日本医放会誌：46（6），804—810，1986（昭61）

For Better Dose Distribution in Radiation Therapy for Pancreatic Cancer

Kiyoshi Ohara, Mitsuyoshi Wada, Hideo Tatsuzaki,
Susumu Kubota and Masayoshi Akisada
Department of Radiology, Institute of Clinical Medicine, The University of Tsukuba
Takeshi Todoroki and Toru Takeshima
Department of Surgery, Institute of Clinical Medicine, The University of Tsukuba

Research Code No. : 606

Key Words : Pancreatic cancer, Intraoperative radiotherapy, Treatment planning, Teflon mesh

膵癌放射線療法における線量分布改善のための工夫

筑波大学臨床医学系放射線科
大原　潔　和田　光功　立崎　英夫
久保田　進　秋貞　雅祥
筑波大学臨床医学系外科
轟　　健　竹　島　徹

（昭和60年11月20日受付）

膵癌の放射線療法において，より理想的な線量分布を得るために2つの工夫を行った．一番目は，術中照射を腫瘍切除の前後に分割して行うことである．これにより2回目の照射における照射筒の大きさ，選択する電子線エネルギーの減少が期待される．二番目は，術中照射後病巣の拡がりに合致させて裁断したTeflon meshを局所に縫着することである．この処置により外部照射計画に用いるCT像上でTarget Volumeが自明となることが期待される．

11例の局所進行膵癌術中照射例に本法を試みてきた．分割術中照射に関しては，3例の腫瘍非切除例を含む5例に対して分割照射が行われ，照射筒の大きさ及び電子線エネルギーが各々2例において減少可能となった．Teflon mesh縫着は11例全例に適用され，最長18カ月の観察期間中この処置に起因すると考えられる合併症は経験されなかった．外部照射は10例に追加された．CT像上Teflon meshの陰影は以下の如き特徴を示し，本法は照射計画に有用な手段の一つであると考えられた．1）金属クリップでみられるようなアーティファクトが発現しない．2）腫瘍の腹腔側の形状が曲線として描出され，Target Volumeが自明に示される．

Introduction

The role of radiation therapy in the treatment of pancreatic cancer has been revolutionizing in the last decade.

Traditionally pancreatic cancer was regarded as a radioresistant tumor and the indication of radiation therapy was restricted to only palliative intentions. However, some advances in radiation technique that have enabled us to distribute highly concentrated doses to the target volume have brought more active roles for radiation therapy. Nowadays it is postulated that in some instances pancreatic cancer may be radiocurable[1].

In most of the cases, the authors had been coping with advanced pancreatic cancer by means of intraoperative ratiotherapy (IOR)[2]. And in recent years, IOR has been fractionated and external irradiation has been supplemented as well. For external irradiation, we have exploited some technique to show the target volume distinctly on X-ray computerized tomography (CT) for treatment planning. Details and further implications of these modifications and the techniques are reported.

Materials and Methods

Between January 1979 and June 1985, 24 cases with locally advanced pancreatic cancer were candidates for IOR, in the University Hospital of Tsukuba. Of these, after February 1982, twice fractionated IOR and supplementary external irradiation as mentioned below was intended for 11 patients (Table 1).

Of these 11 cases, 9 males and 2 females, the age distribution was from 44 to 84 with an average age of 63.6 years old.

The essential technique of IOR in the University of Tsukuba was referred elsewhere[3]. The radiation unit for IOR is Shimadzu BTR 25 Betatron next door to the operation room, which permits electron beam irradiation in energy of 4—25 MeV with 12 steps.

1) Fractionated IOR:

In 13 cases between January 1979 and 1982, IOR had been used to be undergone in a single fraction with standard dose of 30 Gy. However, IOR has been fractionated twice with standard total dose of 20 Gy since 1983. Because of the idea that even for advanced cancer, enforcement of tumor volume reduction by means of pancreatectomy is feasible for improvement of local control followed by radiation therapy except for an unresectable case, IOR could be more valid when carried out in two fractions. That is, the first fraction bears a role of preoperative irradiation, intending to reduce the viability of the tumor cells that could be spilled onto the operation field during the tumor resection. The second fraction is reserved for a role of postoperative irradiation to the tumor bed, or to the remaining tumor mass.

