Radiotherapy and Oncology 107 (2013) 195–199

Contents lists available at SciVerse ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Gastric cancer

Risk of endocrine pancreatic insufficiency in patients receiving adjuvant chemoradiation for resected gastric cancer ☆

Cengiz Gemici [a,*], Mehmet Sargin [b], Oya Uygur-Bayramicli [c], Alpaslan Mayadagli [a], Gokhan Yaprak [a], Resat Dabak [b], Mihriban Kocak [a]

[a] Department of Oncology; [b] Department of Endocrinology-Diabetes, Dr. Lutfi Kirdar Kartal Education and Research Hospital; [c] Department of Gastroenterology, Maltepe University Medical Faculty, Turkey

ARTICLE INFO

Article history:
Received 7 June 2012
Received in revised form 10 February 2013
Accepted 10 April 2013
Available online 3 May 2013

Keywords:
Gastric cancer
Adjuvant radiotherapy
Endocrine pancreatic insufficiency
Diabetes mellitus

ABSTRACT

Background: Adjuvant radiotherapy combined with 5-fluorouracil based chemotherapy has become the new standard after curative resection in high risk gastric cancer. Beside many complications due to surgery, the addition of chemotherapy and radiotherapy as adjuvant treatment may lead to both acute and late toxicities. Pancreatic tissue irradiation during this adjuvant treatment because of incidental and unavoidable inclusion of the organ within the radiation field may affect exocrine and endocrine functions of the organ.

Materials and methods: Fifty-three patients with gastric adenocarcinoma were evaluated for adjuvant chemoradiotherapy after surgery. While 37 out of 53 patients were treated postoperatively due to either serosal or adjacent organ or lymph node involvement, 16 patients without these risk factors were followed up regularly without any additional treatment and they served as the control group. Fasting blood glucose (FBG), hemoglobin A1c (HBA1c), insulin and C-peptide levels were measured in the control and study groups after the surgery and 6 months and 1 year later.

Results: At the baseline there was no difference in FBG, HbA1c, C-peptide and insulin levels between the control and the study groups. At the end of the study there was a statistically significant decline in insulin and C-peptide levels in the study group, (7.5 ± 6.0 vs 4.5 ± 4.4 IU/L, p: 0.002 and 2.3 ± 0.9 vs 1.56 ± 0.9 ng/ml, p: 0.001) respectively.

Conclusions: Adjuvant radiotherapy in gastric cancer leads to a decrease in beta cell function and insulin secretion capacity of the pancreas with possible diabetes risk. Radiation-induced pancreatic injury and late effects of radiation on normal pancreatic tissue are unknown, but pancreas is more sensitive to radiation than known. This organ should be studied extensively in order to determine the tolerance doses and it should be contoured during abdominal radiotherapy planning as an organ at risk.

Radiation therapy is unavoidably associated with early and late side effects and the normal tissue toxicity is the major obstacle to effective radiation dose administration. Acute and especially late side effects are the major concern in treated patients.

There is an increased use of radiotherapy with concomitant chemotherapy after surgery in the management of gastric cancer [1]. The possibility of encountering late radiation-related side effects increases with increase in survival of these patients.

The tolerance of the spinal cord, kidneys, liver, small bowel, stomach to radiation has been well defined and incorporated into radiation plan evaluations. In contrast, the potential early and late side effects of radiotherapy on normal pancreatic tissue are not well defined. The exact dose of radiation that causes 5% of the patients to have radiation induced pancreatic complications within 5 years is unknown and no late toxicity related to pancreatic tissue exposure to radiation has been mentioned in major textbooks of radiotherapy. Pancreas is not cited among the organs at risk, either in the Emami late tissue toxicity report or in quantitative analyses of normal tissue effects in the clinic (QUANTEC) report [2,3]. The pancreas lies inferior to the stomach and it is situated within the field of radiation with inevitable exposure to irradiation during adjuvant treatment of gastric cancer.

Pancreas has both exocrine and endocrine functions. Acinar cells belong to the exocrine pancreas, and constitute more than 90% of the organ. They secrete digestive enzymes. Islets of Langerhans are responsible for the endocrine function of the organ [4]. Loss of exocrine function of the pancreas causes malabsorption and loss of endocrine function of the pancreas leads to diabetes mellitus (DM).

