Journal of Nuclear Medicine, published on August 3, 2017 as doi:10.2967/jnumed.117.189712

# Therapy-related hematological malignancies after peptide receptor radionuclide therapy with $^{177}$Lu-DOTATATE: Incidence, course & predicting factors in patients with GEP-NETs

Running title: Hematological malignancies after PRRT

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**ABSTRACT**

Peptide Receptor Radionuclide Therapy (PRRT) may induce long-term toxicity to the bone marrow (BM). The aim of this study was to analyze persistent dysfunction of the hematopoietic system after PRRT with $^{177}$Lu-DOTATATE in patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

*Methods:*

The incidence and course of persistent hematological dysfunction (PHD) was analyzed in 274 (=GEP-NET) out of 367 patients with somatostatin receptor-positive tumors. PHD was defined as diagnosis of Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), Myeloproliferative Neoplasms (MPN), Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN) or otherwise unexplained cytopenia (for more than 6 months). Using data from the Dutch cancer registry, the expected number of hematopoietic neoplasms (MDS, AML, MPN. MDS/MPN) was calculated and adjusted for sex, age and follow-up period.

Assessment of risk factors was performed in 274 GEP-NET patients with the following risk factors: gender, age over 70 years, bone metastasis, prior chemotherapy, prior external beam radiotherapy, uptake on the OctreoScan®, tumor load, grade 3-4 hematological toxicity during treatment, estimated absorbed BM dose, elevated plasma chromogranin A, baseline blood counts and renal function.

*Results:*

We identified 11 (3.7%) out of 274 GEP-NET patients with PHD following treatment with $^{177}$Lu-DOTATATE: 8 (2.9%) patients developed a hematopoietic neoplasm (4 MDS, 1 AML, 1 MPN, 2 MDS/MPN) and 3 (1.1%) patients developed BM failure characterized by cytopenia and BM aplasia. The median latency period at diagnosis (or first suspicion

of a hematological malignancy) for 11 patients was 41 (range 15 - 84) months. The expected number of hematopoietic neoplasms for our 274 GEP-NET patients was 3.0 resulting in a relative risk of 2.7 (CI 0.7 – 10.0).

No risk factors for PHD could be identified for the GEP-NET patients, including bone metastasis and estimated BM dose. Seven patients with PHD developed anemia in combination with a rise in mean corpuscular volume.

*Conclusion:* The prevalence of persistent hematological dysfunction after PRRT with $^{177}$Lu-DOTATATE is 3.7% in our specific patient population. The median time when PHD can develop is 41 months after the first PRRT cycle. The RR for developing a hematopoietic neoplasm is 2.7.

No risk factors were identified for developing PHD in GEP-NET patients.

Keywords: PRRT · $^{177}$Lu-DOTATATE · Bone marrow · Toxicity · MDS · Leukemia · Neuroendocrine tumor · NET

## INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) has been in use for twenty-five years as second-line therapy in patients with inoperable (metastatic) gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Indium-111 radiolabeled somatostatin analogs were used in early studies (*1,2*). Besides encouraging results with regard to symptom relief, the reported number of objective responses was low. Myelodysplastic syndrome (MDS) or leukemia was reported in half of the NET patients who received a very high dosage (>100 GBq) of [$^{111}$In-DTPA$^{0}$]Octreotide. PRRT with $^{177}$Lu-DOTA$^{0}$-Tyr$^{3}$-octreotate ($^{177}$Lu-DOTATATE) results in a better radiological response rate of 15 – 35% (*3-6*). In general, side effects are mild, although serious hematological toxicity has been reported, making the bone marrow (BM) the main dose-limiting organ. In 11% of the patients, (sub)acute grade 3-4 hematological toxicity is observed after PRRT with $^{177}$Lu-DOTATATE (*7*). Also long-term hematological toxicity like acute myeloid leukemia (AML) and MDS were reported in 1-2% of the patients treated with $^{177}$Lu and/or $^{90}$Y based PRRT (*8-11*). Up to now, no in depth report of therapy related long-term hematological toxicity in patients treated with $^{177}$Lu-DOTATATE has been published.

The aim of this study was to analyze long-term persistent hematological dysfunction (PHD) after PRRT with $^{177}$Lu-DOTATATE in GEP-NET patients. Incidence, clinical course and predicting factors were evaluated in a large group of GEP-NET patients.

## MATERIALS AND METHODS

### Patients

In this study, Dutch patients were analyzed who were treated from January 2000 to December 2007. Follow-up data were used up to December 2012 since we expected therapy related malignancies within 5 years after therapy and because of changes in our follow-up protocol after December 2012. Only Dutch patients were selected, because loss to follow-up was limited in these patients. Only GEP-NETs were selected in our analysis, since $^{177}$Lu-DOTATATE is indicated for this group of patients.

Inclusion criteria were: patients with somatostatin receptor-positive tumors and baseline tumor uptake on somatostatin receptor scintigraphy with [$^{111}$In-DTPA$^{0}$] octreotide (OctreoScan®; Mallinckrodt, Petten, The Netherlands) with accumulation in the tumor at least as high as in normal liver tissue; no prior treatment with a radionuclide therapy; baseline serum hemoglobin ≥6 mmol/l; white blood cell count ≥2×10$^{9}$/l; platelet count ≥75×10$^{9}$/l; serum creatinine ≤150 µmol/l or creatinine clearance ≥40 ml/min and Karnofsky performance status ≥50.

The intensity of tumor uptake and the extent of tumor burden were scored according to simple scaling systems (*3*).

This study was part of the ongoing prospectively designed study in patients with neuroendocrine tumors treated with $^{177}$Lu-DOTATATE at the Department of Radiology and Nuclear Medicine, Erasmus University Medical Center Rotterdam. The hospital's medical ethics committee approved the study. All patients gave written informed consent for participation in the study.

### Treatment

[DOTA$^0$,Tyr$^3$]octreotate was obtained from BioSynthema (St. Louis, MO). $^{177}LuCl_3$ was supplied by IDB-Holland (Baarle-Nassau, The Netherlands) and $^{177}$Lu-DOTATATE was prepared locally (*12*).

Granisetron 3 mg, or ondansetron 8 mg was injected intravenously 30 min before infusion of $^{177}$Lu-DOTATATE. Infusion of amino acids (2.5 % arginine and 2.5 % lysine, 1 l) was started 30 min before administration of the radiopharmaceutical and lasted for 4 h. The radiopharmaceutical was coadministered for 30 min using a second pump system. Cycle dosage(s) of 1.85 GBq (50 mCi) was given in 1 patients, 3.7 GBq (100 mCi) in 13 patients, 5.6 GBq (150 mCi) in 12 patients, and 7.4 GBq (200 mCi) in the remaining patients, injected over 30 min. The interval between treatments was 6 – 16 weeks. The intended cumulative dose was 29.6 GBq (800 mCi) $^{177}$Lu-DOTATATE. The median number of therapy cycles was 4 (range 1-8) with a median cumulative activity of 29.6 GBq (range, 7.4–59.2 GBq) of $^{177}$Lu-DOTATATE. However, the dose was lowered if the calculated kidney dose was higher than 23 Gy. Other reasons for dose reduction or cessation of further therapy were recurrent grade 3 or 4 hematological toxicity and/or persistent low blood counts.

