

Diabetes mellitus and its effects on all-cause mortality after radiopeptide therapy for neuroendocrine tumors

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ABSTRACT

We aimed to assess the risk of developing diabetes mellitus and its effects on all-cause mortality after radiopeptide therapy for neuroendocrine tumors (NET).

Methods: NET patients received somatostatin radiopeptide therapy with yttrium-90-DOTATOC and/or lutetium-177-DOTATOC. The incidence of diabetes mellitus and its mortality were assessed using univariate and multivariate regression.

Results: Overall, 1535 NET patients were enrolled, and received 3807 treatment cycles. After treatment, 72 patients developed diabetes mellitus, including 47 cases after yttrium-90-DOTATOC and 25 cases after combined treatment. The diabetes mellitus risk was higher before than after DOTATOC (Estimate: 0.0032, $p < 0.001$), and overall survival was similar in patients with and without diabetes mellitus (HR: 1.13, 95%CI: 0.91-1.39, $n = 1535$, $p = 0.27$).

Conclusions: Radiopeptide therapy does not appear to increase the risk of developing diabetes mellitus in NET patients, while diabetes mellitus does not appear to increase the mortality of NET patients undergoing receptor-targeted radiopeptide therapy.

Key Words: sstr₂, metabolic therapy, targeted therapy, adverse event, toxicity

INTRODUCTION

Radiolabeled somatostatin analogues are successful examples of targeted tumor therapy (1) (**Figure 1**), which can achieve meaningful clinical responses in patients with locally advanced and metastatic neuroendocrine tumors (NET) (2-4).

NET patients are generally at risk of experiencing impaired glucose metabolism from a variety of first-line therapies. Pancreatic surgery reduces the amount of functional parenchyma, streptozotocin is cytotoxic to pancreatic β -cells, octreotide and everolimus reduce insulin secretion, and everolimus also increases insulin resistance (5,6). A potential consequence of these therapies is the onset of pre-diabetes or diabetes mellitus, which is commonly associated with increased long-term, all-cause mortality in oncological patients (7).

The high expression of somatostatin receptors by the pancreas, and especially in the pancreatic islets (8), has led to the theory that treatment with radiolabeled somatostatin analogues might cause destruction of endocrine pancreatic parenchyma and subsequent development of diabetes mellitus. However, the incidence of diabetes after radiopeptide therapy and its effect on all-cause mortality in NET patients remained unknown.

Herein, we report the risk of developing diabetes mellitus after treatment with radiolabeled somatostatin analogues and its effects on all-cause mortality, to provide a framework for improved clinical management of NET patients.

MATERIALS AND METHODS

Patients

We performed a cross-sectional post-hoc follow-up on diabetes-related outcomes in NET patients that had been enrolled in a prospective trial investigating the benefit of treatment with radiolabeled DOTATOC (tetraazacyclododecane-tetraacetic acid (DOTA) modified somatostatin analog Tyr³-octreotide (TOC)), performed between 1997 and 2010.

Patients had been enrolled and treated as previously described (2-4). In brief, patients with progressive metastatic NET and tumor uptake in somatostatin receptor imaging were enrolled to receive somatostatin receptor-targeted radiopeptide therapy with yttrium-90-DOTATOC, lutetium-177-DOTATOC, or their combination at the University Hospital Basel, Switzerland. Patients were excluded in case of concurrent anti-tumor treatment, pregnancy, breast-feeding, urinary incontinence, preexisting grade 3/4 hematological toxicities, and severe concomitant illness.

The study was designed and carried out according to good clinical practice, Swiss drug laws and the Declaration of Helsinki. It was approved by the Basel ethics committee for human studies (#120/1997) and registered (*ClinicalTrials.gov* number NCT00978211). Written informed consent was obtained from all participants or legal representatives.

Follow-up & Outcomes

Primary outcome was the diagnosis of diabetes mellitus, before or after start of DOTATOC treatment, made by the referring centers or primary practitioners. Data on the diagnosis of diabetes mellitus were actively obtained from the referring physicians and primary practitioners, and approved for completeness at the study center.