☆ The study has been presented as an abstract at the 2008 American Society for Therapeutic Radiology and Oncology (ASTRO) meeting, September 21–25, 2008, Boston, MA, USA.

* Corresponding author. Address: Fatih Mah. Omurkent Cad. No: 22 E, B1, D:7, Orhanli, Tuzla, Istanbul, Turkey.
E-mail address: cegemici@yahoo.com (C. Gemici).

0167-8140/$ - see front matter © 2013 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.radonc.2013.04.013

Glucose and glycosylated hemoglobin (HbA1c) levels are necessary for the diagnosis of diabetes. Plasma insulin and C-peptide levels can give information about the function of beta cells. C-peptide is used to monitor insulin production and its measurement determines endogenous insulin production capability of the beta cells.

In some animal studies, researchers have investigated morphologic and functional response of the irradiated pancreatic tissue [5,6]. Unfortunately these studies do not give us information about delayed effects of irradiation on the organ. One important observation regarding pancreatic radiation toxicity is the higher incidence of diabetes mellitus in survivors of childhood cancers who had undergone abdominal radiotherapy [7–9].

Pancreas as an organ at risk for radiation related late toxicity is not studied extensively and the underlying mechanism of the damage is not known.

This study is primarily designed for the evaluation of late radiation induced endocrine functional disturbance of the pancreatic tissue after being exposed to irradiation during adjuvant treatment of patients with operated gastric cancer.

Materials and methods

Patients with histologically proven nonmetastatic gastric adenocarcinoma who had curative surgical resection were evaluated for adjuvant treatment and were included in the study. Pathological staging was done according to the staging criteria of the American Joint Commission on Cancer [10]. Patients presenting with serosal (pT3), and or adjacent visceral organ (pT4) invasion, or with involved regional lymph nodes were considered suitable for adjuvant treatment. Thirty-seven patients were eligible for the adjuvant treatment and comprised the study group, while 16 patients (pT1, pT2 and N0) who did not receive adjuvant chemoradiotherapy comprised the control group. Patient characteristics comprising T, N stages, extent of lymph node dissection, surgical resection type were summarized in Table 1. No patients in the study group had T4 disease due to the direct involvement of pancreas, and none of the patients in the study group had undergone pancreatic tissue resection.

Adjuvant treatment plan was similar to the intergroup study presented in 2001 by MacDonald et al. [1]. Patients received bolus 5-fluorouracil and leucovorin; one cycle before, two cycles concomitant to and one cycle after radiation treatment. Radiation was delivered with either 6 or 15 MV photons by anterior and posterior parallel opposed fields to total dose of 46 Gy in 23 fractions with 2 Gy fractions per day, 5 days per week for 5 weeks. The radiation field included the tumor bed and the regional lymphatics according to the technique described by Smalley et al. [11]. Radiation planning was 2-dimensional as in MacDonald's study. All or most part of the pancreatic tissue was included in the radiation field due to 2-dimensional radiation planning and most of the pancreatic tissue has received the whole radiation dose calculated at midplane.

All patients gave informed consent. Blood samples were taken after operation and regularly at 3 or 6 month intervals and 1 year after surgery for the patients receiving no adjuvant treatment, and 1 year after the end of radiotherapy for patients receiving adjuvant treatment. One year time period was considered enough for late radiation toxicity evaluation.

Age, gender, height, weight and body mass index (BMI) were recorded. Fasting blood glucose, hemoglobin A1c, insulin and C-peptide levels were measured initially, at the 6th month and at the end of the study. All of the routine biochemical tests were carried out on Roche Diagnostics Modular Systems autoanalyser. Levels of insulin and C-peptide were measured by chemiluminometric immunoassay.

In addition to measurement of insulin and C-peptide levels, there are indirect methods for the assessment of insulin resistance and pancreatic beta cell function named as HOMA indices [12]. HOMA indices are formulated as follows:

HOMA-IR = [insulin × glucose]/22.5, which shows insulin resistance.
HOMA-Beta = [20 × insulin]/[glucose − 3.5], which shows insulin secretion capacity of the pancreas and beta cell function.

Both groups were similar according to, age, gender and BMI.
The study was approved by the local ethics committee.

