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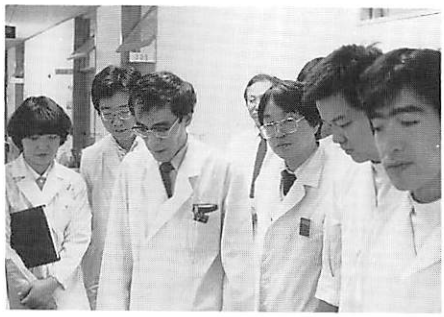
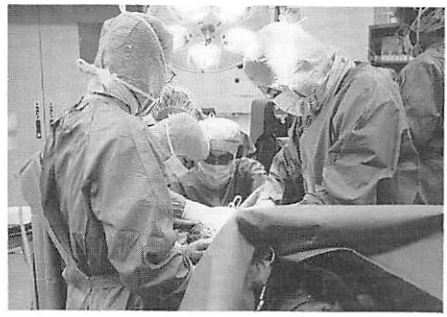
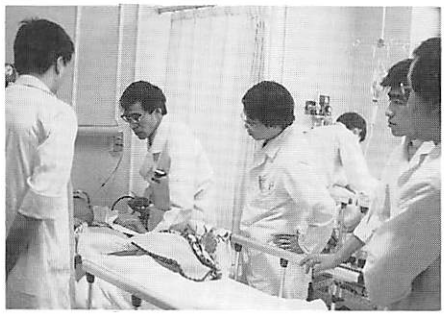
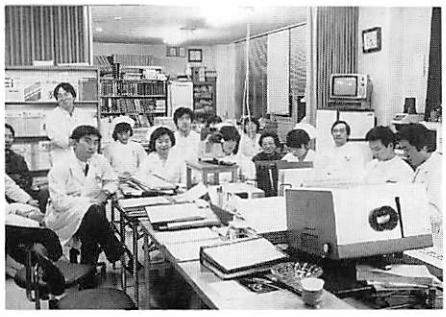
Surgery




DEPARTMENT OF SURGERY

GENERAL SUMMARY

Just ten years have passed since the Department of Surgery was set up in 1977 as an addition to the Internal Medicine. In 1985 Prof. Mai was promoted to Chief of Surgery and has served with the eager cooperation of the members of this department. They have devoted themselves to the early detection of cancer, and to improvement of treatment of cancer patients, especially cancer of the gastrointestinal tract. Approximately 10143 visits have been recorded annually in the out-patient service of surgery, and 245 patients with cancer were admitted to the hospital in 1986. During the last ten years we have carried out gastrectomy on 850 cases with gastric cancer, including approximately 40% of early gastric cancer confirmed in the mucosal and submucosal layer, with an excellent survival rate of over 95%. Recent dietary changes to western style are bringing us new problems of colonic cancers. From this aspect, the main activities during recent years have been focussed on clinical and basic research in surgical oncology of the gastrointestinal tract. One project concerns light and electron microscopic studies on the pathogenesis of gastric carcinoma by the team of Prof. Nakanishi, 1st Dept, Faculty of Pathology. Dr. Ooi made an immunohistochemical study of endocrine differentiation of gastric adenocarcinoma. He suggests that chromogranin A is a reliable marker for gastric carcinoma with endocrine differentiation and heterogeneous expression of some polypeptide hormones and serotonin. Dr. Minamoto clarified the pathogenesis of the desmoplastic reaction of scirrhous gastric carcinoma by light and electron microscopic immunohistochemical studies using collagen type specific antibodies. According to his study type V collagen, as well as type I and III collagens, are involved in the formation of desmoplastic stroma, and these collagens are actively synthesized by fibroblasts and myofibroblasts in some interaction with the invading carcinoma. Another project promotes the study of cancer biology and pre-clinical application in human cancer therapy. Dr. Takahashi and his associates had already reported the effect of a conjugate of MMC and an antibody to human AFP on the human AFP producing stomach cancer xenotransplanted into nude mice, i.e. missile therapy. They are also interested in cancer chronology for the determination of biological malignancies by using doubling time in individual patients or in human tumor transplanted into nude mice. This is being done through the cooperation of Prof.Kusama, Showa Univ. He has recently investigated tumor growth and the chemosensitive difference between primary tumor and metastases of the same patients transplanted into nude mice, showing heterogeneity among them. As a therapeutic experiment, Dr. Ohta studied the antitumor effect by combination therapy with IFN-β and MMC on xenotransplanted human gastric and colonic cancer into nude mice. Regarding the chemosensitivity test Dr. Sawaguchi and Dr. Suga developed studies with the DNA histogram involving the tumor cell cycle, using flowcytometry (FCM). This method should be useful in clinical practice in the near future.

(1) Study on intramucosal infiltrating modes of two histological types of gastric microcarcinoma and their diagnostic ability.