**Follow-up & Toxicity Assessment**

Hematology, and liver and renal function tests were performed during the 6 weeks before the first therapy, 4 and 6 weeks after each therapy cycle, and at follow-up visits. Subacute hematological toxicity was assessed according to Common Terminology Criteria for Adverse Events v3.0 (*13*). This version was used because of well-defined grades (1 to 5) for adverse events in platelets, leucocytes and hemoglobin.

Patient with PHD were defined as having one or more characteristics: MDS, AML, myeloproliferative disorders (MPN), myelodysplastic/myeloproliferative neoplasms (MDS/MPN) according to the revised WHO 2008 diagnostic criteria (*14*) or unexplained hematological toxicity grade 3-4 (> 6 months) in hemoglobin, platelets and/or white blood cells (with/without requirement of multiple blood transfusions).

Latency period was defined as the time from the 1st treatment with $^{177}$Lu-DOTATATE to the date of diagnosis. If no diagnosis was made, the date of the first BM biopsy or aspiration was used. In case of no available BM biopsy/aspiration, the date of diagnosis was replaced by the date when hematological malignancy was suspected in the patient's medical file.

The estimated absorbed BM dose was calculated based on a group-averaged estimated BM dose in 23 patients (*7*). Therefore, this mean BM dose per administered activity of 0.067 ± 0.007 mGy/MBq (*7*) was multiplied by the individual cumulative injected activity of $^{177}$Lu-DOTATATE.

**The Netherlands Cancer Registry**

The expected number of patients with hematopoietic neoplasms was calculated using data of Dutch cancer figures (www.cijfersoverkanker.nl). This database contains the statistics on cancer in the Netherlands that are registered in the Netherlands Cancer Registry, which is managed by the Netherlands Comprehensive Cancer Organization. Data on incidence, prevalence, survival, mortality and risk are available on this website. Users can make their own graphs and tables on cancer incidence according to localization, region, sex and age. Data are available from 1989 to 2016.

The incidence (number of cancers per 100,000 persons a year) of hematopoietic neoplasms was used for four categories; MDS, AML, MPN and MDS/MPN.
Data were categorized by sex and age (in 5-year cohorts). Average incidence rates (per 100.000 residents) between 2001-2011 of the four categories were calculated. Expected cases per category were compiled, based on the number of patients and years of follow-up in our study. Expected numbers were adjusted for sex, age and duration of follow-up period.

**Statistics**

The SPSS software (SPSS 19; IBM, New York, N.Y., USA) was used for statistical analysis. Distributions were examined for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. Correlations between distributions were evaluated using the Chi-squared and unpaired-t test.
PHD was analyzed as a discrete variable. The following baseline variables were included in the analysis: gender, age over 70 years, presence of bone metastases, prior chemotherapy, prior external beam radiotherapy, uptake on the OctreoScan®, tumor load, grade 3-4 hematological toxicity during treatment and plasma chromogranin A >2,000 µg/l (ref < 100 µg/l). Continuous variables included in the analysis were: baseline hemoglobin, baseline platelet count, baseline white blood cell count and estimated absorbed BM dose. The creatinine clearance was estimated with the Cockcroft-Gault formula and evaluated as a continuous variable.

**RESULTS**

In total 367 patients with somatostatin receptor-positive tumors were treated of whom 274 with GEP-NETs, 34 NETs with unknown primary/other location and 59 with other tumors. In the group of GEP-NET patients, 22 out of 274 patients did not meet the inclusion criteria for various reasons e.g. low tumor uptake, concomitant radiotherapy. The median follow-up time of the 274 GEP-NET patients was 29 (range, 0 - 142) months. Twenty-six (10%) out of 274 GEP-NET patients had been treated with cytotoxic chemotherapy in the past and/or 18 out of 274 patients with external beam radiation therapy. Full patient characteristics are summarized in table 1.

**Long-term Hematological Toxicity**

We identified 11 patients (6 females and 5 males) with PHD out of 274 GEP-NET patients following treatment with $^{177}$Lu-DOTATATE (3.7%). Eight patients developed a hematopoietic malignancy (4 MDS, 1 AML, 1 MPN, 2 MDS/MPN) and 3 patients developed BM failure characterized by cytopenia and BM aplasia (table 2). Two patients were excluded since they did not have GEP-NETs (see inclusion criteria); one patient with thyroid carcinoma died two weeks after a BM biopsy demonstrating BM hypoplasia. Another patient with a NET (unknown primary) developed BM failure most likely due to significantly decreased kidney function (GFR < 50 ml/min). Characteristics of the 11 GEP-NET patients with persistent dysfunction of the hematopoietic system are shown in table 3.

The median latency period from initiation of PRRT to the diagnosis of hematopoietic disease in 11 out of 274 GEP-NET patients was 41 (range 15-84) months (Fig. 1).

In 5 out of 11 patients, PRRT was interrupted and the planned cumulative activity of 29.6 GBq $^{177}$Lu-DOTATATE was not administered. The median cumulative estimated BM

dose in 263 patients without PHD was 2.0 Gy (range, 0.2 - 4.0 Gy). In the group of GEP-NET patients with PHD (n=11), the median BM dose was 1.8 Gy (range, 1.0 -2.0 Gy) (Fig. 2). Seven out of 11 patients received a BM dose of less than 2.0 Gy.

A total of 274 (139 male and 135 female) GEP-NET patients were analyzed for calculating the expected number of patients with hematopoietic neoplasms. The cumulative follow-up was 1113 person years, resulting in an expected number of MDS, AML, MPN and MDS/MPN cases of 1.10, 1.27, 0.48 and 0.19 respectively, with a total number of 3.0 patients based on Netherlands Comprehensive Cancer Organization data (Fig. 3).

The RR is the chance that a hematopoietic neoplasms occurs when exposed (8/274) to PRRT, divided by the chance that hematopoietic neoplasms occur when non-exposed (3/274). This results in an RR of 2.7 (95% CI 0.7 – 10.0) meaning that patients treated with PRRT have more than three times higher risk of developing hematopoietic neoplasms than patients not treated with PRRT.