Statistical analysis was performed with SPSS program. A p value less than 0.05 was considered statistically significant. Results were expressed as mean ± SD. Comparison between the groups were made with Student's t-test.

Results

Demographic features of the study and control group are summarized in Table 2. At baseline there was no difference in age, body weight, BMI, FBG, insulin, C-peptide, HbA1c levels between the control and the study group (Tables 2 and 3). Since radiation planning was 2-dimensional, no dose-volume histogram data are available for organs at risk including the pancreas.

In regard to FBG and HbA1c there was no difference between both groups at the 6th month and at the end of the study compared

Table 1
Patient characteristics comprising T, N stages, extent of lymph node dissection, and surgical resection type.

	Study group Radiotherapy (+)	Control group Radiotherapy (−)
T stage		
T1	–	4 (25%)
T2	10 (27%)	12 (75%)
T3	22 (59%)	–
T4	5 (14%)	–
N stage		
N0	5 (13.5%)	16 (100%)
N1	14 (38%)	–
N2	13 (35%)	–
N3	5 (13.5%)	–
Extent of lymph node dissection		
D0	3 (8%)	–
D1	26 (70%)	11 (68.7%)
D2	8 (22%)	5 (31.3%)
Surgical procedure		
Subtotal	20 (54%)	10 (62.5%)
Total	17 (46%)	6 (37.5%)

Table 2
Comparison of the study group (radiotherapy +) and the control group (radiotherapy −) according to age, gender, BMI, insulin, C-peptide and HbA1c at the beginning of the study.

	Study group Radiotherapy (+)	Control group Radiotherapy (−)	p
N	37	16	
Age (years)	52.92 ± 12.3	59.62 ± 11.3	N.S.*
Gender (F/M)	12/25	7/9	N.S.
BMI (kg/m^2)	23.06 ± 3.84	24.76 ± 4.74	N.S.
Insulin (U/L)	7.51 ± 6.0	8.25 ± 5.8	N.S.
C-peptide (ng/dl)	2.30 ± 1.0	2.65 ± 1.2	N.S.
HbA1c (%)	5.54 ± 0.5	5.89 ± 0.7	N.S.

* N.S.: non-significant.

Table 3
Comparison of the study group (radiotherapy +) and control group (radiotherapy −) according to endocrine functions of the pancreas at initial, 6 and 12 months of the study.

	Study group Radiotherapy (+)	Control group Radiotherapy (−)	*p*
FBG (mg/dl)			
Initial	92.54 ± 12.2	95.12 ± 22.3	NS
6 months	90.62 ± 12.4	95.19 ± 11.3	NS
12 months	88.46 ± 10.5	90.56 ± 18.0	NS
p	NS	NS	
HbA1c (%)			
Initial	5.54 ± 0.5	5.89 ± 0.7	NS
6 months	5.49 ± 0.5	5.89 ± 0.7	NS
12 months	5.67 ± 0.6	6.15 ± 0.5	NS
p	NS	NS	
Insulin (U/L)			
Initial	7.51 ± 6.0	8.25 ± 5.8	NS
6 months	5.94 ± 5.8	8.51 ± 6.0	0.05
12 months	4.55 ± 4.4	10.47 ± 12.0	0.001
p	0.002	NS	
C-peptide (ng/dl)			
Initial	2.30 ± 1.0	2.65 ± 1.2	NS
6 months	1.78 ± 1.0	2.40 ± 1.5	0.05
12 months	1.56 ± 0.9	2.62 ± 1.9	0.007
p	0.001	NS	
HOMA-B			
Initial	85.73 ± 38.4	84.90 ± 32.1	NS
6 months	73.26 ± 28.5	82.49 ± 41.5	0.005
12 months	71.37 ± 24.3	81.49 ± 61.3	0.002
p	0.02	NS	

to the initial levels. Similarly, there was no difference in insulin, C-peptide and HOMA-Beta levels at the baseline and at the end of the study in the control group, but there was a statistically significant decrease in insulin, C-peptide and HOMA-Beta levels in the study group; these measurements were lower both at 6 months and at one year (after 1 year; 7.5 ± 6.0 vs 4.5 ± 4.4 IU/L, *p*: 0.002; 2.3 ± 0.9 vs 1.56 ± 0.9 ng/ml, *p*: 0.001 and 85.73 ± 38.4 vs 71.37 ± 24.3, *p*: 0.02) respectively (Table 3). Decrease in insulin, C-peptide and HOMA-Beta levels start as early as 6 months and continue throughout the end of study without any recovery. However none of the patients in the study group were diagnosed with diabetes mellitus at the end of one year.