T. Itoh, M. Mai and A. Ooi

The term microcarcinoma in this article is defined as a tumor of less than 5mm in the largest diameter and full suggestions of clinico-pathological correlations to study incipient phase of cancer developement, intramucosal infiltrating modes and their diagnostic ability by endoscopy. During the last 12 years we have experienced 53 lesions of gastric microcarcinoma in 49 cases, encountering 16 lesions in 14 cases with undifferentiated microcarcinoma and 37 lesions in 35 cases with differentiated microcarcinoma. Out of 16 lesions of the undifferentiated type, 9 were preoperatively diagnosed by endoscopic biopsy, while the remaining 7 lesions were incidentally detected by serial sections of the resected stomach. On the other hand, differentiated type carcinomas of 9 lesions were also preoperatively diagnosed out of 37 lesions, and another 28 lesions were detected as incidental findings. From the viewpoint of correlation between macroscopic findings and histological types, the former had mainly IIb and IIc type appearance in both undifferentiated and differentiated carcinomas. In undifferentiated carcinoma, the characteristic feature of the endoscopic finding was vague redness. The early infiltration of the undifferentiated microcarcinoma was limited to areas in or around the neck zone of the ordinary gastric mucosa surrounded by intestinal metaplasia of slight degree on the adjacent mucosa. In proportion of enlargement in diameter, carcinoma invaded the superficial surface in places with slight erosion, involving the whole mucosa with eroded depression, and superficial ulceration in the affected area of micro-IIc. While differentiated microcarcinoma occupied the whole mucosa in the early stage, bearing no relation to its size, there was atrophy of glands just below the microcarcinoma, and intestinal metaplasia of ordinary surrounding mucosa was present in most cases. Especially, as undifferentiated carcinoma having arisen from the neck portion of ordinary mucosa with mild atrophy, diagnostic ability of the dye endoscopy was superior to conventional endoscopy.

Fig. 1. Growth mode of undifferentiated microcarcinoma of the stomach.

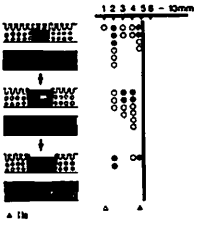


Fig. 2. Growth mode of differentiated microcarcinoma of the stomach.

(2) Growth patterns and prognosis in early gastric cancer with reference to the risk factors of recurrence.

T. Asai, H. Ueda, T. Minamoto and M. Mai

Early gastric cancer treated surgically in Japan has shown an extremely favorable prognosis, with a 5-year survival rate greater than 90% both for mucosal and submucosal cancers. However, the clinicopathologic characteristics of cases showing recurrence have not been fully investigated. Therefore we studied the clinicopathologic features of early gastric cancer to elucidate the risk factors relating to its recurrence. Among 730 cases of gastric cancer resected in the last 11 years in our institute, 299 cases (41% of all cases) were diagnosed as early cancer. These cases included mucosal (60%) and submucosal (40%) cancers showing a 10-year survival rate of 100% and 95% respectively. Although 24 patients have died, only 4 cases suffered death from recurrence (Table). The morphological characteristics of these cases are as follows; 1) an elevated lesion with or without central depression, massively invading the submucosal layer in gross appearance and 2) well differentiated carcinoma with a high incidence of lymphatic and/or blood vessel involvement on histological examination. The clinical course of recurrence was hematogenic metastasis to the liver or lung. According to the analysis of the growth patterns in early gastric cancer reported by Inokuchi et al, they were classified into the small mucosal type, the superficially spreading type (super type) and the penetrating growth type (pen type). The small mucosal and super types had an excellent prognosis, the 10-year survival rate being about 90%. In contrast, the 10-year survival rate of 65% in the penetrating pen type was rather poor, equivalent to that of advanced cancer. The pen type cancer is characterized by a predominantly elevated lesion usually revealing well differentiated carcinoma, a relatively high incidence of vessel invasion and lymph node metastasis, and poor prognosis after surgery due to early recurrence in the form of liver metastasis. The four cases with recurrence in our institute were considered to correspond to the pen type early cancer. Therefore, we must give greater attention to this type when developing a surgical and therapeutic approach.

Table. Recurrent cases of early gastric cancer

	Case	Age	Sex	Type	Hist.	Depth	Stroma	ly	v	n	Prog.
1	S.T.	66	M	11a + 11c	tub1 + tub2	sm	inter.	2	0	1	4Y Lung meta.
2	T.M.	70	M	1 + 11a	pap	sm	med.	1	1	1	2Y Lung meta.
3	T.Y.	79	M	11c + 11a	tub1	sm	med.	0	0	–	2Y6M Liver meta.
4	S.Y.	52	M	11c + 11a	tub2	sm	inter.	3	1	2	1Y4M Liver meta.

(3) Gastric adenocarcinoma with endocrine differentiation. An immunohistochemical and immunoelectron microscopic study.

