Brachytherapy Reirradiation with Hyaluronate Gel Injection of Paraaortic Lymphnode Metastasis of Pancreatic Cancer: Paravertebral Approach - A Technical Report with a Case -

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Reirradiation/Paraaortic lymphnode/High dose rate brachytherapy/Hyaluronate/Risk organ/Pancreas cancer/Small intestine.

Paraaortic lymph nodal (PALN) recurrence is not a rare scenario of abdominal malignancies including pancreas cancer, even after radiotherapy. The role and indication of reirradiation is limited because it is often associated with significant late toxicity in the surrounding normal organs. We developed a new approach and technique of brachytherapy to overcome this difficult situation, with a paravertebral approach and hyaluronate gel injection (HGI). We encountered a patient with pancreatic cancer who developed PALN metastasis as in-field recurrence, 6 months after resection of pancreatic cancer with 50 Gy of preoperative radiotherapy. The applicator brachytherapy needles and gel injection needles were advanced by percutaneous paravertebral approach under local anesthesia, and by injection of a hyaluronate gel to separate the surrounding small intestines and the target. A single fraction of 18 Gy was delivered to the tumor (75.6 Gy equivalent in conventional schedule calculated with LQ model at $\alpha/\beta = 3$) and total estimated D2cc (the minimum dose to the most irradiated volume of 2 cc, calculated at $\alpha/\beta = 2$) in the small intestines was 61.6 GyE with HGI and 80.6 GyE without. No complications have been observed for six months. Three months later, FDG accumulation had disappeared, the tumor size was reduced, and serum CA-19-9 value decreased from 5150 U/mL to 36.6 U/mL (normal range < 37.5). Conclusively, the brachytherapy with the HGI procedure by paravertebral approach was thought safe and effective in reirradiation of PALN recurrence.

INTRODUCTION

Though reirradiation shows comparable effectiveness in local tumor control or in pain reduction to that in the first attempt,1–3) the reirradiation treatment is associated with significant incidences of late toxicities attributable to accumulated dose in anatomically vicinity-at-risk organs involved in the first and the second irradiation.4,5) Current new technologies as IMRT-IGRT which promised accurate and selective dose delivery still have limited usefulness when the target was closely surrounded by at risk organs.

Paraortic lymph node (PALN) recurrence is one of the frequent problems in oncology and it occurs even after radiotherapy, however, reirradiation was limited with the above mentioned difficulty.5,6) We had proposed a solution separating the target and the risk organs by injection techniques.6–10) Temporary separation by percutaneous hyaluronate gel injection (HGI) provided a safe and practical spacing during high dose rate brachytherapy (HDRBT).

In this paper we describe a technique of paravertebral approach with a case description in whom a eradicative dose reirradiation to PALN metastasis from pancreas cancer was safely performed avoiding involvement of small intestines. Its feasibility, safety and effectiveness were discussed.

PATIENT

A 67 years old female was readmitted to our clinic with PALN metastasis with elevated serum CA19-9 level at 6298.7 U/mL (normal < 37.5 U/mL), which developed 2 months after successful (R0) distal pancreatectomy with...
celiac axis resection (DP-CAR) for a locally advanced body-tail pancreatic cancer staged at T4N3M0, after 50 Gy of preoperative radiotherapy. Chemotherapy with 1200 mg of tegafur, 33.6 mg of gimeracil and 117.6 of oteracil, each other day was started with radiotherapy. One month after the surgery the chemotherapy was restarted and continued, however, CA19-9 level stayed at high level (Fig. 1). X-ray CT study revealed a new development of PALN metastasis and the tumor kept growth in size up to 14 cc despite of chemotherapy. The tumor showed a significant FDG accumulation in PET study (Fig. 2). She began to feel back pain.

We planned a single fraction reirradiation treatment of 18 Gy to the tumor, by paravertebral needle approach, preserving the surrounding small intestine by HGI keeping the minimum dose to the most irradiated small intestinal volume of 2 cc less than 6 Gy.

Before treatment, informed consent was obtained from the patient. Treatments were performed with standard institutional approval.

**Preparation of hyaluronate gel**

180 mg sodium hyaluronate of 3.4 million Daltons of median molecular weight (Suvenyl, Chugai/Roche, Tokyo, Japan) was used to prepare 60 mL of mixture with saline and 5 mL of contrast medium (Iopamiron 300 mgI/ml, Bayer, Germany).

**Monitoring and premedication**

The patient was kept under monitoring ECG, PaO2, respiration and blood pressure throughout the procedure, and underwent awake sedation with 25 mg of hydroxyzine pamoate, to enable her report any abnormal sensation till completion of needle deployment and HGI.

**HGI and applicator needle deployment via paravertebral approach**

Under X-ray CT (SCT-7000, Shimazu, Kyoto, Japan) guidance two gel injection needles, 21-gage, with steeped tops with side holes (improved shape for straight-line insertion) were advanced via paravertebral approach, and were inserted into the anterior pararenal space. Similarly, the brachytherapy applicator needles of 1.1 mm in external diameter and 20 cm in length were inserted to the target. By injection of the gel, the tumor surface was clearly contoured. A distance of minimal 20 mm from the target of the closest part of small intestine was created with 60 ml of HGI (Fig. 3). Time required for HGI procedure was approximately 20 minutes. All interventional procedure was achieved by a qualified interventional radiologist.