There was no local recurrence in both groups during the study period affecting the pancreas and pancreatic function.

Discussion

Pancreatic tissue is subjected to ionizing radiation primarily during treatment of pancreatic cancer either in the postoperative setting or as definitive therapy. Patients with pancreatic carcinoma have low life expectancy and radiation effects on the organ are not fully documented. Longer survival in operated gastric cancer patients can give us the opportunity to study the late side effects.

Data about radiation related pancreatic tissue toxicity in the literature are based mainly on animal studies or abdominal irradiation for pediatric solid tumors or total body irradiation (TBI) for bone marrow transplantation in hematologic malignancies [5–9,13–18]. Acinar cells of the pancreas are much more sensitive to radiation damage than islet cells and the pathophysiology of radiation damage is mainly due to chronic vascular injury with eventual fibrosis and atrophy of the gland [5–7,19–21].

Ahmadu-Suka et al. [5] evaluated gross and histopathologic changes in the pancreas and duodenum of dogs by autopsy after intraoperative irradiation (IORT). The pancreatic tissue showed atrophy after irradiation and exocrine pancreatic insufficiency occurred in one dog after 25 Gy IORT. Histopathologic evidence of radiation damage was observed on acinar cells. There was pancreatic fibrosis and damage to blood vessels and ducts which showed a dose response relationship. However islet cell lesions were not apparent. The authors stated that exocrine pancreatic insufficiency and diabetes mellitus may be potential late complications of 25 Gy or higher doses of IORT.

In another animal study, designed to study short and long term endocrine and exocrine insufficiency of the pancreatic tissue induced by IORT, authors observed a significant decrease in insulin secretion in dogs treated with 30–35 Gy IORT [21]. Contrary to endocrine function, exocrine function was not affected very much. 25 Gy IORT is found safe in regard to endocrine and exocrine insufficiency.

Pieroni et al. [6] studied the effect of irradiation on the pancreatic tissues of six dogs. They administered 40 Gy equivalent radiation in 6 weeks which is the dose mostly used in the treatment of upper abdominal malignancies. There was microscopic evidence of diffuse interstitial fibrosis and marked reduction of acinar cells after irradiation. The enzyme output was reduced (>90%) after 3 months. Despite reduction in exocrine function, no clinical evidence of DM and no change either in FBG or the glucose tolerance test were observed in the dogs. Authors stated that islet cells are relatively radioresistant compared to acinar cells and suggested that radiation of upper abdomen for any reason may cause pancreatic damage and exocrine insufficiency.

In patients, information on the radiation related pancreatic toxicity is sparse and often obscured by other gastrointestinal side effects of the treatment. Clinical signs and radiologic findings of chronic pancreatitis were reported years later after abdominal irradiation at doses ranging from 36–45 Gy [22–24]. The pancreatic tissue of these patients is normally functioning and exposed to radiation during abdominal irradiation for lymphoma and mimics the situation we are trying to investigate.

Similar findings to animal studies have been observed in humans undergoing IORT for pancreatic and periampullary carcinomas [25]. There was a significant decline in pancreatic exocrine function without an important endocrine deficiency.

Nishimura et al. [26] reported histopathological findings of the nonirradiated normal parts of pancreatic tissue after IORT for advanced pancreatic cancer. Although no extensive destruction of the islet cells was detected in the irradiated field, interstitial fibrosis was seen in the atrophied glandular tissue. Fibrous thickening of the intima resulted in luminal stenosis of blood vessels. IORT enhanced the decline of the pancreatic exocrine function and decreased pancreatic juice output at the early postoperative period.