In each fraction, standard dose is 10 Gy. Furthermore, treatment cone and/or energy of electrons could be decreased in the second fraction.

2) Measure to define the target volume for external irradiation[4]:

Table 1　Patients in this study

Patient no.	Age	Sex	Tumor location	Tumor size (cm)
1	72	Male	Entire	12×3×2.5
2	62	Male	Head	8×6×5
3	69	Male	Entire	4×3.5×3
4	65	Male	Head	4×5×5
5	44	Male	Head	5.5×5×4.5
6	72	Male	Entire	12×5×4
7	84	Male	Head	5×5.5×4.5
8	64	Female	Head	4×3.5×3.5
9	76	Male	Head	8×8×5
10	54	Male	Head	4×4×4.5
11	68	Female	Head	6×4.5×4.0

All patients but no. 7 had vascular invasion

All patients had regional node involvement but revealed no distant metastasis.

no. 4 : Ascites was found at the time of operation.

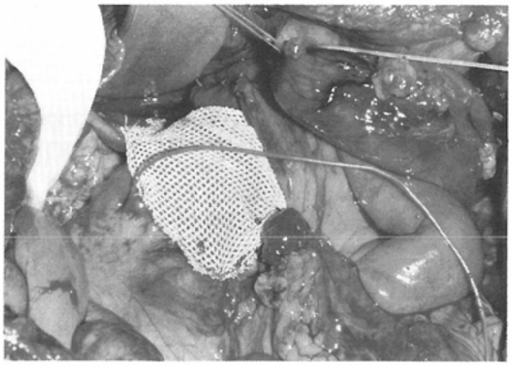

Fig. 1 Teflon mesh is left on the area of palpable pancreatic tumor for unresectable case. Teflon mesh is tailored to the size of treatment cone in IOR.

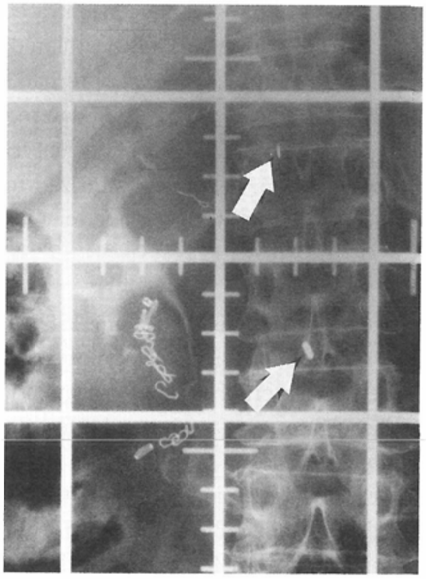

Fig. 2 Anteroposterior simulator film to set preliminary treatment fields. Metal clips (arrow) indicate the cephalocaudal edges of the tumor bed (resected case). Subtotal gastrectomy was performed to give rise to duodenal ulcer by IOR. Teflon mesh is not recognized.

Following IOR, a piece of Teflon mesh (USCI' A Division of C.R. Bard, Inc., U.S.A.) tailored to the extent of the tumor or treatment field of IOR is sewed onto the target volume for the treatment planning of successive external irradiation. Metal clips are also left at the cephalocaudal edges of the target volume (Fig. 1). Teflon mesh left in the body has already been proven to be innocuous for a long time[5].

3) Treatment planning for external irradiation:

Treatment planning is carried out routinely aided by CT. Prior to CT examination, preliminary treatment fields are determined with an X-ray simulator that relies on the location of the metal clips. Fluoroscopically, the metal clips show not only the location in cephalocaudal direction but also the respiratory movement of the target volume (Fig. 2).

After putting radioopaque catheters for angiography on the skin to show the treatment fields, CT examination is undergone.

Then the practical treatment fields are settled relying on the relationship between the shadows of the Teflon mesh and the catheters on the skin. Further CT examination may be repeated to confirm the adequacy of the practical treatment fields.