**Risk Factors and Course**

Risk factor assessment was performed in 274 GEP-NET patients, including 11 GEP-NET patients with PHD. The presence of bone metastases or prior chemotherapy was not more prevalent in NET patients with PHD as compared to those without PHD. For the other defined risk factors (gender, age over 70 years, prior external beam radiotherapy, uptake on the OctreoScan®, tumor load, grade 3-4 hematological toxicity during treatment, estimated absorbed BM dose, elevated plasma chromogranin A, baseline blood counts and renal function), no significant differences were found between GEP-NET patients with and patients without PHD.

Seven patients with PHD had anemia in combination with an elevated mean corpuscular volume, for example patient no. 185 (Fig. 4).

Incidence of PHD, expected number of hematopoietic neoplasms and risk assessment was also performed in all 367 patients with somatostatin receptor-positive tumors, see table 4.

## DISCUSSION

MDS covers a heterogeneous group of myeloid malignancies and occurs in 2-4 individuals per $10^5$ persons per year in the Dutch population (*15*). AML and related precursor neoplasms occur in 3-4 individuals per $10^5$ persons per year in the European population (*16*). The incidence of myeloid neoplasms and leukemia are strongly determined by age and sex. Also exposure to radiation increases the frequency of hematological malignancies (*17*).

The total observed incidence of hematopoietic neoplasms after PRRT is a summation of *de novo* incidence (e.g. without exposure to radiation) and therapy-related (with radiation exposure) incidence. The total number of patients with PHD after PRRT is significantly higher than we would expect, based on the expected number of (*de novo)* hematopoietic neoplasms. Our incidence of PRRT related PHD is 3.7%, however this percentage is patient-group dependent since sex, age and previous (chemotherapeutic) treatments influence the incidence of hematopoietic neoplasms. In a large retrospective analysis of a $^{90}$Y-DOTATOC phase II trial, only 2 (<1%) out of 1109 patients developed myeloproliferative diseases (*10*). Considering the number of patients and mean follow-up of 23 months in this study, one would expect an incidence of more than 2 *de novo* hematopoietic neoplasms alone. Therefore the reported number of myeloproliferative

events after PRRT in this study does not seem accurate. Bodei *et al.* found in a large retrospective study of 807 NET patients treated with $^{177}$Lu and/or $^{90}$Y-labelled somatostatin analogs, an incidence of MDS and acute leukemia of 3.3% (*8*). This is in line with our findings. In the same retrospective study of Bodei *et al.* a mean latency time of 45 and 57 months was reported between start of PRRT and the development of MDS or leukemia, respectively (*8*). Our median latency period was 41 months, which is approximately the same as reported by Bodei *et al. (8)*.

PRRT with $^{177}$Lu-DOTATATE has significant similarities to therapy with radioiodine ($^{131}$I), like the physical decay characteristics and the human biodistribution in blood and BM. In patients with thyroid cancer treated with radioiodine ($^{131}$I), a leukemia incidence of 0.2 - 0.3% is observed in comparison to the general population (*18,19*). In a comprehensive meta-analysis the pooled RR for development of leukemia increased 2.5-fold in patients treated with $^{131}$I as compared with thyroid cancer survivors not treated with radioiodine (*20,21*). In our study, we found a RR in our GEP-NET patients treated with $^{177}$Lu-DOTATATE, which was similar to that in thyroid cancer patients treated with $^{131}$I. However, the number of *de novo* (=expected) MDS and leukemia cases is age dependent. Therefore, the incidence can vary between studies in patient populations with a different age distribution. Also in the radio immunotherapy, myelosuppression is the primary toxicity and raised concerns about the risk of treatment-related MDS or acute leukemia. In the database of the radioiodine ($^{131}$I) labeled monoclonal antibody (Bexxar), 35 (3.5%) out of 995 non-Hodgkin lymphoma patients developed MDS or acute leukemia (*22*). Whereas, clinical studies with the yttrium-90 or indium-111 labeled

monoclonal antibody (Zevalin), reported an incidence of 2.3% and the malignancies were diagnosed 23 months after radioimmunotherapy (*23*).

In our study, we did not find a difference in cumulative estimated BM dose between patients with or without PHD. This is in line with BM dose calculation of Bodei and colleagues (*8*), for a comparison see Fig. 5. However, about half of our patients with PHD, did not receive the intended cumulative administered activity of 29 GBq $^{177}$Lu-DOTATATE. These patients were also excluded for salvage therapy with $^{177}$Lu-DOTATATE, therefore creating a bias in our results. Despite this selection bias, about 30% of our patients received a cumulative injected dose of > 30 GBq with an estimated BM dose of more than 2 Gy. However, none of these patients developed PHD. Therefore, the cumulative administered activity of $^{177}$Lu-DOTATATE and estimated BM dose is currently not a dominant factor for predicting PHD after PRRT with $^{177}$Lu-DOTATATE using our treatment regimen.

In general, signs and symptoms in patients with MDS are non-specific. Many patients are asymptomatic at diagnosis and only come to the physician's attention based upon abnormalities found on routine blood counts (e.g., anemia, neutropenia, and thrombocytopenia) (*24*). First, common causes of anemia have to be excluded, like nutrient deficiencies (iron, folate, and vitamin B12) and anemia secondary to renal failure (*25*). In our patient group, the red blood cells are the most frequently affected cell line followed by a reduction in platelets and/or white blood cells. In more than half of our patients, we observed a decrease in Hb combined with a rise in mean corpuscular volume. The decrease in red blood cells reflects the imbalance between their production

and survival, whereas the increased mean corpuscular volume represents an increase in size resulting from an abnormal blood cell production.

In another paper, we have identified several risk factors for (sub)acute hematological toxicity following PRRT with $^{177}$Lu-DOTATATE, like: impaired renal function, low white blood cells, extensive tumormass, high tumoruptake on the OctreoScan® and/or advanced age (*7*). As for long-term hematological toxicity, Bodei *et al.* reported the following risk factors associated with MDS and leukemia after PRRT with $^{177}$Lu-DOTATATE (*8*): previous chemotherapy, tumor invasion of the BM, platelet toxicity grade and other previous myelotoxic therapies. In our study, we could not identify any risk factors for GEP-NET patients who develop PHD after PRRT with $^{177}$Lu-DOTATATE. However, analysis in all 367 patients with somatostatin receptor positive tumors positive demonstrated a significantly lower white blood cells in patients with PHD (table 4). Also a trend was observed, where subacute hematological toxicity (grade 3-4) during PRRT was more frequent in patients with PHD in comparison to patients without PHD.

In a recent study, a high incidence (20%) of MDS/AML after chemotherapy and PRRT with $^{177}$Lu-DOTATATE was reported in a small group of metastatic GEP-NET patients (*26*). A critical response was written about the limited (biased) group of patients in this study (*27*). The high dose of alkylating chemotherapy was the main contributing factor for development of MDS/AML in these patients. In our study, the number of patients treated with chemo(embolization)therapy prior to PRRT is low. Therefore, the statistical power of this (possible) risk factor is limited in our study.