As a summary of these animal and human studies mentioned above [5–7,19–26], there is relative sensitivity of the exocrine part of the pancreas to irradiation in comparison to the endocrine part of the organ. Vascular damage is the most common cause of radiation toxicity [5–7,19–26]. The irradiated pancreatic tissue shrinks in size and becomes extremely fibrotic. There is atrophy and loss of acinar cells, however the islets of Langerhans are well preserved. Although the islets of Langerhans are preserved histologically after radiation, they lose their functional capacity. The exact dose of radiation that causes 5% of the patients to have radiation induced pancreatic complications within 5 years (TD 5/5) is not known, but exocrine pancreatic insufficiency and relatively less commonly endocrine insufficiency occurs after either administering above 25 Gy IORT, or 40 Gy equivalent doses of classical fractionated radiation. Although exocrine insufficiency is observed early, several weeks to months after radiation, endocrine insufficiency occurs relatively lately, several months to years after irradiation [5–7,19–26].

Some antineoplastic drugs like L-asparaginase and streptozocin can also induce diabetes mellitus [27,28]. Busulphan has been

shown to cause damage to pancreatic beta-cells in the rats [29]. Streptozotocin causes beta cell necrosis, inflammation of the islets and a delayed onset hyperglycemia [30]. Pancreatic toxicity has not been reported in the literature with 5-fluorouracil.

Recent studies suggest that cancer survivors whose treatment included bone marrow transplantation have an increased prevalence of DM, particularly those who were treated with TBI [9,14,17,31–34]. Development of DM after TBI is considered to be multifactorial. Growth hormone deficiency resulting from cranial tissue exposure to irradiation, hypogonadism resulting from testicular and ovarian tissue exposure to irradiation and abdominal obesity resulting in turn from growth hormone deficiency and hypogonadism were accused to be associated with development of hyperinsulinemia and insulin resistance [9,13,14,33,34]. But development of DM after TBI, rather being multifactorial as suggested in the literature, may be related to the direct effect of radiation on the pancreas and beta cells.

Childhood cancer survivors whose treatment included abdominal irradiation for curable tumors like Wilms tumor have also increased risk of DM [7–9]. The mechanism of DM with abdominal irradiation in contrast to TBI is not so complex and it is directly related to radiation induced beta cell damage. Childhood cancer survivor study is a retrospectively ascertained North American cohort of long-term survivors who were diagnosed between 1970 and 1986 as well as 2936 randomly selected siblings of the survivors [9]. The main outcome of the study was self-reported DM. The survivors were 1.8 times more likely than the siblings to be diabetic. They received TBI, cranial radiotherapy or abdominal irradiation for either hematologic (leukemia, lymphoma), cranial (central nervous system tumors) or abdominal malignancies (renal tumors, neuroblastoma, soft tissue sarcoma). Survivors who received abdominal radiotherapy for neuroblastoma, Wilms tumor or Hodgkin's lymphoma were significantly more likely to be diabetic than their siblings. Neuroblastoma survivors who were treated with abdominal irradiation had a 9-fold increased likelihood of being diabetic in comparison to their siblings, while those who were not treated with abdominal irradiation did not have an increased risk of diabetes. Similar risk of DM has been observed in survivors who were exposed to abdominal irradiation for Wilms tumor and Hodgkin's lymphoma. Association of abdominal irradiation with diabetogenic effect has not been elucidated clearly. But it is evident that pancreatic exposure to radiation causes DM and the most common cause for this diabetogenic effect is the beta cell damage. In another retrospective review of 121 Wilms tumor survivors, 8 (6.6%) developed DM [7]. The prevalence of diabetes in this population is higher than expected in young adults. DM was diagnosed after 11–13 years of follow up, so long term follow up is necessary before the onset of diabetes. Abdominal irradiation related DM is not only observed for childhood cancer survivors but also for abdominal radiation exposure during adulthood as well. In a study originally initiated to investigate the long-term cancer risk of abdominal irradiation in adults who were treated for peptic ulcer disease, it has been observed that DM risk had increased [35]. In this study individual radiation doses were estimated to specific organs from radiotherapy records and phantom experimental measurements. Doses calculated to the pancreas ranged from 1 to 38 Gy. Relative risk of death due to diabetes increased with increased pancreatic dose, being highest for 17–38 Gy dose levels.