**Brachytherapy planning and irradiation**

Fine pitch (3 mm) X-ray CT images were then acquired and transferred to the treatment planning computer and 3D treatment plan was created (PLATO version 14.2, as the latest version, Nucletron, Veenendaal, Netherlands). 18 Gy in one fractions was prescribed. The minimum dose to the most irradiated volume of 2 cc (D2cc) of small intestine was 5.9 Gy. Equivalent dose calculated with linear quadratic model at $\alpha/\beta = 2$ of D2cc was 11.6 Gy GyELQ2, $\alpha/\beta = 2$ with HGI, and 30.6 GyELQ2, $\alpha/\beta = 2$ without HGI (Fig. 4), showing approximately 2.6 times safer improvement of D2cc. The interval from the end of previous irradiation was 7 months.

The planned data were transported to a I-192 remote after

![Fig. 1. Clinical course. Abbreviation, EBRT: external beam radiotherapy.](image1)

![Fig. 2. Fusion images of X-ray CT image and FDG-PET image before (a) and three months after treatment of brachytherapy (b). Three months after the reirradiation, the tumor size and the FDG accumulation was decreased. Abbreviation: SUVmax = maximum standardized uptake value.](image2)
The needles were promptly removed after the completion of the irradiation and she was dismissed. After free resting time the patient left the clinic on foot. There was no procedure related complication. No additional medication was required. She was dismissed in the after noon and followed-up at our clinics.

**Outcome**

No complications were observed during the follow-up period over 9 months. The back pain has been disappeared. Follow up PET-CT and MRI study showed negative FDG accumulation and reduction of the tumor size (Fig. 2B). The serum level of CA19-9 was decreased from 5545 U/mL (normal range = <37) to 36.6 U/mL seven months after the reirradiation.

**DISCUSSION**

A safe and eradicative PALN reirradiation

PALN metastasis is a frequent clinical sequel in various abdominopelvic malignancies, including pancreas cancer, and rationale of the surgery is limited.12) A eradicative PALN reirradiation is ideal but the safe dose is usually limited by surrounding radiosensitive organs: mostly intestines. In a reirradiation case, besides the intestines, spinal cord and kidneys may narrow the range of available beam angle. To date, only a few report is published about reirradiation in the abdomen and palliative doses were used.13,15) We provide a safe and eradicative reirradiation plan to PALN recurrence.

**Intestinal toxicity**

To date, no definitive consensus or guidelines exist regarding tolerance level of the small intestines in reirradiation or in brachytherapy. Streitpath et al. proposed D1cc thresholds of 11 Gy for general gastric toxicity and 15 Gy for ulceration,14) which were equivalent to 35.75 GyE $\alpha/\beta = 2$ and 63.75 GyE $\alpha/\beta = 2$. Abusaris et al. proposed a tolerance cumulative “bowel” (not specified) dose level of 90 Gy in external beam reirradiation with an interval over six months.15) The small intestines are generally thought more sensitive than the large bowel, being different by parts, and which tolerance level may be rather close to that of stomach.

**Paravertebral approach in brachytherapy**

We introduced a technique of paravertebral needle approach which is a safe and sure interventional procedure16) that is substantially unaffected by respiratory movement. With this technique under step by step X-ray CT-guidance, a stable, precise needle deployment and gel injection was achievable.

**Hyaluronate**

The native-type hyaluronic acid is a non-allergenic, single straight chain existing in the in the extracellular space of...
human body and degraded naturally by innate enzyme hyaluronidase.
It is known that hyaluronate binding to CD44, RHAMM (Receptor for hyaluronic acid-mediated motility) and ICAM-1 (Intercellular adhesion molecule-1) initiates receptor mediated cellular migration, proliferation and inflammatory responses, and vascular leakiness, which are promoted by low molecular weight hyaluronate that is abundant in produced in broken tissue, and suppressed by high molecular hyaluronate. Clinical tissue protective effects were reported for radiation dermatitis and for prevention of adhesion.

The spacing effect usually lasted for a few to several hours mainly depend on its concentration the and molecular weight of the hyaluronate. A time proof artificially stabilized variant of HA was used during IMRT, HDRBT and LDRBT. Appropriate selection was recommended to avoid allergic or infectious events to the artificial product.

Cost, and time effectiveness

The cost for the native-type hyaluronate is much inexpensive in comparison to cross-linked type (approx. 1/60 of an artificial type) and time required for the procedure is 10 to 15 minutes in most cases.

CONCLUSION

In this case, by HGI, a minimally invasive procedure done in the outpatient clinic, we treated the patient with an eradicative dose by HDRBT equivalent to 75.6 Gy in normally fractionated schedule at a/b = 3, with a safely involvement of the at-risk organ. This HGI procedure was thought was helpful in improving the therapeutic ratio of HDRBT in eradicative dose reirradiation of PALN metastasis.

REFERENCES


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