**CONCLUSION**

The prevalence of therapy-related persistent hematological dysfunction after PRRT with $^{177}$Lu-DOTATATE in GEP-NET patients was 3.7% implying a RR of 2.7. The median latency time to disease development was 41 months.

In the group of GEP-NET patients, no risk factors could be identified for the development of therapy-related persistent hematological malignancies. Anemia combined with a rise in MCV occurred in half of the patients with therapy-related hematological malignancies after PRRT with $^{177}$Lu-DOTATATE.

## Compliance with Ethical Standards

### Ethical approval

“All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.”

## Conflicts of interest

Dik J. Kwekkeboom and Eric P. Krenning:

| **Category of disclosure:** | **Description of Interest/Arrangement** |
|---|---|
| Advanced Accelerator Applications (Adacap) | Shareholder |
| Advanced Accelerator Applications (Adacap) | Scientific Advisor |

Wouter W. de Herder:

| **Category of disclosure:** | **Description of Interest/Arrangement** |
|---|---|
| Speaker fees | Ipsen/Novartis |
| Research support | Ipsen/Novartis |

The other (co)authors declare that they have no conflict of interest.

## Funding

None

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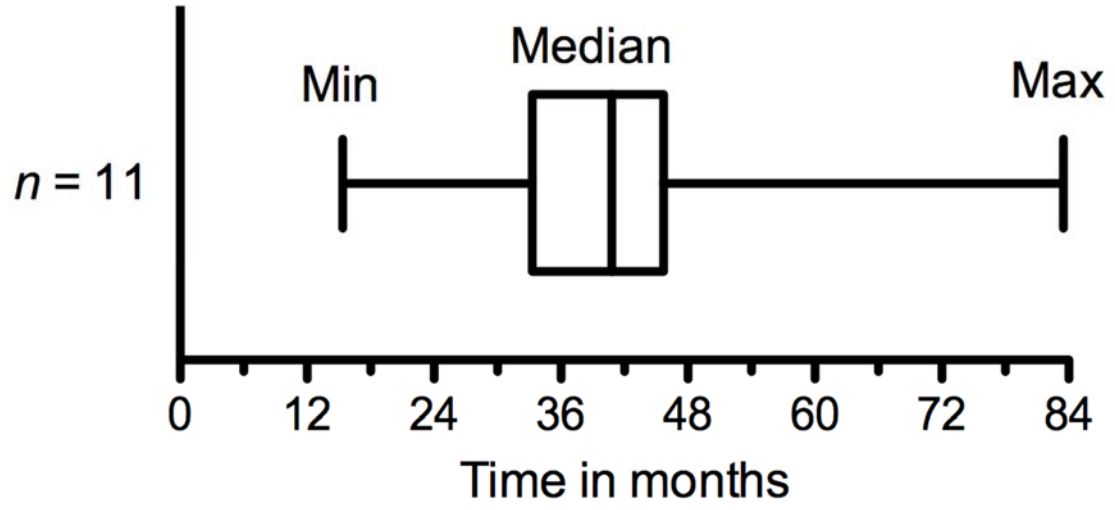


**Fig. 1** – Median latency time in 11 patients with persistent hematological dysfunction. Whisker boxplot of latency time (period between first treatment and date of diagnosis) in 11 out of 274 GEP-NET patients with persistent hematological dysfunction (PHD) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE. Whiskers represent minimum (15 months) and maximum (84 months) latency time. The width of the box shows the interquartile range and the vertical line in the box is the median (41 months) latency time.

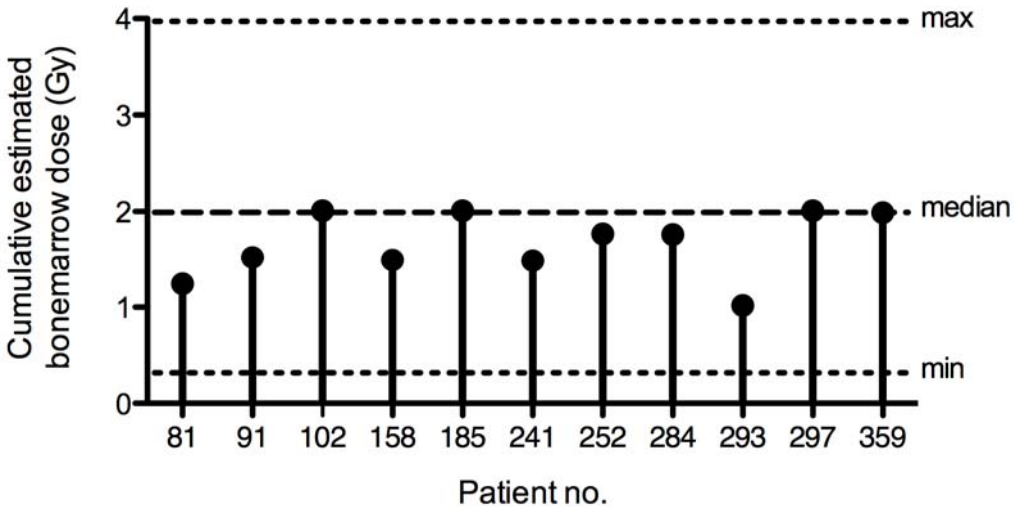


**Fig. 2** – Estimated bonemarrow dose in 11 GEP-NET patients with persistent hematological dysfunction. Spikeplot of cumulative estimated bonemarrow (BM) dose in 11 GEP-NET patients with persistent hematological dysfunction (PHD) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE.
Note the median (and range) estimated BM dose (dashed lines) in 263 NET patients without PHD.