A. Ooi, M. Mai and I. Nakanishi

It is well known that some conventional gastric adenocarcinomas contain endocrine differentiated cells as an integral tumor component. However, there has been no general accordance about their frequency detected by silver impregnation methods. In the present study we employed immunoperoxidase method using antisera against chromogranin A(CGA), as a novel endocrine cell marker, in order to detect those cases from a large series of gastric adenocarcinomas accumulated in our institute, and we evaluated the frequency, the correlation with histologic types and possible multihormone production on those cases. CGA-positive cells were detected in 28 out of 212 cases, although the number of positive cells varied in individual cases. No definite correlation could be recognized between the appearance of endocrine cells and histologic features classified by their dominant patterns. The 28 cases were broadly divided in 3 groups according to the distribution of CGA-positive cells: 12 cases in which scattered CGA-positive cells were located in neoplastic glands: 6 cases of scirrhous carcinoma in which CGA-positive cells or cell cords were separated by an increase in fibrovascular tissue: 10 cases in which the positive cells were present focally or in large clusters. By further immunostaining using antisera against a variety of peptide hormones and serotonin, these CGA-positive cells were proved to be serotonin, somatostatin, gastrin, glucagon or PYY-positive. Metastasis to regional lymph nodes were observed in 15 cases, and 10 of these cases contained CGA-positive cells. They had almost the same composition of amine and peptide hormones to those of the primary tumors. In 9 cases in which electron microscopic observetion was done, neuroendocrine type-dense core granules were observed in the cytoplasm of the carcinoma cells, and in 6 of them CGA-immunoactivity could be confirmed in the secretory granules by the immunogold technique (Fig.). In conclusion, CGA was a reliable marker for gastric carcinoma with endocrine differentiation, and the frequency detected by this marker, 13.2% (28/212), meant that endocrine differentiation is not a rare phenomenon in gastric adenocarcinoma.

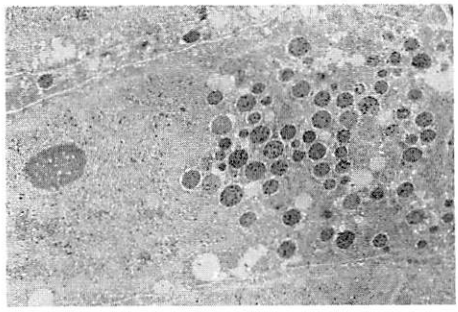


Figure. Immunoelectron micrograph of the cancer cell showing secretory granules labelled by 15 nm particles for chromogranin A.

(4) Early gastric carcinoma in patients with a Billroth II partial gastrectomy.

H. Ueda and M. Mai

Partial gastrectomy has been performed rather frequently since the 1950s for the treatment of benign gastroduodenal diseases, especially peptic ulcer in Japan. Recently a high incidence of newly arising carcinoma in the remnant stomach, or stump carcinoma, has been recognized among those persons who had undergone gastrectomy. As the etiologic factor of stump carcinoma, high frequency bile reflux following gastrectomy has been cited as promoting carcinogenesis in special relation to atrophic hyperplastic gastritis with partially cystic dilatation, i.e. gastritis cystica polyposa (GCP:Littler et al.), but it remains unclear precisely what factors in these high risk cases are operative in gastric mucosa of remnant stomach.

The histological changes in the neighboring mucosa apart from the minute lesion of gastric stump carcinomas were studied by examination of the resected remnant stomach, and the mucosal changes in the stump were studied by endoscopic biopsy specimens, including the relationship between reconstruction methods of Billroth I and II, following gastrectomy. Thirteen cases (1.6%) of remnant gastric carcinoma out of 803 cases involving consecutively resected stomach for gastric carcinoma were detected at our Institute. Among them 5 cases were early stump carcinoma. Clinical data and pathological findings are summarized in Table. In all cases exhibiting early stump carcinoma, histology disclosed poorly or moderately differentiated adenocarcinoma associated with GCP. In order to investigate the histological changes in the remnant stomach, endoscopic biopsies were performed in 50 patients with Billroth I (38 cases) or Billroth II (12 cases) anastomosis for benign or malignant diseases. Mucosal atrophy of varying degrees was seen in almost all cases of the resected stomach and foveolar duct hyperplasia, and cystic dilatation of the gland was commonly seen in a Billroth II anastomosis. Results were 90.9% and 63.3% respectively as compared to these of 63.2% and 18.4% in a Billroth I.

From our clinical and pathological findings we must be especially aware that stump carcinoma may occur frequently in patients who have been gastrectomized.

Case	Age	Sex	Type	Site	Depth	Hist.	Size	Gastritis	Billroth	Interval
1	78	M	minute (IIc)		m	por	0.3cm	atrophic hyper-plastic	II Braun(-)	25Y
2	54	M	minute (IIb)		m	sig	0.2cm	〃	II Braun(-)	33Y
3	44	M	minute (IIc)		m	por	0.4cm	〃	II Braun(-)	13Y
4	64	M	IIb		m	tub_2	3.0X0.5 cm	〃	II Braun(-)	15Y
5	65	M	IIb		m	tub_2	5.0X1.5 cm	〃	II Braun(-)	15Y

Table. Patients with early gastric stump carcinoma

(5) Desmoplastic reaction of gastric carcinoma. A light and electron microscopic immunohistochemical study by using collagen type-specific antibodies.

