Letter to the Editor

Gastric cancer: Today here, tomorrow where?

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To the Editor:

My thoughts on gastric cancer take me back some 40 years, to the time when I was a medical student. It was in 1958 when I first saw a patient who had gastric cancer. My clinical tutors told me to study the patient, read the textbook, and ask them about whatever I did not understand. The patient suffered from anorexia and weight loss, presenting with a palpable abdominal mass. I assisted at the operation. The surgeon removed the cancer by subtotal gastrectomy with omentectomy. The tumor had spread to the adjacent greater omentum. The resection was considered “curative”, because all visible tumor had been excised.

I remember reading more on gastric cancer in several textbooks of surgery from the medical school library. There was little information on the cause of the disease, except that salted or preserved food and hereditary factors might have some relationship. The books described the routes of spread, and mentioned the importance of radical resection.

I stored all this information in my medical student’s brain, but rather uncomfortably. I thought stomach cancer was nothing like lobar pneumonia, which could be cured with penicillin, or malaria, with quinine. So I asked my clinical tutor, “If we do not know what actually causes gastric cancer, how can we treat it, and can we really cure it?” He replied, “It really does not matter. As long as a radical resection can be done, many patients will be helped, and even cured.” At his suggestion, I looked up the publications of Brunschwig [1] and McNeer and James [2] and other pioneers of radical gastric cancer surgery, which confirmed what he had said.

Three months later, the patient was readmitted to the hospital with acute intestinal obstruction caused by diffuse peritoneal metastases, and he died soon afterwards. My tutor told me, “This is how gastric cancer behaves despite the best we can do”.

In the ensuing 40 years I have seen and treated

hundreds of gastric cancer patients. My failures as a surgeon to cure gastric cancer have made me humble, and also sad. As a clinical tutor myself, I have been asked by students many questions which I find even more difficult to answer. In the 1960s and 1970s I read with enthusiasm the work of Sugimura and associates [3], in which they showed that N-nitroso compounds such as nitroso-guanidine were potent gastric carcinogens. In recent years, I learnt about the epidemiological evidence implicating *Helicobacter pylori* infection in the development of gastric cancer. Yet my students asked, “Why do we still have so many gastric cancers?”. I had to say, “It will take many years to prove such an association, and many decades to devise a workable and effective prevention method.” The looks on the faces of my students told me they were not impressed. Still, I assured them, research work was underway.

I remember teaching a group of students who had just come from a rotation in Gynecology. They were excited to have learnt that by means of the Papanicolaou smear test, cancer of the uterine cervix could be diagnosed at a very early stage, and treated with almost zero mortality. I told them that since the 1950s, a nationwide screening program in Japan, by means of the gastroscope and, later, the fiberoptic gastroscope, has successfully diagnosed gastric cancer in an early stage, with survival rates exceeding 95% after treatment. “Why is this not being done in Hong Kong, in the United States, or in Europe?” they asked. Such population screening is very expensive and not cost-effective, I explained, except when the incidence is very high, as in Japan. “Does that mean we will always have to see many advanced gastric cancers”? My answer, regrettably, was yes.

Some months later, I had the pleasure of teaching one of the last groups of students, just before their final medical degree examination. One student said to me, “I read in one of the textbooks that you, among others,

advocate big radical operations and extensive lymph node dissections for the surgical treatment of gastric cancer [4]". I thought he was giving me a compliment, but he went on to ask, "Is it not strange that you do so for gastric cancer, while others are advocating more and more conservative surgery for cancer of the breast, the larynx, the lung, and other sites"?

I found myself with no ready answer to this challenging question. Luckily, I quickly found a clue: it was breast cancer. "We are treating gastric cancer today perhaps in the way we treated breast cancer in the 1950s and 1960s", I tried to explain. In those days, surgery was the principal method of treatment for breast cancer, while radiotherapy and chemotherapy were being developed and largely ignored by the surgeons. In those days, surgeons had to devise ever-bigger resections, beyond the Halstead type of radical mastectomy, to try to achieve local control of advanced breast cancer. For example, in addition to removing the whole breast and the pectoral muscles, the ultra-radical mastectomy, with dissection of the internal mammary lymph nodes, and even chest wall resection, was advocated and performed on many patients in specialized centers, such as the Memorial Sloan-Kettering Cancer Center in New York [5]. Such ultra-radical mastectomies resulted in some dramatic cures of even very advanced breast cancers. "Today, as you all know," I reminded my students, "the radical mastectomy and the ultra-radical mastectomy operations are rarely seen. The standard treatment program for breast cancer now consists of breast-conserving resection, radiation therapy, and chemotherapy, and survival has been improved over what could be achieved with ultra-radical surgery". I ventured to assure the students, "I believe the day will come when we can perform only a minimal operation for gastric cancer, and non-surgical modalities of therapy will help produce a cure". I must say neither my students nor I felt too convinced.