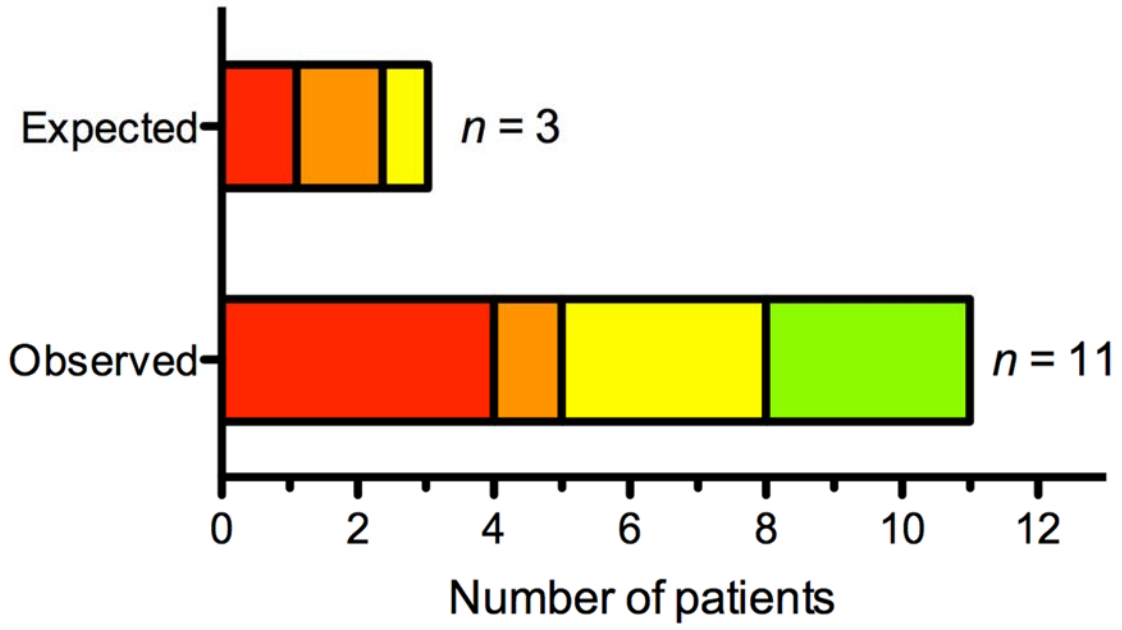


**Fig. 3** – Expected number of patients (3) with hematopoietic neoplasms and type, based on data from The Netherlands Cancer Registry. Observed number of patients (11 out of 274 GEP-NET patients) with persistent hematological dysfunction (PHD) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE including 8 patients with hematopoietic neoplasms and 3 with bonemarrow failure.

Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), Myeloproliferative Neoplasms (MPN) + Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN) and Bone Marrow failure.

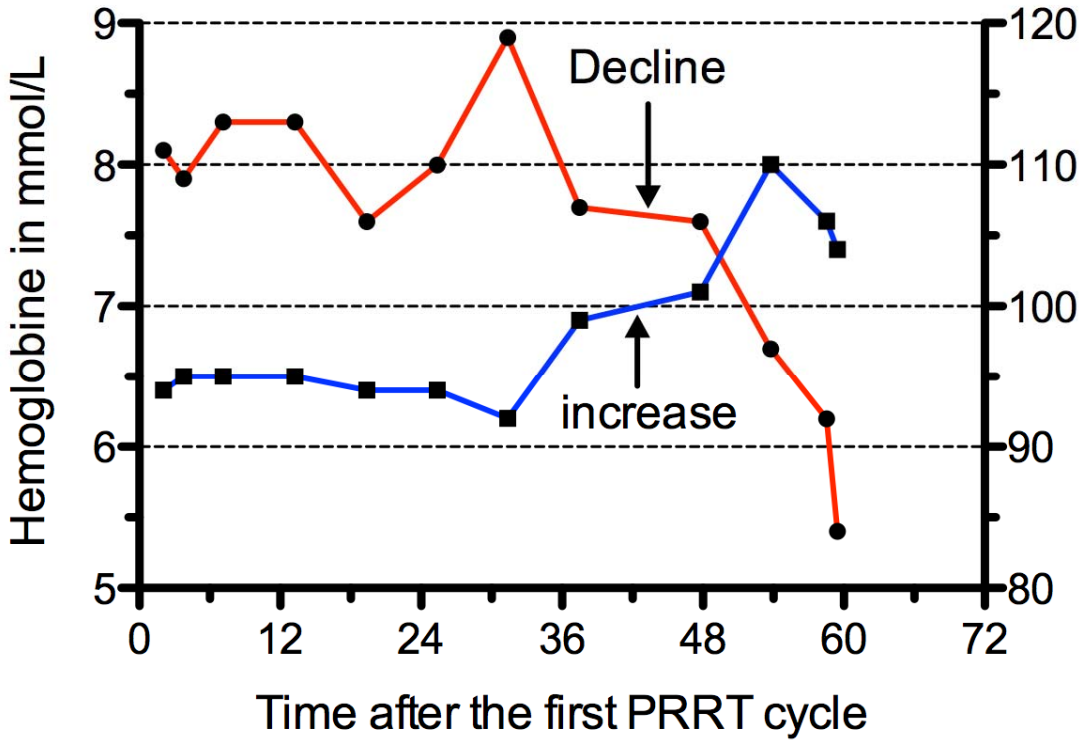


**Fig. 4** – Course of hemoglobin (Hb) and mean corpuscular volume (MCV) in patient no. 185 diagnosed with myelodysplastic syndrome (MDS)/Myeloproliferative disease (MPN) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-octreotate. Time zero is the date of the last PRRT cycle. A decline in Hb (upper red arrow) was followed by an increase in MCV (lower red arrow).