T. Minamoto, M. Mai, A. Ooi and I. Nakanishi

The desmoplastic reaction in gastric carcinoma was investigated light and electron immunohistochemically by using monospecific antibodies to collagen types. In addition to type I and III collagens, type V collagen was constantly recognized in the fibrous stroma, increasingly of the scirrhous carcinoma. Type IV collagen, one of the major components of basement membrane, delineated the basement membrane of carcinoma nests linearly with occasional discontinuity. However, in the scirrhous carcinoma, it was present an unusual localization along the thick bundles of collagenous fibers. Immunoelectron microscopic studies revealed that type I and III collagens were distirbuted on the collagen fibers and type V collagen was stained in the margin of these fibers. These antibodies also reacted in the rough endoplasmic reticulum of fibroblasts or myofibroblasts in a few cases (Figure). Type IV collagen was localized in the periphery of smooth muscle cells, endothelical cells of collapsed capillaries and myofibroblasts scatterd in the stroma of scirrhous carcinoma, and it seemed to correspond to the unusual localization on light microscopic observation. Carcinoma cells were not reactive with any antibodies examined. These findings suggest that type V collagen, as well as type I and III collagens, is involved in the formation of desmoplastic stroma, and that these collagens are reactively synthesized by fibroblasts and myofibroblasts in some interaction with invading carcinoma cells. In terms of the formation of desmoplastic stroma, the previous proposal that matrix collagens are synthesized by carcinoma cells themselves is presumed to be negated.

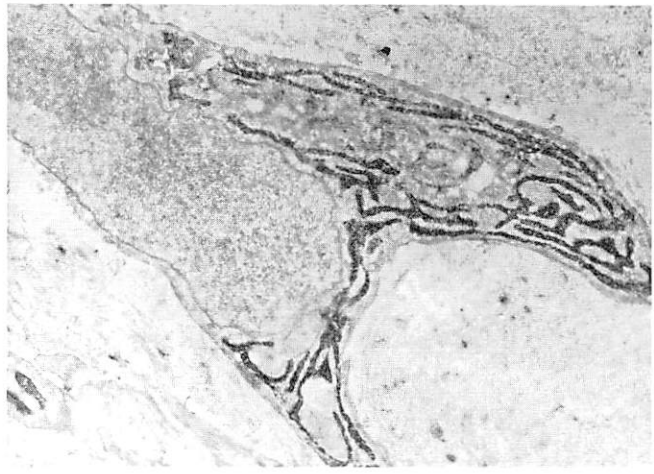


Figure. Immunoelectron microscopic localization of type V collagen on gastric scirrhous carcinoma. Type V collagen is stained along the collagen fibers and its immunoreactivity is also recognized in the rough endoplasmic reticulum of the myofibroblast.

(6) An immunological study on tumoricidal activity of peripheral blood lymphocytes in patients with gastric cancer.

M. Ueno, M. Mai, N. S. Sakai and S. Koshimura

In the present study we examined tumoricidal activity of peripheral blood lymphocytes (PBL) of gastric cancer patients in order to evaluate an enhancing effect of the immune system for cancer patients, using NK activity stimulated by rIL-2 and OK432-induced-IL-2 production. The subjects were 32 patients with gastric cancer who had undergone gastrectomy at our Institute over the past two years (1984-1986).

Results: Enhancing effect of NK activity stimulated by rIL-2 in PBL; As shown in Fig. 1, the NK activity stimulated by rIL-2 was significantly enhanced in both the healthy adult (control) and in gastric cancer patients of stage II&III. Consequently, rIL-2 stimulation of PBL resulted in a significant increase in NK activity even in advanced staged patients, suggesting the usefulness of IL-2 for immunotherapy (Fig.1). IL-2 production is stimulated by OK432; In order to clarify the insight mechanism for OK432 we examined IL-2 production stimulated with OK432 incubated for 48 hours of PBL in gastric cancer patients. IL-2 production showed a tendency to decrease in relation to staging, but not significantly. In each stage IL-2 production varied markedly from case to case in the healthy adult cancer patient. A high responder group which exceeds 10 unit/ml were encountered appoximately 50% in healthy adults and 33% in cancer patients (Fig.2). Our result suggests that the mechanisms is probably dependent upon the immune responsiveness regulated by individual variation. This result indicates that IL-2 production stimulated by OK432 would be a more useful indicator in predicting the efficacy of OK432.

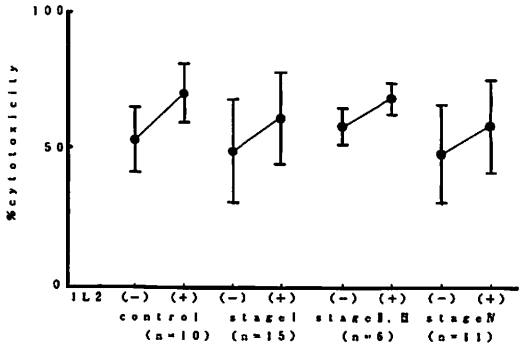


Fig. 1. NK activity by IL2 stimulstion of limphocyts in each stages gastric cancer.