Secondary outcome was survival after DOTATOC in patients with and without diabetes mellitus. Survival data were obtained from referring physicians, primary practitioners or from the patient, and approved for completeness at the study center.

Additional outcomes were changes in the serum levels of glucose and C-peptide after start of DOTATOC treatment. They were investigated in all patients receiving lutetium-177-DOTATOC and in age and gender matched patients who received yttrium-90-DOTATOC.

Blood samples

Blood samples were drawn before each treatment cycle from the non-fasting patient and immediately centrifuged. Blood serum was collected, and stored at -20°C. Serum glucose (Glucose GOD-PAP, Roche Diagnostics) and C-peptide (IMMULITE 2000 Immunoassay System, Siemens Healthcare) were measured in duplicates with standardized protocols using one assay batch.

Statistical Analyses

The primary hypothesis was an increased incidence of diabetes mellitus after DOTATOC. The incidence before and after DOTATOC was compared via estimation of difference between a binomial- and the Aalen-Johansen estimator. The incidence before DOTATOC was calculated conditional on study entry. To include groups without diabetes cases, proportional hazard regression was used as previously described, and profile likelihood-based confidence intervals were calculated for confirmation (9,10). Co-variables were gender (female vs. male), age (per year), histology (pancreatic NET vs. carcinoids vs. rare NET), disease duration (in months), pretreatment (surgery vs. chemotherapy vs. radiotherapy), treatment regimen (yttrium-90-DOTATOC vs. lutetium-177-DOTATOC vs. their combination) and cumulative administered activity (per GBq). Insulinoma and glucagonoma cases were excluded due to their abnormal glucose metabolism. Subgroup analyses were performed to compare the incidence of diabetes mellitus after yttrium-90-DOTATOC, lutetium-177-DOTATOC, or their combination. Intention-to-treat analysis was applied. A worst-case scenario analysis was performed assuming diabetes mellitus developed in all patients who were lost to follow-up.

The secondary hypothesis was a shorter survival in NET patients with diabetes mellitus. The survival with and without diabetes mellitus was compared using multivariate Cox regression with the co-variables listed above. Sensitivity analyses in patients with and without pancreas surgery were performed for all analyses to detect effects of pancreas surgery.

Glucose and C-peptide serum profiles were generated via the random intercept model and smoothed using the LOESS method (11). Two-sided p-values below 5% were considered statistically significant. Effect estimates were expressed as hazard ratios (HRs) with 95% confidence intervals (CI).

RESULTS

Between February 1997 and February 2010, 2041 patients were screened for eligibility. Of these, 130 patients (6.4%) were not eligible due to absent visible tumor uptake in pre-therapeutic imaging, poor physical condition, or impaired bone marrow function. Furthermore, 360 patients (17.6%) were eligible but not enrolled, as they received other treatment, lost transferability to the treatment center, or died before the first treatment cycle (**Figure 2**). The remaining 1551 patients (76.0%) were enrolled from over 100 centers in 29 countries, and were treated with 3807 treatment cycles (median: 2 cycles per patient; range: 1-11 cycles per patient). Eight insulinoma patients (0.4%) and 8 glucagonoma patients (0.4%) were excluded from the analyses. The characteristics of the included 1535 patients are shown in **Table 1**.

Risk of developing diabetes mellitus

At the time of enrollment, 186 of 1535 patients (12.1%) had a pre-existing diabetes mellitus. In the remaining 1349 patients, 72 patients (5.3%) developed diabetes mellitus after DOTATOC treatment. Thereby, the only clinical predictor for developing diabetes mellitus was the diagnosis of pancreatic NET (**Table 2**).

The risk for developing diabetes mellitus was significantly higher before than after DOTATOC treatment (Estimate: 0.0032, estimation of difference between a binomial- and the Aalen-Johansen estimator, $p < 0.001$; **Figure 3A**). Sensitivity analyses including patients with or without pancreatic surgery confirmed these results.