The association of DM following TBI in children and adults is thought to occur with a complex underlying mechanism, but development of DM with abdominal radiotherapy results clearly from direct beta cell damage. This damage is time and dose dependent with a very long latency period ranging from 6 to 20 years [22]. Radiation doses above 40 Gy with classical fractionation or above a 25 Gy single fraction as in IORT or 9–15 Gy single or hyperfractionated doses as in TBI are clearly toxic to endocrine pancreatic tissue. Our study confirmed that beta cell damage or functional loss occurs as early as 6 months to 1 year after classical fractionated 46 Gy of abdominal irradiation with no overt DM after 1 year of follow-up.

All these prospectively designed animal and retrospective and prospective human data show that radiation is toxic for pancreatic endocrine and exocrine functions. In the present study, late endocrine side effect of pancreatic irradiation on patients was investigated with the measurement of FBG, HbA1c, insulin, C-peptide and HOMA-Beta levels initially and 6 months to 1 year after abdominal irradiation. In regard to FBG and HbA1c there was no difference at the end of the study compared to initial levels. Insulin, C-peptide and HOMA-Beta levels however were lower in the study group even after 6 months and at the end of 1 year. This decrease was the result of radiation related beta cell or its function loss and there is no recovery of the damage starting at 6 months and continues throughout the study period. But despite this decrease in endocrine pancreatic reserves none of the patients developed overt DM, because the development of diabetes takes years and necessitates the depletion of all pancreatic islet cell reserves. These patients should be followed up for a longer period of time and evaluated routinely for the development of diabetes. Risk of death due to complications of DM may increase in gastric cancer patients who received adjuvant radiotherapy.

Conclusion

Abdominal radiotherapy leads to a decrease in beta cell function which may lead to possible diabetogenic effect years later. Radiation-induced pancreatic injury and late effects of radiation on normal pancreatic tissue are unknown and not investigated extensively. Late radiation related pancreatic toxicity is a new concept and should be considered in radiation treatment and radiation toxicity reports.

Future prospective studies will be necessary and the pancreas should be contoured during abdominal radiation treatment planning in order to construct dose volume histogram and determine safe radiation doses to the organ.

Conflict of interest

No potential conflict of interest exists.

References

[1] MacDonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:2343–51.
[2] Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic radiation. Int J Radiat Oncol Biol Phys 1991;21:109–22.
[3] Bentzen SM, Constine LS, Deasy JO, et al. Quantitative analyses of normal tissue effects in the clinic (Quantec): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys 2010;76:3–9.
[4] American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;33:s64–71.
[5] Ahmadu-Suka F, Gillette EL, Withrow SJ, et al. Pathologic response of the pancreas and duodenum to experimental intraoperative irradiation. Int J Radiat Oncol Biol Phys 1988;14:1197–204.
[6] Pieroni PL, Rudick J, Adler M, et al. Effect of irradiation on the canine exocrine pancreas. Ann Surg 1976;184:610–4.
[7] Teinturier C, Tournade MF, Caillat-Zucman S, et al. Diabetes mellitus after abdominal radiation therapy. Lancet 1995;346:633–4.
[8] Cicognani A, Cacciari E, Mancini AF. Abnormal insulin response to glucose following treatment for Wilms' tumor in childhood. Eur J Pediatr 1997;156:371–5.
[9] Meacham LR, Sklar CA, Li S, et al. Diabetes mellitus in long-term survivors of childhood cancer. Increased risk associated with radiation therapy: a report for the childhood cancer survivor study. Arc Intern Med 2009;169:1381–8.
[10] AJCC (American Joint Committee on Cancer). In: Edge SB, Byrd DR, Compton CC, et al., editors. Cancer staging manual. New York: Springer; 2010. p. 117.