In external irradiation, box field technique with cobalt unit is usually employed. Planned total dose is 30—40 Gy at 1.6—1.8 Gy per fraction and 5 fractions a week.

The indication of chemotherapy has been left in the surgeon's hands.

Results

1) Fractionated IOR (Table 2)

Fractionated IOR was carried out in 5 cases and in 2 of them, the tumor was resected by total pancreatectomy. 4 cases underwent IOR in a single fraction because of evident unresectability. Of another 2

Table 2　Treatment methods and results

Patient no.	Operation	IOR Field size(cm), Energy(MeV), Dose(Gy) Before resection	After resection	Duration between IOR and external irrad. (weeks)	External irrad. Gy/Fraction/Day	Survival time (months)
1	T.P.	—	6∅, 10, 20	9	41.6/24/36	18
2	unresected	8∅, 20, 10	6∅, 20, 10	3	39.6/22/30	8
3	T.P.	—	6∅, 16, 20	5	41.6/24/37	13
4	unresectable	6∅, 14, 20	—	3	23.8/14/18	3
5	T.P.	8∅, 14, 10	8∅, 10, 10	5	5.4/ 3/ 3	12
6	unresected	6×10*, 12, 15	6∅, 12, 15	4	28.8/16/23	6.5
7	unresected	6∅, 12, 20	—	—	—	14.5
8	T.P.	8∅, 10, 10	8∅, 8, 15	5	41.4/23/24	6
9	unresectable	8∅, 16, 20	—	5	41.4/23/24	4
10	unresected	8∅, 14, 10	8∅, 14, 10	4	30.6/17/29	7.5 alive
11	unresectable	8∅, 16, 20	—	5	30.6/17/24	6.5 alive

T.P.: total pancreatectomy
unresected: Resection was attempted but could not resected.
*oval shaped treatment cone
no. 7: Resection was not indicated because of his age.
Gastrectomy was performed in all patients but no. 6.

cases when first using these methods, the tumor could be resected but IOR was not fractionated.

As for execution of fractionation, there was no trouble or difficulty, because the rooms for operation and radiation adjoined each other.

In 4 out of 5 cases fractionated IOR was performed, size of treatment cone or energy of electron beam could be decreased in the second fraction.

2) Application of Teflon mesh

In regard to the perpetual application of Teflon mesh onto the tumor or tumor bed, no complications were observed during survival periods of all 11 cases. Teflon mesh showed shape and extent of the tumor and tumor bed self-evidently as a curvilinear shadow with little burdensome artifact in each CT slice (Fig. 3), except in that of cephalocaudal edges of target volume where metal clips had been left.

Application of this technique was useful for the treatment planning (Fig. 4), as the ventral and lateral boundaries of target volume was self-evident, especially for the tumorresected case, while it would be indefinite without this technique. So, more actual dose distribution of IOR was disclosed (Fig. 5).

3) External Irradiation

Supplemental external irradiation was planned for all cases with one exception of an 84 year-old unresected case. The term between IOR and external irradiation was from 3 to 9 weeks, the average being 4 to 5 weeks. In 2 cases out of the 10, irradiation was discontinued because of intestinal bleeding. Bleeding was caused by tumor invasion into the duodenal mucosa, as for case number 4 and by an ulcer in the anastomosed jejunum out of IOR field in the case of number 5. For the other 8 cases, 28.8 to 41.6 Gy of target dose was irradiated and they tolerated these serial treatments well.

4) Survival

Survival time after IOR of 9 expired cases, were from 3 to 18 months, with a mean of 9.4 months with 4 cases surviving more than a year. Of these 9 cases, all were judged to have had cancer at death. 4 were disclosed at autopsy and 5 were concluded by their clinical course, although the case number 9 expired of acute cardiac failure 4 months after IOR. As of present (December, 1985) there are 2 survivors for 7.5 and 6.5 months. No case other than case number 6, which expired of excessive bleeding from duodenal ulcer presumably caused by irradiation, suffered from serious radiation injury.