Nine patients were lost to follow-up, three of whom had diabetes mellitus before DOTATOC treatment. A worst-case scenario analysis with the remaining six patients assigned as diabetes mellitus cases generated results in line with the primary analysis (HR: 1.09, 95% CI: 0.58 - 2.06, proportional hazard regression, n = 1093, p = 0.78).

Diabetes mellitus and mortality

Overall, 637 of 1535 patients (41.5%) died and nine (0.6%) patients were not available for follow-up. The median survival time after start of DOTATOC treatment was 41.9 months (CI: 37.3 - 45.3 months). Patients with and without diabetes mellitus had a similar survival, as confirmed by multivariate analyses (HR: 1.125, 95%CI: 0.913-1.386, proportional hazard Cox regression model, n = 1535, p = 0.27, **Figure 3B**) and univariate analyses (log rank test, n = 1535, p = 0.50).

Diabetes mellitus after lutetium-177-DOTATOC and/or yttrium-90-DOTATOC

During follow-up, diabetes mellitus developed in 47 of 969 patients (4.9%) that received yttrium-90-DOTATOC, and in 25 of 263 patients (9.5%) that received yttrium-90-DOTATOC plus lutetium-177-DOTATOC. None of the 117 patients (0%) that received lutetium-177-DOTATOC developed diabetes mellitus (HR: 0.000, SE: 0.182, profile likelihood CI: 0.000-0.498, proportional hazard regression, and profile likelihood, n = 117, p < 0.001; **Figure 3C**).

After yttrium-90-DOTATOC, increased glucose levels (estimate: 0.038, linear mixed model, n = 70, p = 0.004, **Supplemental Figure 1A**) were found, but no significant changes in C-peptide levels (estimate: -0.032, linear mixed model, n = 70, p = 0.485, **Supplemental Figure 1B**). After lutetium-177-DOTATOC, no significant changes in glucose levels (estimate: 0.044, linear mixed model, n = 71, p = 0.122, **Supplemental Figure 1C**) or C-peptide levels (estimate: 0.011, linear mixed model, n = 71 p = 0.950, **Supplemental Figure 1D**) were found.

DISCUSSION

The present results revealed no increased risk of developing diabetes mellitus after somatostatin receptor-targeted radiopeptide therapy in NET. Conversely, the results suggest a higher risk of developing diabetes mellitus in patients prior to radiopeptide therapy. This observation may in part be due to a stringent diagnostic work-up coinciding with detection of NET, or exposure to therapies with diabetogenic potential prior to radiopeptide treatment. Furthermore, there is no evidence of increased mortality in patients developing diabetes mellitus after radiopeptide therapy. Finally, the comparison of different treatment regimens suggests a lower diabetogenic potential of lutetium-177- over yttrium-90-based therapies.

Strengths and limitations

Strengths of the present study include the large patient number, the systematic data assessment, and the thorough follow-up, all of which contributed to robust statistical analyses. These analyses did not detect effects on diabetes mellitus incidence or disease-specific mortality. However, these analyses do not exclude the possibility of such effects, which might be detectable by a much larger trial.

Further strengths include a comparison of yttrium-90-DOTATOC and lutetium-177-DOTATOC, which used clinically relevant endpoints and biomarkers, and which was supported by a worst-case scenario analysis.

However, the present study was not a randomized trial, and has the known limitations of a non-randomized non-controlled study. Furthermore, the diagnosis of diabetes was obtained from the referring physicians. In patients where the presence of diabetes mellitus was uncertain, the referring physicians were contacted again to provide clarification. Systematic assessment of fasting plasma glucose and oral glucose tolerance tests were not feasible in stage IV cancer patients, who travelled to undergo oncological treatment. Also, an ascertainment bias, as primary care physicians may have decreased their surveillance for diabetes mellitus in patients with the more serious neoplastic illness cannot be excluded.

Comparisons with other studies

To the best of our knowledge, this is the first study to systematically assess the risk for developing diabetes mellitus after radiopeptide therapy and its disease-specific mortality. One report of 131 patients did not find changes in serum HbA_{1c} after radiopeptide therapy (12), which is in line with our results.