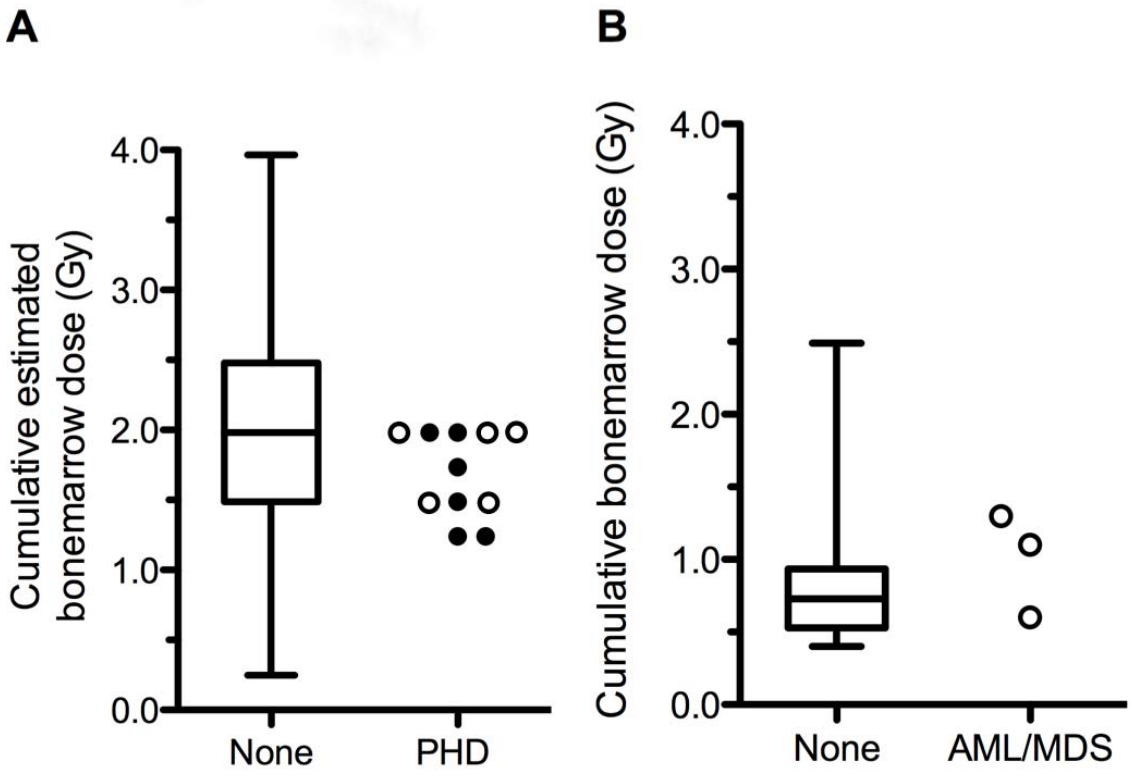


**Fig. 5** – Comparison of hematological malignancies and cumulative dose to the bonemarrow. **A.** Whisker and scatter plot of cumulative estimated bone marrow dose in 11 patients (including 5 AML/MDS patients ⭘) with persistent hematological dysfunction (PHD) and 263 patients without PHD. **B.** Whisker and scatter plot of marrow dose in 3 patients with AML/MDS (⭘) and 28 patients without AML/MDS. Data of dosimetry analysis in a subgroup of 807 patients adopted from bodei *et al.* (*8*).
Whiskers represent minimum and maximum (estimated) bone marrow dose in Gy. The height of the box shows the interquartile range and the horizontal line in the box is the median (estimated) bone marrow dose in Gy.

**Table 1** - Baseline characteristics of 274 Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs).

| | Number of patients (%) | |
|---|---|---|
| **Patient characteristics** | **Yes** | **No** |
| Male | 139 (51) | 135 (49) |
| Age ≥ 70 | 52 (19) | 222 (81) |
| KPS ≤ 70 | 38 (14) | 236 (86) |
| Elevated Chromogranin A | 72 (26) | 202 (74) |
| Bone metastases | 59 (22) | 215 (78) |
| Patients who met inclusion criteria | 252 (92) | 22 (8) |
| *Previous therapy* | | |
| - Chemotherapy | 26 (10) | 248 (90) |
| - Radiotherapy (external) | 18 (7) | 256 (93) |
| *NET Location* | | |
| - Gastrointestinal | 172 (63) | |
| - Pancreas | 86 (31) | |
| - Bronchus | 16 (6) | |
| *Tumor uptake on baseline Octreoscan* | | |
| - Less to normal liver | 8 (3) | |
| - Equal or more to normal liver | 203 (74) | |
| - Higher than kidneys | 63 (23) | |
| *Tumor mass on baseline OctreoScan* | | |
| - Limited and Moderate | 223 (81) | |
| - Extensive | 51 (19) | |
| *Cumulative administered activity ($^{177}$Lu-DOTATATE)* | | |
| - up to 22.2 GBq | 73 (27) | |
| - 22.3 to 29.6 GBq | 122 (44) | |
| - 29.7 Gbq to 44.4 GBq | 71 (26) | |
| - 44.5 to 59.2 GBq | 8 (3) | |
| *Age range at first treatment* | | |
| 15-29 | 1 (0.5) | |
| 30-44 | 31 (11.5) | |
| 45-59 | 109 (40) | |
| 60-74 | 110 (40) | |
| 75-89 | 23 (8) | |

**Table 2 –** Classification of 11 out of 274 Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) patients with persistent hematological dysfunction (PHD) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE. Eight patients were classified according to the World Health Organization (WHO) (*14*). Three patients were classified as bone marrow failure with specific characteristics.

| Classification | Number of patients |
|---|---|
| **Hematopoietic Neoplasms according to WHO** | |
| *Myelodysplastic syndrome (MDS)* | |
| - RAEB-II | 1 |
| - RARS | 1 |
| - *Other* | 2 |
| *Acute myeloid leukemia and related neoplasms (AML)* | |
| - Acute myeloid leukemia with recurrent genetic abnormalities | 1 |
| *Myeloproliferative Neoplasms (MPN)* | |
| - Myelofibrosis | 1 |
| *Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)* | |
| - Chronic Myeloid Leukemia (CML) | 1 |
| - Chronic myelomonocytic Leukemia (CMML) | 1 |
| | |
| **Bone marrow failure characterized by (not WHO)** | |
| - BM hypoplasia | *1* |
| - BM aplasia | *1* |
| - Pancytopenia | *1* |

**Table 3** – Characteristics of 11 out of 274 Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) patients with persistent hematological dysfunction (PHD) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE ($^{177}$Lu). Neuroendocrine tumor (NET), Neuroendocrine tumor of the pancreas (PNET), cold Octreotide (Octreotide), External beam radiotherapy (EBRT), Hemoglobin (Hb), Platelets (PLT), White Blood Cells (WBC).
Myelodysplastic syndrome (MDS), Refractory anemia with ringed sideroblasts (RARS), Chronic myeloid leukemia (CML), Refractory Anaemia with Excess Blasts type II (RAEB-II), Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN), chronic myelomonocytic leukemia (CMML), Acute Myeloid Leukemia (AML), Myeloproliferative neoplasms (MPN).

| Patient | | | | Previous | Administered Activity | PRRT | | Bone marrow | | Latency period |
|---|---|---|---|---|---|---|---|---|---|---|
| no. | sex | Age | Diagnosis | therapy | (GBq) | Interrupted | Protocol | Cytopenia | Diagnosis | (months) |
| 359 | f | 70 | NET | Octreotide | 30.0 | No | On | Hb | MDS, RARS | 42.4 |
| 297 | f | 60 | NET | Octreotide | 18.6 | Yes, maximum kidney dose | On | Hb, PLT, WBC | Hypoplasia | 36.3 |
| 293 | m | 61 | PNET | chemo-embolisation | 29.3 | No | On | Hb, PLT | CML | 42.3 |
| 284 | m | 57 | PNET | - | 29.7 | No | On | Hb | MDS, RAEB-II | 33.3 |
| 252 | f | 64 | NET | Octreotide | 30.0 | No | On | Hb, WBC | Pancytopenia | 45.7 |
| 241 | f | 41 | PNET | - | 26.3 | Yes, hematological toxicity | On | Hb, PLT, WBC | Aplasia | 34.3 |
| 185 | m | 74 | PNET | - | 26.4 | No | On | Hb, PLT | MDS/MPN: CMML-1 | 63.6 |
| 158 | m | 62 | NET | Octreotide | 22.2 | Yes, maximum kidney dose | Off | Hb, PLT, WBC | MDS, RAEB-II | 15.4 |
| 102 | m | 68 | NET | - | 30.0 | no | On | Hb, PLT, WBC | MDS, Hypocellular | 20.2 |
| 91 | f | 59 | NET | Octreotide, local EBRT | 22.7 | Yes, maximum kidney dose | On | Hb, PLT, WBC | AML | 83.5 |
| 81 | f | 58 | NET | Octreotide | 22.3 | Yes, maximum kidney dose | On | Hb, PLT, WBC | Myelofibrosis/MPN | 40.8 |