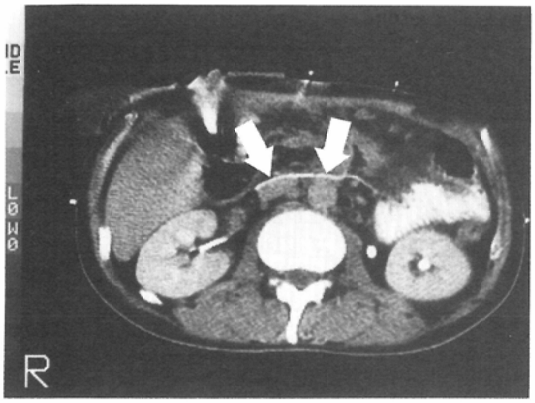

Fig. 3 A slice of CT of the upper abdomen with contrast enhancement. Diluted Gastrografin^R was introduced into the upper GI. Teflon mesh left on the tumor bed shows a curvilinear shadow (arrows) with appropriate density. Shadows of catheters for angiography put on the skin indicate the preliminary treatment fields.

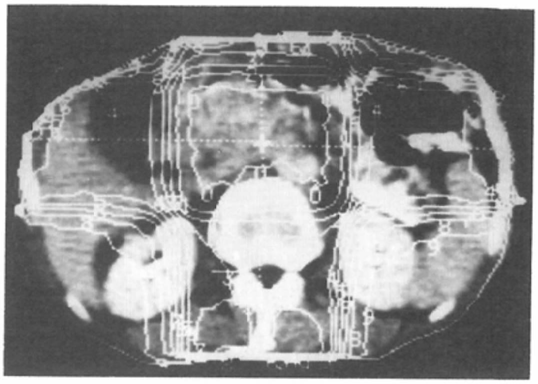

Fig. 4 Isodose distributions of box field technique using cobalt unit. The ventral and lateral boundaries are indicated by the shadow of teflon mesh. Figures 0, 1 and 2 show 100, 90 and 80% isodose values respectively.

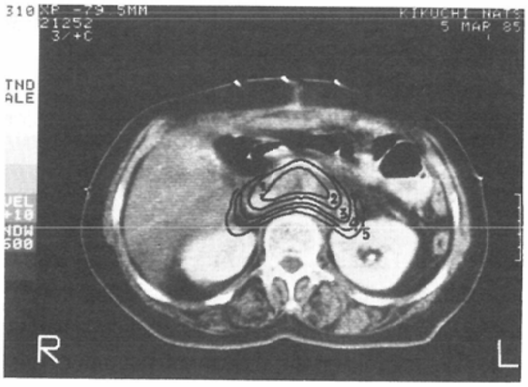

Fig. 5 Isodose distributions of IOR. The size of treatment cone is 8 cm in diameter and the energy of electron beams is 10 MeV. Dose distributions are adopted to the curved surface of the tumor bed shown by teflon mesh. Figure 1 to 5 correspond to 90, 80, 60, 40 and 20% isodose values respectively.

Discussion

The role of radiation therapy for pancreatic cancer had been disposed to palliative intent exclusively, because of a reputation of "radioresistance" in the orthovoltage era. One of the main reasons of this repute is presumed to be the dose restriction to the target volume by radiation tolerance of the tissues or organs adjacent to the pancreas, such as bowel, liver, kidneys and so on. However, the advent of megavoltage equipment and advances in radiation technique have altered the role of radiation therapy from palliative to a more radical one. They are, precision high dose (PHD) techniques with high energy electrons and photons[6], the application of comformation radiotherapy[7], ^{125}I seed implantation[8][9], heavy ion irradiation[10], IOR[11], the combination of these[12][13][14] and so on, with and without chemotherapy. A common advantage of these techniques is superiority in dose distribution.

On the other hand, a clinical trial exploiting the theoretical advantage of higher LET, RBE and lower OER in neutron irradiation failed to show the improvement of survival because of severe complications[15]. These results are considered to be largely attributable to inferior dose distribution of neutron beams as stated by Catterall[16]. Thus the best dose distribution is considered to be essential in radiation therapy[17] for pancreatic cancer.