Implications

In the clinical routine, diabetic patients should not be excluded from somatostatin receptor-targeted radiopeptide therapy. However, lutetium-177-based treatment regimens might be considered in diabetic patients or those at high risk for developing diabetes, especially if other diabetogenic treatment modalities are part of their therapeutic regimen. On the other hand, increased awareness of glycemic control might be considered after yttrium-90-based treatment regimes in patients with pre-diabetic metabolism.

Further research that focuses on quality-of-life aspects related to glycemic control and on the recovery of diabetes mellitus and catabolic metabolism after completion of radiopeptide treatment might be valuable. Future studies should also implement data on co-morbidities and medication with potential influence on diabetes mellitus.

Until additional studies are available, guidelines should consider somatostatin receptor-targeted radiopeptide therapy as relatively safe in regard to alterations of glucose metabolism. Routine assessment for diabetogenic toxicity after radiopeptide therapy in general does not seem justified based on the current results.

CONCLUSIONS

The current results suggest that receptor-targeted radiopeptide therapy is relatively safe in regard to alterations of glucose metabolism. Radiopeptide therapy does not seem to increase the risk of developing diabetes mellitus in NET patients, while the development of diabetes mellitus in NET patients following receptor-targeted radiopeptide therapy does not seem to result in increased mortality.

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TABLES

Table 1. Patient Baseline Characteristics (n = 1535)

Characteristic		Yttrium-90- DOTATOC (n = 1093)	Lutetium-177- DOTATOC (n = 141)	Lutetium-177- DOTATOC plus Yttrium-90- DOTATOC (n = 301)	All Patients (n = 1535)
Gender	Females	471 (43.1%)	59 (41.8%)	120 (39.9%)	650 (42.3%)
	Males	622 (56.9%)	82 (58.2%)	181 (60.1%)	885 (57.7%)
Age [y]	Median	58.9	62.4	59.0	59.2
	Range	11.2-86.5	14.8-83.4	23.2-82.1	11.2-86.5
Disease Duration [m]	Median	22.8	16.6	18.7	21.8
	Range	0.0-460.0	1.2-374.7	0.8-623.4	0.0-623.4
Pretreatment	Surgery	597 (54.6%)	79 (56.0%)	194 (64.5%)	870 (56.7%)
	Chemotherapy	344 (31.5%)	46 (32.6%)	82 (27.2%)	472 (30.7%)
	Radiation	143 (13.1%)	17 (12.1%)	31 (10.3%)	191 (12.4%)
Pancreas surgery		301 (27.5%)	25 (17.7%)	81 (26.9%)	407 (26.5%)
DOTATOC cycles	Median	2	2	3	2
	Range	1-10	1-5	2-11	1-11
Cumulative activity [mCi]	Median	350	400	600	380
	Range	45-1680	200-1000	320-1630	45-1680
Histology	Carcinoids	482 (44.1%)	61 (43.3%)	145 (48.2%)	688 (44.8%)
	PNET	326 (29.9%)	26 (18.4%)	88 (29.2%)	440 (28.7%)
	Rare NET	100 (9.1%)	24 (17.0%)	26 (8.6%)	150 (9.8%)
	Unknown Primary	185 (16.9%)	30 (21.3%)	42 (14.0%)	257 (16.7%)
Diabetes mellitus at baseline		124 (11.3%)	24 (17.0%)	38 (12.6%)	186 (12.1%)

Table 2. Predictors for diabetes mellitus (n = 1535)