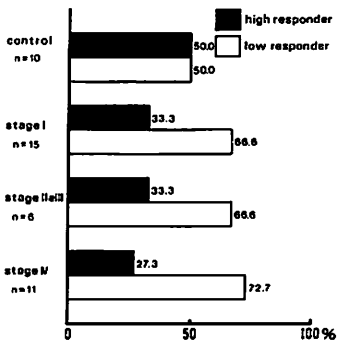


Fig. 2. Response rate (%) of OK432 stinulated IL2 production in gastric cancer. High responder indicates the case who exceeded 10 U/ml.

(7) An evaluation of the immune response induced by OK432 for gastric cancer.

M. Mai, M. Ueno, N. S. Sakai and S. Koshimura

Particular attention has been paid by pathologists to the prognostic significance of lymphatic and other cellular reactions occurring in tumor stroma. According to our statistical data, patients with lymphoid stroma type gastric cancer had a 83.6% cumulative disease free interval at five years compared to all patients with ordinary stroma whose corresponding disease free interval was 40.3%. From our clinicopathological view point there is no doubt that tumor infiltrating lymphocytes might play an important role against the host defence mechanisms with a special reference to the immunologic capacity. In order to induce infiltrating lymphocytes in the tumor stroma, OK432, a streptcoccal preparation, was endoscopically injected (using an injection needle) into cancerous tissue and its boundary at ten sites 10 days prior to surgery. The dose was 10KE (Klinische Einheit) dissolved in 10ml of physiological saline. In 14 out of 18 cases with intratumoral injection of OK432 infiltrating lymphocytes appeared which proved to be positive for OKT3, 4 and Leu7 by the enzyme labelled antibody method with monoclonal antibody of lymphocyte subsets. Interestingly, in half of the 10 cases with long term injection of OK432, gastric tumor showed morphological improvement such as disappearance, shrinking or flattening of the cancer crater. Our result led to the suggestion that cytotoxicity of tumor infiltrating lymphocytes might be induced by OK432 probably by intervention of IL-2 production mechanisms. In cases of long term injection for the non-operation group, half of them showed morphological improvement with favorable results, and in some a rapid response to OK432 was observed after two or three injections. However, we also noticed marked variation in the responce against OK432. In conclusion, OK432 can augument immunity against tumor cells in the high responder group.

Table. Morphological improvements in cases treated by endoscopic injection of OK432

Case No.	Age	Sex	Gross	Histology	Reason for nonresection	Total dose (KE)	Systemic therapy	Morphological changes	Survival period in months (Outcome)
1	63	M	Borr 2	tubular adenoca.	poor risk (lung Tbc)	900KE	Tegafur	Disappearance of tumor Biopsy: neg. for cancer cells	27(alive)
2	54	M	Borr 3	tublar adenoca.	multiple liver metastasis	100KE	FAM-OK432	Flattening of marginal elevation Shrinking of ulceration	8(died)
3	57	M	Borr 2	poorly diff. adenoca.	poor risk (lung Tbc)	70KE	Tegafur	Flattening of elevation Shrinking of tumor → Resection	12(alive)
4	80	F	Borr 3	tubular adenoca.	high age	120KE	Tegafur	Shrinking of ulceration	8(alive)
5	73	F	Borr 3	tublar adenoca.	poor risk (chr. hepatitis)	60KE	MTX.5FU	Flattening of elevation	7(alive)

(8) The growth rate of human esophageal carcinoma and its clinical significance.

T. Ogino, Y. Takahashi and M. Mai.

It is of importance to understand the history of esophageal carcinoma due to its high potential in biological malignancies. Therefore, in order to know the tumor growth rate of esophageal carcinoma, we made retrospective follow-up studies of eleven cases examined by the barium X-ray technique. The period of observation was from 5 to 26 months at the Tokyo Women's Medical College and the Depertment of Surgery, Cancer Research Institute, Kanazawa University.

The histological depth of carcinoma invasion in 11 cases showed submucosal invasion in 5 lesions, and over the muscle layer (mp) to the adventitia (al-3) in 9 lesions. Radiologic appearance of esophageal carcinoma was classified into three types, (1) single type (solitary focus not surrounded by superfically spreading lesions), (2) mixed type (surrounded by superficially spreading lesions), (3) multicentric type (focus accompanied by intramucosal metastasis or multiple primary cancer). We calculated doubling time (DT) by measuring the longitudinal length of carcinoma invasion employing the following formula, i.e.
$DT=1/3.\ \log 2t/\log\alpha 2-\log\alpha 1$. The results are as follows.

1) The lesions of single type and multicentric types showed exponential growth, but the growth rates of lesions of mixed type were indistinct.

2) In cases of submucosal carcinoma (sm, 3 cases) the doubling time (DT) averaged 4.4±0.3 months. On the other hand DT in advanced carcinoma (mp-al, 3 cases) averaged 3.9±1.5 months. The growth rates of submucosal and advanced carcinoma were similar to those for overall esophageal carcinoma.

3) The DT of gastric carcinoma is from one to twenty times as long as the DT of esophageal carcinoma, and the DT of colonic carcinoma is from two to twelve times as long as the DT of esophageal carcinoma.

