supportive care. Identification of effective agents that are not toxic to skin and proliferating oral mucosa is needed to fully exploit this model of drug delivery.

Thromboembolic events are the most catastrophic event of i.a. chemotherapy in HNSCC. The develop-

ment of thrombotic events is related to several factors, including endothelial damage by the catheter tip, endothelial damage from a high concentration of therapeutic agent, induction of turbulence by the catheter and thrombotic potential of patients. Addition of low doses of heparin (1000–5000 U/day) to the infusate and a single coated aspirin per day were used to decrease the tendency of patients to develop adverse thrombotic events during the use of radiologic catheters.[11,13] However, 5–10% incidence of central nervous system complications has been reported with this therapeutic combination.[13,26] The convulsion and hemiparesis which developed in one of our patients occurred soon after the beginning of i.a. chemotherapy. Retrograde flow of chemotherapy agents and spill into the internal carotid circulation,[27] or inadvertent dislodgment of a pre-existing atherosclerotic plaque during the radiologic catheter placement may account for this complication.[28] The seventh cranial neuropathy which developed in our patient did not appear to have been embolic in origin and may have been due to cisplatin-based neurologic toxicity because nerve problems did not occur immediately, but developed within 3 days of the chemotherapy.[29]

When the femoral artery is used for percutaneous insertion of angiographically positioned catheters, there is rarely sufficient catheter tip stability. Catheter movement generated by motion of the insertion site is an important factor in catheter tip instability. Therefore, our patients were instructed to refrain from walking or movement of the insertion site during the course of the i.a. therapy. This was quite inconvenient to the patients and reduced their compliance. Since the i.a. catheter needed in this trial was only used for short-term access, the use of an angiographic catheter via the brachial artery was preferable to a surgical placement of a catheter in the future trial.

The baseline survival for patients of resectable stage III and IV HNSCC following standard therapy with surgery and/or radiotherapy is approximately 40% at 5 years; whereas the unresectable disease the survival is closer to 20%.[30,31] We had a survival rate of 46% (six of 13) for the resectable disease and 29% (eight of 28) for the unresectable diseases. The role of i.a. chemotherapy in the treatment of advanced bulky BSCC still remained to be defined. However, based on our results, a high response rate, particularly, and an at encouraging degree of CR rate was seen in advanced BSCC given the fact that only one cycle of i.a. chemotherapy was added to the conventional i.v. chemotherapy. It is also important to stress that eight out of the 41 patients (18.5%) who entered in the study were cured without surgical intervention. This indicates that a minority of patients with advanced tumor may well have actually benefited from this therapy in avoiding morbid and extensive surgery, and may represent a more favorable situation regarding the quality of life.

Conclusion

Using i.a. chemotherapy as a cytoreductive therapy followed by subsequent i.v. chemotherapy produced a high response rate, particularly, and an at encouraging degree of CR rate in advanced bulky BSCC. A minority of patients with advanced tumor may well have actually benefited from this therapy in avoiding morbid and extensive surgery. However, the catheter placement will need to be improved in order to better define the role of this therapy in advanced bulky BSCC.

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