**Table 4** – Results of analysis in 367 patients with somatostatin positive tumors after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE ($^{177}$Lu). Persistent hematological dysfunction (PHD), Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs), Bonemarrow (BM), Not calculated (NC) because of low statistical power.
* Patients with non GEP-NET, e.g. NET unknown primary, thyroid carcinoma, paraganglioma.

| Characteristic | All patients | Lung + GEP-NET | Non GEP-NETs* |
|---|---|---|---|
| Total number of patients | 367 | 274 | 93 |
| PHD patients | 13 | 11 | 2 |
| Prevalence | 3.5% | 3.7% | 2.2% |
| Median latency period (and range) in months | 36 (5 - 84) | 41 (15 – 84) | 5.8 (5 – 7) |
| Median FU time (and range) in months | 24 (0 - 143) | 29 (0 - 142) | 12 (0 – 116) |
| Cumulative median BM dose (and range) in Gy: | | | |
| without PHD | 2.0 (0.2 - 4.0) | 2.0 (0.2 - 4.0) | 1.5 (0.2 – 3.9) |
| with PHD | 1.5 (1.0 - 2.0) | 1.76 (1.0 – 2.0) | 1.2 (1.0 – 1.5) |
| Expected number of MDS/leukemia | 4.4 | 3.0 | <1 |
| Follow-up in years | 1309 | 1113 | |
| Relative Risk (RR) and | 1.9 | 2.7 | |
| 95% Confidence Interval | (1.0 - 3.6) | (0.7 – 10.0) | |
| Significant Risk factors | - Baseline WBC was significantly lower (p=0.01) in the 13 NET patients with PHD.<br>- Subacute hematological toxicity grade 3-4 during PRRT was marginally significantly (p=0.053) different in patients with PHD. | None | NC |
| Remark | - Including a non GEP-NET patient* treated with $^{131}$I, resulting in BM failure, 5 months after the first PRRT cycle. | | |

**Supplemental Data**

# Therapy-related hematological malignancies after peptide receptor radionuclide therapy with $^{177}$Lu-DOTATATE: Incidence, course & predicting factors in patients with GEP-NETs

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## MATERIALS AND METHODS

### Uptake and Extent Scale

The intensity of tumor uptake on OctreoScan® and the extent of tumor burden is to be scored according to simple scaling systems, see supplemental figs. 1 and 2.

### Method - The Netherlands Cancer Registry

The expected number of patients with dysfunction of the hematopoietic system was calculated using the website of Dutch cancer figures (www.cijfersoverkanker.nl).

The incidence (number of cancers per 100,000 persons a year) was used for four categories with the following selection criteria:

1. Myelodysplastic Syndrome (MDS) – the selected tumor group was “MDS and Myelodysplastic/myeloproliferative disorders” with subgroup “Myelodysplastic Syndrome”.

2. Acute myeloid leukaemia (AML) – the selected tumor group was “Acute Myeloid Leukaemia” including all subgroups.

3. Myeloproliferative disorders (MPN) - the selected tumor group was “Myeloproliferative disorders” with subgroup “Myeloproliferative neoplasm, other”.

4. Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) - the selected tumor group was “MDS and Myelodysplastic/myeloproliferative disorders” with subgroup “Myelodysplastic/Myeloproliferative disorders” plus tumor group “Myeloproliferative disorders” with subgroup “Chronic Myeloid Leukaemia”.

Incidence data extracted from the website, sorted by 5-years age category and sex can be found in supplemental table 1 - 10. Expected numbers were adjusted for sex, age and duration of follow-up period.

Patient age, sex and follow-up characteristics in all 367 and 274 Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs) patients with expected number of expected number of hematopoietic neoplasms can be found in supplemental table 11 - 14.

**Method – Relative Risk**

The Relative risk (RR), it's standard error and 95% confidence interval are calculated according to Altman (*1*).

The relative risk or risk ratio is given by

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

where *a* is the number of exposed patients with a positive (bad) outcome, *b* is the number of exposed patients with a negative (good) outcome, *c* is the number of non-exposed patients with a positive (bad) outcome and *d* is the number of non-exposed patients with a negative (good) outcome.

The standard error of the log relative risk is

$$SE\{\ln(RR)\} = \sqrt{\frac{1}{a} + \frac{1}{c} - \frac{1}{a+b} - \frac{1}{c+d}}$$

with a 95% confidence interval of

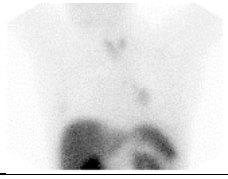
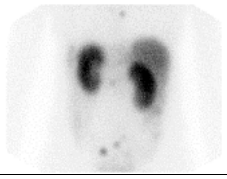
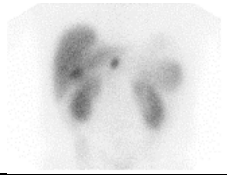
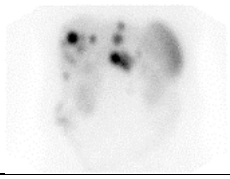
$$95\%CI = exp(\ln(RR) - 1.96 \cdot SE\{\ln(RR)\}) \text{ to } exp(\ln(RR) + 1.96 \cdot SE\{\ln(RR)\})$$

Where zeros cause problems with computation of the relative risk or its standard error, 0.5 is added to all cells (a,b,c,d) (*2,3*).

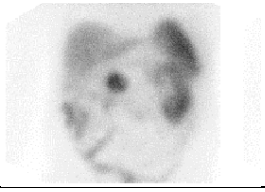
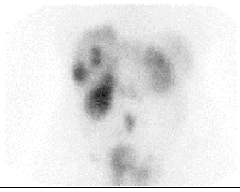
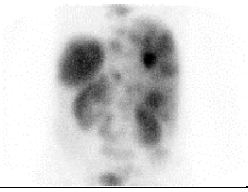
**Results**

In total 367 patients were treated of whom 324 patients met the inclusion criteria. Forty-three patients were off-protocol for various reasons (see table 15). The tumor type of 93 non GEP-NET patients can be found in supplemental table 16.