[11] Smalley SR, Gunderson L, Tepper J, et al. Gastric surgical adjuvant radiotherapy consensus report; rationale and treatment implementation. Int J Radiat Oncol Biol Phys 2002;52:283–93.
[12] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentration in man. Diabetologia 1985;28:412–9.
[13] Chemaitilly W, Boulad F, Oeffinger KC, et al. Disorders of glucose homeostasis in young adults with total body irradiation during childhood: a pilot study. Bone Marrow Transplant 2009;44:339–43.
[14] Lorini R, Cortona L, Scaramuzza A, et al. Hyperinsulinemia in children and adolescents after bone marrow transplantation. Bone Marrow Transplant 1995;15:873–7.
[15] Neville KA, Cohn RJ, Steinbeck KS, et al. Hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus in survivors of childhood cancer: prevalence and risk factors. J Clin Endocrinol Metab 2006;91:4401–7.
[16] Traggai C, Stanhope R, Nussey S, et al. Diabetes mellitus after bone marrow transplantation during childhood. Med Pediatr Oncol 2003;40:128–9.
[17] Baker KS, Ness KK, Steinberger J, et al. Diabetes, hypertension, and cardiovascular events in survivors of hematopoietic cell transplantation: a report from the bone marrow transplantation survivor study. Blood 2007;109:1765–72.
[18] Sarri Y, Conill C, Verger E, et al. Effects of single dose irradiation on pancreatic beta-cell function. Radiother Oncol 1991;22:143–4.
[19] Horst E, Seidel M, Micke O, et al. Accelerated radiochemotherapy in pancreatic cancer is not necessarily related to a pathologic pancreatic function decline in the early period. Int J Radiat Oncol Biol Phys 2002;52:304–9.
[20] Zook BC, Bradley WE, Casarett GW, et al. Pathologic effects of fractionated fast neutrons or photons on the pancreas, pylorus and the duodenum of dogs. Int J Radiat Oncol Biol Phys 1983;9:1493–504.
[21] Heijmanns HJ, Mehta DM, Kleibeuker JH, et al. Intraoperative irradiation of the canine pancreas: short term effects. Radiother Oncol 1993;29:347–51.
[22] Levy P, Menzelxhiu A, Paillot B, et al. Abdominal radiotherapy is a cause for chronic pancreatitis. Gastroenterology 1993;105:905–9.
[23] Schoonbroodt D, Zipf A, Hermann G, et al. Histological findings in chronic pancreatitis after abdominal radiotherapy. Pancreas 1996;12:313–5.
[24] Mitchel CJ, Simpson FG, Davison AM, et al. Radiation pancreatitis: A clinical entity? Digestion 1979;19:134–6.
[25] Yamaguchi K, Nakamura K, Kimura M, et al. Intraoperative radiation enhances decline of pancreatic exocrine function after pancreatic head resection. Dig Dis Sci 2000;45:1084–90.
[26] Nishimura A, Nakano M, Otsu H, et al. Intraoperative radiotherapy for advanced carcinoma of the pancreas. Cancer 1984;54:2375–84.
[27] Gailani S, Nussbaum A, Ohnuma T, et al. Diabetes in patients treated with asparaginase. Clin Pharmacol Ther 1971;12:488–90.
[28] Rerup CC. Drugs producing diabetes through damage of the insulin secreting cells. Pharmacol Rev 1970;22:485–518.
[29] Kaduk B, Husslein E-M, Siegfrid A. Morphology of the chronic toxicity of busulfan on the islet of Langerhans in the rat. Hepatogastroenterology 1987;34:108–12.
[30] Like AA, Rossini AA. Streptozotocin-induced pancreatic insulitis: new model of diabetes mellitus. Science 1976;193:415–7.
[31] Smedmyr B, Wibell L, Simonsson B, et al. Impaired glucose tolerance after autologous bone marrow transplantation. Bone Marrow Transplant 1990;6:89–92.
[32] Hoffmeister PA, Storer BE, Sanders JE. Diabetes mellitus in long-term survivors of pediatric hematopoietic cell transplantation. J Pediatr Hematol Oncol 2004;26:81–90.
[33] Neville KA, Cohn RJ, Steinbeck KS, et al. Hyperinsulinemia, impaired glucose tolerance, and diabetes mellitus in survivors of childhood cancer: prevalence and risk factors. J Clin Endocrinol Metab 2006;37:1109–17.
[34] Taskinen M, Saarinen-Pikala UM, Hovi L, et al. Impaired glucose tolerance and dyslipidemia as late effects after bone-marrow transplantation in childhood. Lancet 2000;356:993–7.
[35] Kleinerman RA, Weinstock RM, Mabuchi K. High-dose abdominal radiotherapy and risk of diabetes mellitus. Arch Intern Med 2010;170:1506–7.