4) The growth rate of esophageal carcinoma was more rapid than that of gastric and colonic carcinoma. Therefore, our data indicates that there is a positive correlation between tumor growth rate and its survival. We must add that there might be difficulty in early diagnosis because of the rapid growth of esophageal carcinoma.

Table. Esophageal carcinoma following up retrospectively depth, histological findings and doubling time (DT)

Case No.	Depth	Histologic Type	Follow-up Period	Doubling Time	Average
1	sm	well	7 m	4.5 m	
2	sm	poor	7 m	4.7 m	4.4±0.3m
3	sm	poor	8 m	4.1 m	
4	mp	mod	5 m	2.1 m	
5	al	well	26 m	3.9 m	3.9±1.5m
6	advanced ca. (not resected)	well	18 m	3.7 m	

sm=submucosa. mp=proper muscle. al=adventitia. well=well diff. squamous cell carcinoma. mod=moderately diff. squamous cell carcinoma. poor=poorly dif. squamous cell carcinoma. m=months

(9) Chemosensitive difference between primary tumor and metastases of the same patient transplanted into nude mice.

Y. Takahashi, M. Ueno, T. Ohta and M.Mai.

A knowledge of the biological defference in cancer patients between primary tumor and metastatic tumor is of importance in establishing cancer therapy. However, detailed studies similar to this have never been found. In order to study the biological characteristics of metastatic tumor, we succeeded in establishing experimental models of nude mice transplanted from primary tumor (P), lymph node metastases (N) and hepatic metastases (H) of the same cancer patient. In this report we investigated the difference in chemosensitivities, ie, heterogeneity among three lines of human colonic cancer (KHC-P, KHC-N and KHC-H) to Mitomycin C (MMC) and to a combination of MMC and UFT (UFT-M). One of the schedules for the administration of MMC was 3mg/kg every 4 days, while others were 0.5mg/kg of MMC every a week in addition to intragastric administration of UFT for four weeks. Tumor volume was measured every four days and compared in each line. Response to MMC resulted in sensitivities in KHC-P and KHC-N, but MMC was not sensitive in KHC-N. After a while, response to UFT-M showed that KHC-N and KHC-H were chemosensitive but KHC-P was not sensitive. In other word, drug sensitivities to MMC and UFT-M were different within each line, in spite of the fact that the tumors were all originated from the same patient. These results suggest that the human tumor shows heterogeneity among primary tumor and metastases from the standpoint of sensitivities to anti-cancer drugs.

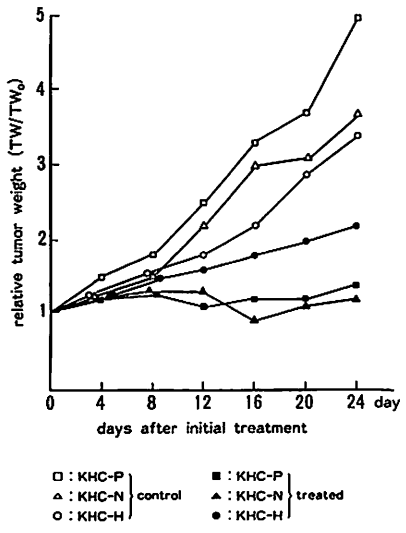


Fig. 1. Response to MMC

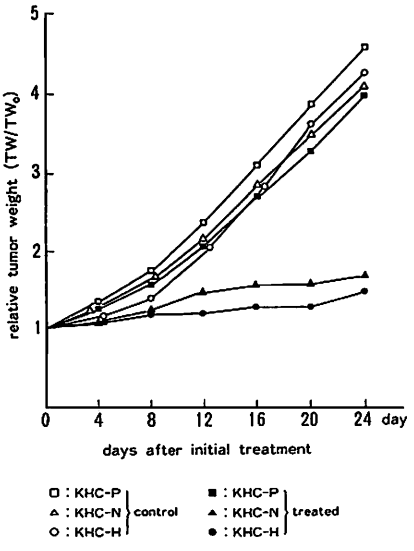


Fig. 2. Response to UFT-M

(10) Antitumor effect of combination therapy with IFN-β and MMC on xenotransplanted human colonic cancer into nude mice.

T. Ohta, Y. Takahashi and M. Mai.

Although it has been mentioned that Interferon(abbr, IFN) is of no validity for digestive cancer, amplification of the antitumor effect using combination therapy with IFN and an anticancer drug were recently reported. In this paper we studied the antitumor effect of Mitomycin C(abbr, MMC) combined with IFN-β on human colonic cancer which was transplanted into nude mice.