Variables		Hazard Ratio (95% CI)*	p-value
Gender	<i>(female vs. male)</i>	1.102 (0.767-1.795)	0.698
Age	<i>(per year)</i>	0.998 (0.978-1.017)	0.806
Duration of Disease	<i>(per month)</i>	1.002 (0.997-1.007)	0.393
Previous Surgery	<i>(vs. no surgery)</i>	0.973 (0.579-1.633)	0.916
Previous Chemotherapy	<i>(vs. no chemotherapy)</i>	0.712 (0.394-1.287)	0.261
Previous Radiation	<i>(vs. no radiation)</i>	0.679 (0.251-1.840)	0.447
Lutetium-177-DOTATOC	<i>(vs. yttrium-90-DOTATOC)</i>	0.000 (0.000-0.498)	-
Combination treatment	<i>(vs. yttrium-90-DOTATOC)</i>	1.023 (0.542-1.931)	0.945
Cumulative activity	<i>(per 1 mCi)</i>	1.000 (0.999-1.001)	0.622
pNET	<i>(vs. Carcinoid)</i>	2.306 (1.364-3.897)	0.002
Rare NET	<i>(vs. Carcinoid)</i>	0.796 (0.261-2.431)	0.688
Unknown primary	<i>(vs. Carcinoid)</i>	0.586 (0.222-1.550)	0.282

* Estimates for each variable have been adjusted for all other variables listed

FIGURES

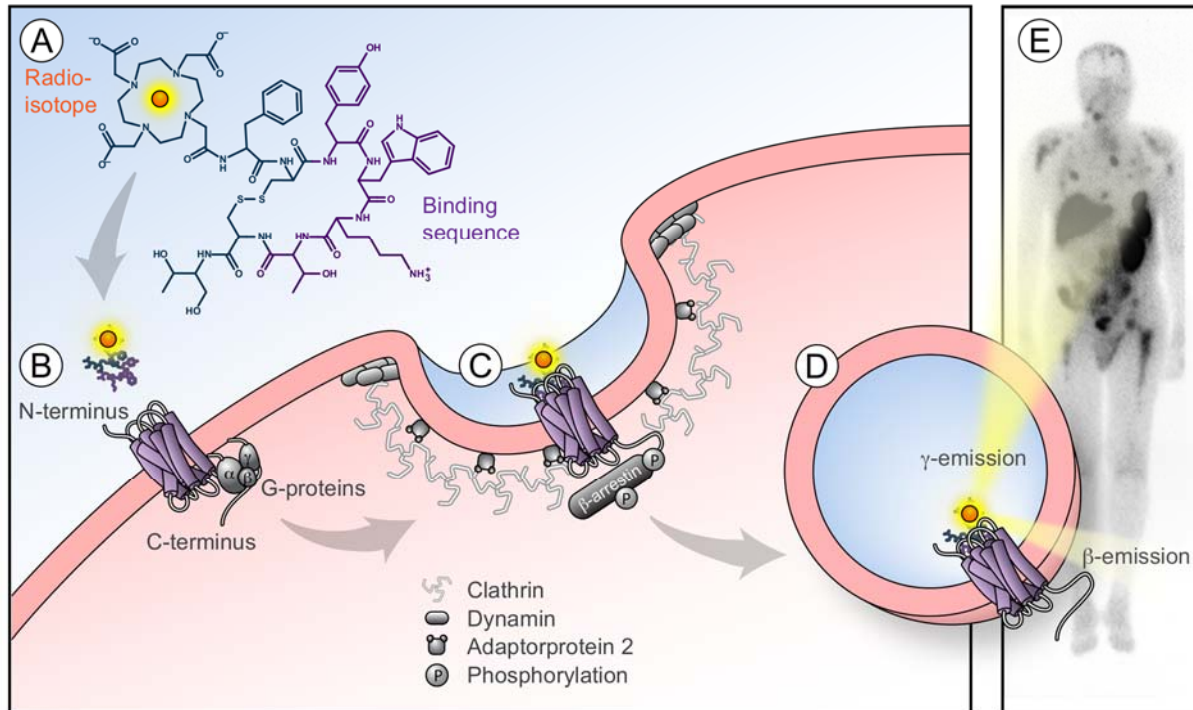


Figure 1. DOTATOC comprises the somatostatin analog TOC and the chelator DOTA for radiolabeling (A). Radiolabeled DOTATOC is injected intravenously and binds to the G-protein coupled somatostatin receptor subtype 2 on the cell surface (B), internalizes via clathrin-mediated endocytosis (C), and enables tumor treatment via β^- -emission (D). Detection of γ -emission allows visualization of tumor uptake and biodistribution of radiolabeled DOTATOC (E). Potential adverse events may result from the biodistribution of DOTATOC.