The authors have been challenging locally advanced pancreatic cancer by means of IOR[2][3] with execution of pancreatectomy as possible, becuase the smaller the tumor volume the lesser radiation dose expected to sterilize or control the tumor. However, viable tumor cells could be spilled onto the operation field during the operation procedure, we modified the method of IOR by fractionating twice. That is, the first fraction of IOR is "preoperative irradiation" to prevent dissemination of tumor cells. This modified method also enables us to improve dose distribution still more by employing decreased cone and/or electron energy at the second fraction of IOR as "postoperative irradiation".

In practice, of 5 cases fractionated IOR was carried out, electron energy could be decreased in 2 cases and cone downed in another 2 cases. Also, when intervals of irradiation was put off more than several hours, cell recovery of sublethal damage would be expected[18] that could improve radiation tolerance of normal tissue especially of the duodenum.

Despite the dose of IOR being as high as 20—30 Gy given in a single fraction or two, as the dose was derived from normal tissue tolerance, the eradication of all tumor cells was considered not to be achievable. So we employed supplemental external irradiation.

Metal clips left around the tumor or tumor bed during the operation had offered importent information for treatment planning of the thoracic, pelvic and abdominal regions. Meanwhile, the exploitation of CT is indispensable for the treatment planning and for the evaluation of the alteration of tumor size after treatment now[19][20][21]. Regrettably, metal clips inevitably yield annoying artifacts on CT. Therefore, some materials that yield little artifact have been chosen. For this purpose, we applied tailored Teflon mesh by sewing it onto the tumor or tumor bed. Teflon is one of the materials proven to be innocuous when left in the human body for a long time[5], and moreover exhibits proper density shadow on CT. In practice, no serious complications caused by application of this technique were encountered.

On the other side, as Teflon mesh is not sufficiently radioopaque to be recognized on X-ray simulation, metal clips were also left at the cephalocaudal edges of tumor, not to be included in the majority of slices of serial CT.

Some advantages of applying this technique to exhibit the tumor extent on CT are considered to be as follows. (1); Little artifact, if any, is manifested as is often the case of metal clips. (2); Teflon mesh is so pliable that it conforms to the entire ventral surface of the tumor or tumor bed, that the shape of the target areas are self-evident in each CT slice. (3); The shadow of Teflon mesh also allows disclosure of the dose distribution more accurately, especially of IOR. (4); These excellent features permit the follow up study after radiation therapy on CT as before.

It is still premature to assess the efficacy of fractionated IOR and of supplemental use of external irradiation at present.

This technique will also be applicable to the other sites of tumors, such as mediastinal and pelvic tumors.

Acknowledgement

The authors would like to thank Yoji Iwasaki, M.D. for his advice and Takehiko Mori, Tch. for providing isodose distributions.