I) Materials and method: Animals; Specific pathogen free BALB/c mice, aged 4-6weeks were purchased from Sankyo labo-service LTD. CO. Tumor; KHC, metastatic lymph node of colonic cancer showing moderately differentiated adenocarcinoma was maintained in nude mice. Drugs; MMC and IFN-β(Hu IFN-β, Toray LTD. CO.). Method; The experiment was started when xenotransplanted tumor into nude mice grew to about 100-200mg in weight. This experimental study was divided into the following four groups, 1) MMC only, 2) IFN-β only, 3) MMC combined with IFN-β, 4) control. The administrated dose of IFN was 60×10^4 U/head every day (0-14days) and 30μg/head MMC was given every third day, both drugs injected into the peritoneal cavity. Judgement of effect; length (L) and width (W) of each tumor in the four groups was measured every third day, and an approximate weight obtained from the formula of $LxW^2/2$ was followed. The antitumor effect was determined by comparing this Figure with the relatively average tumor weight of the control group; ie, the supression rate of a tumor weight less than 42% was judged as an effective group according to Battelle Columbus Labolatories Protocal.

II) Results: Although the supression ratio of tumor weight was 46% in MMC only group and 63.7% in IFN-β only group, MMC+IFN-β group demonstrated a supression ratio of 25.8% on the 12th day and 22.0% on the 15th day. (Fig.)

III) Summary: We have studied the antitumor effect of combination therapy with IFN-β and MMC for KHC employing xenotransplanted nude mice, and our result indicates that IFN-β is effective for KHC combined with MMC. Based on our experimental data, we are applying this to patients with unresectable or recurrent carcinoma with a combination of IFN-β and other antitumor drugs, in some of which the tumors are showing marked regression.

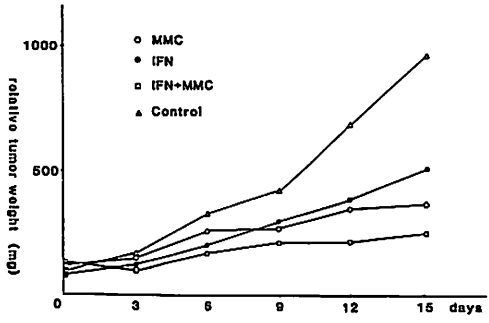


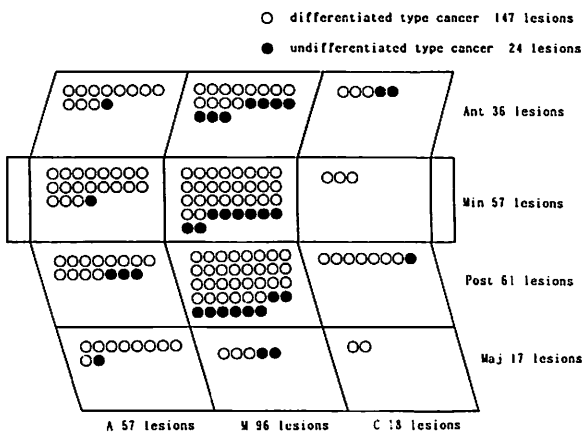
Fig. Antitumor effect of combination therapy with IFN-β and MMC

(11) Clinico-pathological study on multiple simultaneous cancer of the stomach.

T. Kitamura, T. Itoh and M. Mai

Multiple cancers of the stomach are not uncommon, and the surgeon is sometimes troubled about the decision of proximal cut end on gastrectomy. The clinico-pathological study contributed actual circumstances of multiple stomach cancers at surgery. During the last 12 years(1975-1987) 833 cases of gastric cancers were resected in our department. Multiple cancers were detected in 70 cases which equal 8.4% of all the resected cases. The age of patients was widely distributed from 26 to 85, with an average of 62yrs. The incidence of multiple cancers was higher in proportion to the number of high age patients. Although multiple advanced cancers were seen in 3 cases, the combination of early and advanced cancers accounted for 20 cases, while there were 47 cases of multiple early cancers. There were 52 cases of double cancers (75%) and 18 cases of triple cancers or more (25%). Many lesions were located in the atrophic area, while there were 38 lesions located in the middle posterior area and 34 lesions in the middle minor curvature. Multiple minute cancers of the flat and depressed type were unexpectedly found as incidental findings. Histologically differentiated type cancer (tubular and papillary adenocarcinoma) was found in an overwhelming majority (147 lesions, 86%) and undifferentiated type cancers (poorly differentiated and signet ring cell carcinoma) accounted for only 24 lesions (14%). In most background mucosa of differentiated type cancer demonstrated extensive atrophic and intestinized gastritis. There proved to be a close relationship in multiplicity between differentiated type stomach cancer and intestinal metaplasia. In those 70 cases of multiple stomach cancer, the multiplicity was preoperatively diagnosed in only 29 cases. Most lesions were detected as minute cancer by serial sectioning of resected stomach. Therefore it is very important to discriminate between the border of the fundic gland and the atrophic area preoperatively. On carrying out gastrectomy wide resection and careful examination of remnant stomach is recommended.

Table. Location of multiple simultaneous stomach cancers



(12) Preoperative induction chemotherapy for linitis plastica carcinoma of the stomach.