A few months ago, several advanced surgical trainees in a surgical skills course asked me a large number of related questions, including "What is the prognostic importance of finding how many lymph nodes [4,6] have metastatic deposits? How extensive should the lymphadenectomy be? How many centimeters of resection margin we should obtain?" They had diligently read the literature, but found the reports on these and many other aspects of gastric cancer conflicting and difficult to understand. "It is really not so complicated, and not really conflicting," I said. "Every investigator reports his or her data, as in a laboratory experiment, and after statistical analysis, makes certain conclusions". As in bench experiments, some of these reports can be regarded as only exploratory studies involving small numbers of subjects, yielding preliminary hypotheses. The concepts and conclusions need to be vali-

dated, modified, or refuted by controlled experiments with a sufficiently large sample size. The seemingly conflicting reports we read in the literature can probably all be explained and reconciled if looked at in this manner. Thus, the survival benefit of adequate lymph node dissection in a series of 210 North American patients, based on subset analysis of the scope of lymphadenectomy relative to the scope of nodal metastasis [4], was confirmed in a large multicenter, observational study of 1654 patients in Germany and Austria [7].

My advanced surgical trainees went on to discuss the merits of extended lymphadenectomy. "Why is it that despite these and the numerous reports from Japan of high survival rates after extended lymphadenectomy, many surgical leaders remain skeptical of its value?" I was further reminded that, "We are in the age of evidence-based medicine". So this skepticism is not surprising. I had to explain, "Because none of the published prospective randomized trials of extended lymphadenectomy has shown survival benefit [8,9]." Nevertheless, I encourage surgical trainees to learn the operation, and surgical colleagues to perform it. When asked, "How can you justify doing it", my response has been threefold.

First, in experienced hands, extended lymphadenectomy can be performed with no significantly added morbidity [10]. Second, the fact that several randomized trials have not shown positive results does not mean that none exists. It may depend on many factors that affect the statistical power of the designed trial, including the number of patients enrolled, the duration of follow-up, and the number of censored cases. It has been calculated that well over 1000 patients would have to be randomized to detect a marginal change in the overall prognosis with a statistical power of 90% at a significance of 0.05 [7]. The small numbers of patients in the published trials, protocol violations, and the large numbers of postoperative deaths or complications may be masking the true outcome. Third, reports abound of patients who survived for 5 or more years after radical resection with extended lymphadenectomy of gastric cancer which had metastasized to celiac, hepatoduodenal, or other regional lymph nodes not routinely removed except in such procedures [11].

Despite such arguments, most discussions have ended up with half of the people half-convinced. To convince everyone, unless the current trials show a benefit with longer follow-up, we would need an even larger, better designed, better executed, prospective randomized trial to be conducted. In Japan, the D2 operation has been regarded as the minimal standard, and I have been told that a trial of D2 versus D4 has begun. In most other countries, the norm is still D1, and I believe any

improvement must still be compared with this norm. It will take many more years for another D1 versus D2 trial of sufficient size, if it is ever to be done, to arrive at significant conclusions.

In the meantime, my thoughts turn to non-surgical therapy. I hope that more and better non-surgical modalities of treatment for gastric cancer will emerge. We have seen a revolution in the management of breast cancer beginning in the 1970s, with advances in the efficacy of chemotherapy and radiotherapy. More recently, controlled trials have shown the therapeutic efficacy of recombinant monoclonal antibody against the over-expressed product of the HER2/neu proto-oncogene in patients with breast cancer refractory to chemotherapy [12]. For gastric cancer, the possible success of similar non-surgical treatment seems to be only a remote possibility today, but such too must have been the feeling of the surgeon operating on breast cancer in the 1970s.

For the young surgeons who are dissatisfied with what we do for gastric cancer today, I say, "Go read up on the molecular genetics of gastric cancer", or even, "Why not go to the research laboratory and try to discover what better can be done". For example, the various growth factors operating in a gastric cancer can even be determined in an endoscopic biopsy sample [13]. To intrigue them further, I would say, "If we could find which gene products or cytokines promote the transperitoneal spread of gastric cancer, for example, perhaps we could devise means to block their action". Murmuring to myself, I would add, "Then the patient I saw 40 years ago, and many more since, could have been saved."

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