References

1) Dobelbower, R.R.Jr.: Current radiotherapeutic approaches to pancreatic cancer. Cancer 47: 1729–1733, 1981
2) Nishimura, A., Nakano, M., Otsu, H., Nakano, K., Iida, K., Sakata, S., Iwabuchi, K., Maruyama, K., Kihara, M., Okamura, T., Todoroki, T. and Iwasaki, Y.: Intraoperative radiotherapy for advanced carcinoma of the pancreas. Cancer 54: 2375–2384, 1984
3) Todoroki, T., Iwasaki, Y., Okamura, T., Nagoshi, K., Asakura, H., Nakano, M., Inada, T., Tsunemoto, H., Umegaki, Y., Nishimura, A., Nakano, M. and Sato, H.: Intraoperative radiotherapy for advanced carcinoma of the biliary system. Cancer 46: 2170–2184, 1980
4) Ohara, K., Akisada, M., Ishikawa, N., Maruhashi, A., Kitagawa, T., Inada, T., Hayakawa, Y., Fukuda, H., Maki, Y. and Iwasaki, Y.: A treatment planning procedure for proton beam therapy. J. Jpn. Soc. Cancer Ther. 27: 1342–1348, 1985
5) Harrison, J.H.: Synthetic materials as vascular prostheses. III. Long term studies on grafts of Nylon, dacron, orlon, and teflon replacing large blood vessels. Surg. Gyn. Obst. 106: 433–438, 1959
6) Dobelbower, R.R.Jr., Borgelt, B.B., Strubler, K.A., Kutcher, G.J. and Suntharalingam, N.: Precision radioatherapy for cancer of the pancreas: Technique and results. Int. J. Radiat. Oncol. Biol. Phys. 6: 1127–1133, 1980
7) Takahashi, S.: Conformation radiotherapy rotation techniques as applied to radiography and radiotherapy of cancer. Acta Radiol., Suppl. 242, 1960
8) Hilaris, B.S. and Roussis, K.: Cancer of the pancreas. In Handbook of interstitial brachytherapy, Hilaris, B.S., (Ed.). Acton, Massachusetts, Publishing Sciences Group, Inc. 1975, pp. 251–262
9) Syed, A.M.N. and Feder, B.H.: Technique of after-loading interstitial implants. Radiol. Clin. 46: 458–475, 1977
10) Castro, J.r. and Quivey, J.M.: Clinical experence and expectations with helium and heavy ion irradiation. Int. J. radiat. Oncol. Biol. Phys. 3: 127–131, 1977
11) Abe, M., Yamano, K., Imura, T. and Matsuda, S.: Intraoperative radiotherapy of abdominal tumors: Part 1. Intraoperative irradiation to carcinoma of the pancreas head and biliary system. Nippon Acta radiol. 29: 75–85, 1969
12) Gunderson, L.L., Shipley, W.U., Suit, H.D., Epp, E.R., Nardi, G., Wood, W., Gohen, A., Nelson, J., Battit, G., Biggs, P.J., Russell, A., Rockett, A. and Clark, D.: Intraoperative irradiation: A pilot study combining external beam photons with "boost" dose intraoperative electrons. Cancer 49: 2259–2266, 1982
13) Matsuda, T., Onodera, T., Okamoto, A., Ito, I., Ishiwatari, J., Tabata, I., Matsukawa, M., Satomi, T. and Makino, N.: Multi-disciplinary therapy for unresectable pancreatic cancer. Jap. J. Cancer Clin. 26: 988–995, 1980
14) Whittington, R., Dobelbower, R.R., Mohiuddin, M., Rasato, F.E. and Weiss, S.M.: Radiotherapy of unresectable pancreatic carcinoma: A six year experience with 104 patients. Int. J. Radiat. Oncol. Biol. Phys. 7: 1639–1644, 1981
15) Smith, F.P., Schein, P.S., MacDonald, J.S., Woolley, P.V., Ornitz, R. and Rogers, R.: Fast neutron irradiation for locally advanced pancreatic cancer. Int. J. Radiat. Oncol. Biol. Phys. 7: 1527–1531, 1981
16) Catterall, M.: The assessment of the results of neutron therapy. Int. J. Radiat. Oncol. Biol. Phys. 8: 1573–1580, 1982
17) Suit, H.D. and Goitein, M.: dose-limiting tissues in relation to types and location of tumors: Implications for efforts to improve radiation dose distributions. Eur. J. Cancer 10: 217–224, 1974
18) Withers, H.R. and Mason, K.A.: The kinetics of recovery in irradiated colonic mucosa of the mouse. Cancer 34: 896–903, 1974
19) Goitein, M., Wittenberg, J., Mendiondo, M., Doucette, J., Friedberg, C., Ferrucci, J., Gunderson, L., Linggood, R., Shipley, W.U. and Fineberg, H.V.: The value of CT scanning in radiation therapy treatment planning: A prospective study. Int. J. Radiat. oncol. Biol. Phys. 5: 1787–1798, 1979
20) Hobday, P., Hodson, N.J., Husband, J., Parker, R.P. and MacDonald, J.S.: Computed tomography applied to radiotherapy treatment planning: Techniques and results. Radiology 133: 477–482, 1979
21) Munzenrider, J.E., Pilepich, M., Rene-Ferredo, J.B., Tchakarova, I. and Carter, B.L.: Use of body scanner in radiotherapy treatment planning. Cancer 40: 170–179, 1977