M. Mai. H. Ueda. T. Ogino and Y. Takahashi.

Linitis plastica carcinoma (abbr, L.P.) is characterized by an incidious onset, rapid progress and a fetal conclusion. During the last twelve years we have experienced 105 cases with L.P. at our Institution, which is equivalent 12.2% in our series. Its five year survival rate was only 7.8% despite curative gastrectomy. Considering the high potential of biological malignancies of L.P., preoperative induction chemotherapy was applied to 19 patients with L.P., employing FAM-OK432, sequential MTX 5-FU or UFT-M through aortic infusion, and induced hypertensive chemothrapy (IHC) developed at Tohoku University in order to obtain selective enhancement of drug delivery to tumor tissue. These trials were carried out on 19 patients who had L.P., and the antitumor effects resulted in a decrease in tumor markers such as CEA, CA19-9, CA125 of 100% (9/9), shrinking of extended metastatic nodes along the paraaorta or Virchow's nodes 50% (5/10), loss of gastric wall rigidity 26.3% (5/19) and disappearance of pleural or peritoneal fluids 80% (4/5). In one of five cases showing morphological improvement, no viable cells were detected in the resected stomach despite thorough histological examination of the whole stomach. Almost all regional lymph nodes showed multiple foci of fibrogranulomatous lesions in which degenerating or microbiotic atypical cells were seen. Although there was no difference in median survival time (MST) of the curable resection group (22 cases) between the surgery proceeding group and the induction chemotherapy group, MST of the non-curable resection group with preoperative induction chemotherapy resulted in a fairly good prognosis for 9 months as compared to four months of MST for the gastrectomy group (15 cases) (Table). In conclusion our results demonstrated that patients whose tumors were effectively destroyed by preoperative induction chemotherapy against L.P. had an improved prognosis.

Table. Comparison of median survival between neo-adjuvant (preoperative) chemotherapy and proceeding surgery in linitis plastica gastric cancer

	Operation	Number of Case	Extent of Cancer	Survival		
				Alive	Died	Median Survival (mos.)
Induction chemotherapy ↓ Surgery	Curable resection	4	LN (+) 2 LN (-) 2	2 1	0 1	10 mos. (5-24)
	Non-curable resection	8	LN (+++) 2 P (+) 6	0 4	2 2	8 mos (8-15)
Surgery proceeds	Curable resection	7	LN (+) 5 LN (-) 2	4 0	1 2	10 mos. (8-37)
	Non-curable resection	15	LN (+) 7 P (3) 8	0 0	7 8	4 mos. (1-16)
Chemothrapy only	Not done	7	LN (+) P (+) H (+) 7	2	5	6 mos. (1-9)

LN: Lymophnodal involvement
P: Peritoneal dissemination
H: Hepatic matastasis

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(13) A new therapeutic approach for peritoneal dissemination in patients with advanced gastric cancer.

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Peritoneal dissemination is a most common metastatic pattern in advanced gastric cancer, for which we are always facing difficulties in treatment. In our hospital approximately 20% of patients with advanced gastric cancer died of peritonitis carcinomatosa, and the median survival time for these patients was just 7 months with an extremely poor prognosis. We had administrated post operative adjuvant chemotherapy to the patients with peritoneal dissemination, but it was not effective. In a recent trial we have performed a high dose lavage of Mitomycin C(MMC) and OK432 i.p. administration.

1) Treatment for patients with peritoneal dissemination

Since 1982 we have employed intraperitoneal lavage with a high does of MMC(40mg) at surgery in addition to the conventional immunochemotherapy. As shown in the Figure, a significant prolongation of survival time for cases with peritoneal dissemination was obtained. Recently we have applied intraperitoneal administraion of OK432(50KE) in addition to a MMC lavage, and our experience in the treatment of peritoneal dissemination with MMC and OK432 has shown a marked decrease in the incidence of recurrence.

2) A high risk group for peritoneal dissemination and its treatment

Recenctly we have tried to predict a high risk group for peritoneal dissemination based on clinicopathological characteristics, i.e. a) histological type showing poorly or moderately differentiated adenocarcinoma associated with a scirrhous pattern in the tumor stroma, b) cytologically positive cases for cancer cells of peritoneal lavage by saline at surgery. For a high risk group, we have also undertaken intraperitoneal lavage with MMC and administration of OK432 in order to prevent the local recurrence in the peritoneum, and prolongation of the recurrent free interval was obtained. Our results suggest that high dose lavage with MMC and OK432 administration at surgery would be expected to be effective for peritoneal dissemination, particularly in the high risk group.

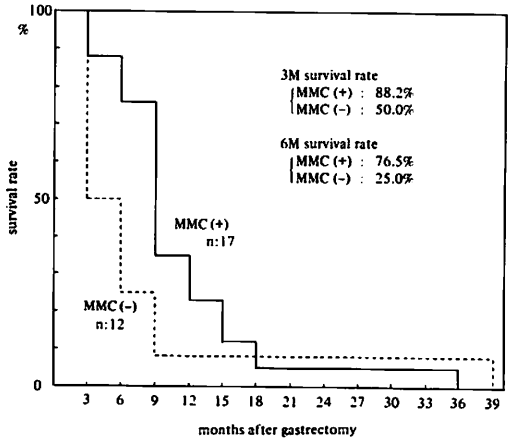

Fig. The effect of MMC lavage on patients with peritoneal dissemination.