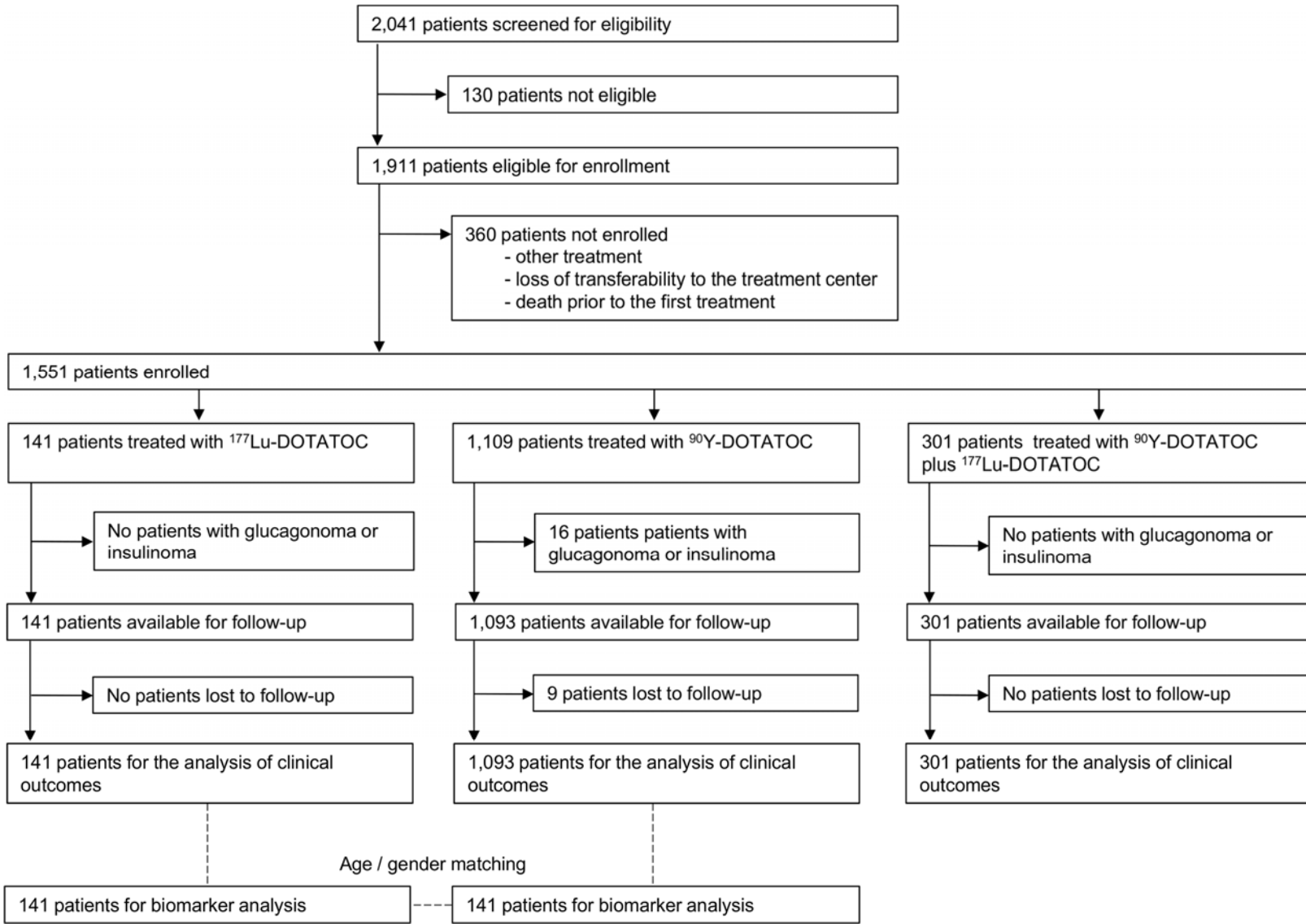


Figure 2. Study profile

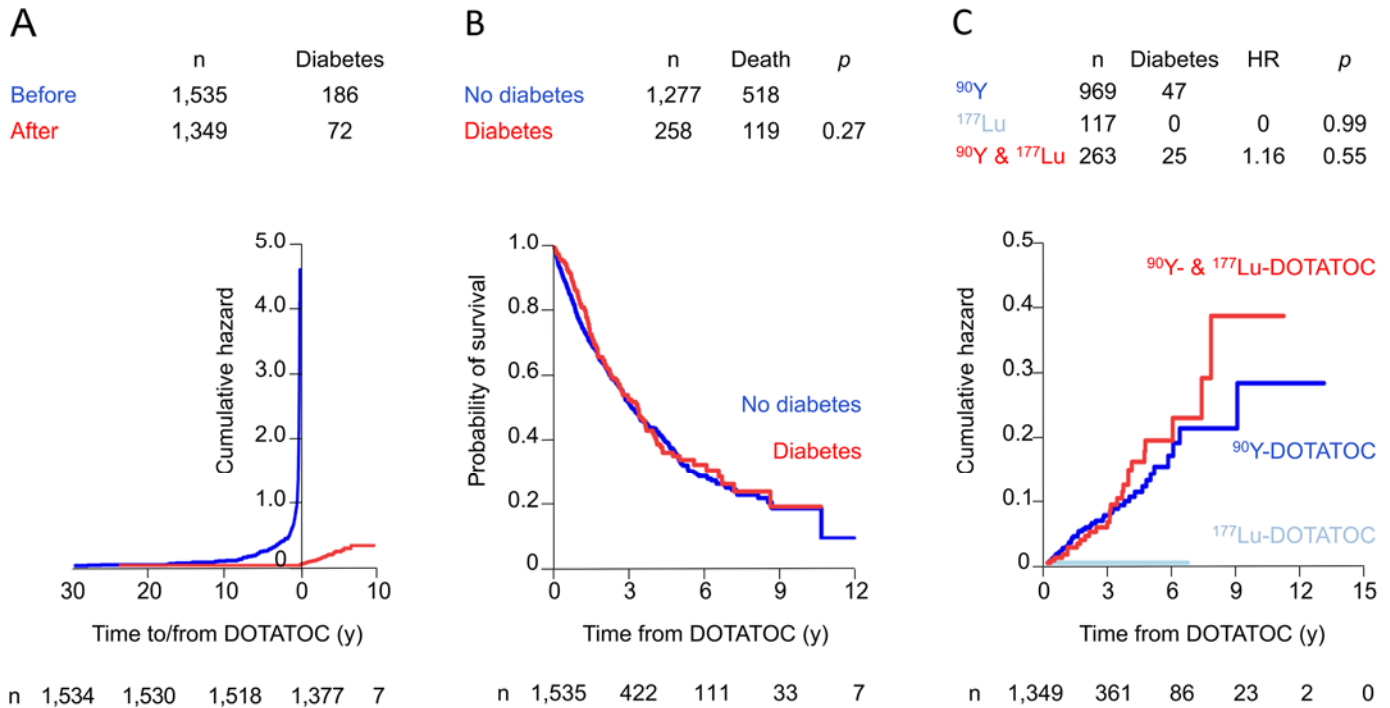


Figure 3. Estimation of difference between a binomial- and the Aalen-Johansen estimator comparing incidence of diabetes mellitus before and after DOTATOC treatment showing significant peak before the treatment and no significant increase after the treatment (A). Survival after DOTATOC in patients with and without diabetes mellitus showing no significant difference (B). Cumulative hazard of diabetes mellitus after the three treatment modalities showing the cumulative hazard of 0 after lutetium-177-DOTATOC and a similar cumulative hazard after treatments with yttrium-90-DOTATOC and yttrium-90 plus lutetium-177 DOTATOC (C).