Patient characteristics of all 13 patients with persistent hematological dysfunction (PHD) can be found in table 17. Calculations of the relative risk can be found in table 18.

|  |  |  |  |
|---|---|---|---|
| 1) <Liver (Excluded) | 2) ≈ Liver | 3) > Liver | 4) Very intense (>>Kidneys, spleen) |

**Supplemental Fig. 1** - Tumor uptake scaling system; 1. Uptake less than the liver (excluded) 2. Uptake equal to the liver 3. Uptake more than the liver 4. Uptake more than kidneys and/or spleen.

|  |  |  |
|---|---|---|
| 1) Limited | 2) Moderate | 3) Extensive |
| Up to 5 sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen) | Multiple sites in up to 2 sites of the body. Neither qualifying for limited nor for extensive. | Many tumor sites in ≥ 2 parts of the body. |

**Supplemental Fig. 2** - Tumormass on OctreoScan; 1. Limited tumor mass is up to 5 sites in one part of the body (head/neck, chest, upper abdomen, lower abdomen) 2. Moderate tumor mass is multiple sites in up to 2 sites of the body, neither qualifying for limited nor for extensive 3. Extensive tumor mass is many tumor sites in ≥ 2 parts of the body. Usually a combination of extensive liver and lymph node involvement or diffuse skeletal metastases. Diffuse liver metastasis with limited abdominal involvement does not qualify.

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**Supplemental Table 1** – Incidence of Myeloproliferative Neoplasms (MPN) in males per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Male | | Incidence Myeloproliferatieve Neoplasms (MPN) (excluding CML) per year | | | | | | | | | | | Average Incidence MPN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | (excluding CML) |
| 1 | 0-4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 2 | 5-9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 3 | 10-14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 4 | 15-19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 5 | 20-24 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.19 | 0 | 0.0 |
| 6 | 25-29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0.0 |
| 7 | 30-34 | 0 | 0 | 0 | 0.16 | 0 | 0 | 0 | 0 | 0 | 0.6 | 0 | 0.1 |
| 8 | 35-39 | 0 | 0.15 | 0 | 0.15 | 0 | 0 | 0 | 0.32 | 0.17 | 0.17 | 0 | 0.1 |
| 9 | 40-44 | 0.16 | 0 | 0 | 0.46 | 0 | 0.3 | 0.15 | 0.15 | 0 | 0.31 | 0 | 0.1 |
| 10 | 45-49 | 0 | 0 | 0 | 0.17 | 0.33 | 0.16 | 0.16 | 0 | 0.46 | 0.31 | 0.46 | 0.2 |
| 11 | 50-54 | 0 | 0.35 | 0.35 | 0.71 | 1.07 | 0.35 | 0.35 | 0 | 0.51 | 1.17 | 0.5 | 0.5 |
| 12 | 55-59 | 0 | 1.38 | 1.67 | 1.44 | 1.05 | 1.75 | 0.9 | 0.55 | 2.02 | 0.73 | 0.73 | 1.1 |
| 13 | 60-64 | 0.81 | 0.79 | 0.76 | 0.49 | 1.2 | 1.58 | 1.66 | 1.96 | 1.7 | 1.65 | 1.47 | 1.3 |
| 14 | 65-69 | 1.95 | 2.25 | 2.53 | 0.92 | 2.4 | 2.04 | 2.28 | 2.21 | 4.26 | 2.58 | 2.67 | 2.4 |
| 15 | 70-74 | 2.4 | 0.39 | 3.48 | 2.29 | 1.89 | 2.61 | 4.77 | 3.94 | 4.52 | 3.03 | 4.57 | 3.1 |
| 16 | 75-79 | 3.85 | 4.91 | 2.7 | 3.19 | 2.59 | 5.05 | 5.4 | 3.36 | 3.75 | 5.98 | 4.06 | 4.1 |
| 17 | 80-84 | 4.93 | 3.76 | 1.79 | 2.57 | 4.18 | 4.93 | 3.22 | 1.57 | 4.57 | 4.4 | 5.64 | 3.8 |
| 18 | 85-89 | 2.24 | 0 | 4.42 | 4.38 | 2.07 | 0 | 0 | 0 | 4.73 | 1.52 | 5.86 | 2.3 |
| 19 | 90-94 | 0 | 0 | 0 | 0 | 6.86 | 0 | 0 | 0 | 0 | 5.64 | 0 | 1.1 |
| 20 | 95-99 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| Total | 0-99 | | | | | | | | | | | | 1.0 |

**Supplemental Table 2** – Incidence of Chronic Myeloid Leukemia (CML) in males per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Male | | Incidence Chronic Myeloid Leukemia (CML) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | CML |
| 1 | 0-4 | 0 | 0 | 0.19 | 0.19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 2 | 5-9 | 0.2 | 0.2 | 0 | 0.2 | 0 | 0.2 | 0 | 0 | 0.19 | 0 | 0.4 | 0.1 |
| 3 | 10-14 | 0.4 | 0 | 0.39 | 0 | 0.19 | 0.39 | 0.2 | 0 | 0.2 | 0 | 0 | 0.2 |
| 4 | 15-19 | 0 | 0.21 | 0.61 | 0 | 0.2 | 0 | 0.39 | 0.39 | 0.19 | 0 | 0 | 0.2 |
| 5 | 20-24 | 0 | 0.41 | 0.41 | 0.2 | 0.2 | 0 | 1.02 | 0.6 | 0.79 | 0.39 | 0.19 | 0.4 |
| 6 | 25-29 | 0.18 | 0.57 | 1.36 | 0.6 | 0 | 1.01 | 0.2 | 0.8 | 0.8 | 0.2 | 0.79 | 0.6 |
| 7 | 30-34 | 0.6 | 0 | 0.93 | 0.81 | 0.17 | 1.46 | 0.38 | 0.59 | 0.6 | 1.59 | 0.2 | 0.7 |
| 8 | 35-39 | 0.59 | 0.44 | 1.04 | 0.45 | 0.75 | 0.15 | 1.24 | 0.63 | 0.66 | 1.22 | 1.46 | 0.8 |
| 9 | 40-44 | 0.79 | 1.72 | 0.46 | 1.21 | 0.45 | 0.6 | 1.06 | 1.37 | 0.61 | 1.07 | 1.38 | 1.0 |
| 10 | 45-49 | 0.52 | 0.68 | 1.85 | 0.5 | 1.15 | 0.81 | 1.91 | 1.1 | 1.55 | 1.23 | 0.61 | 1.1 |
| 11 | 50-54 | 0.51 | 1.74 | 0.88 | 1.07 | 1.07 | 1.23 | 1.22 | 0.87 | 0.85 | 0.5 | 1.98 | 1.1 |
| 12 | 55-59 | 1.29 | 2.36 | 1.3 | 0.54 | 1.92 | 0.88 | 1.44 | 1.46 | 0.92 | 1.28 | 2 | 1.4 |
| 13 | 60-64 | 2.42 | 1.05 | 1.53 | 0.74 | 0.96 | 1.81 | 2.08 | 1.17 | 1.32 | 2.2 | 1.65 | 1.5 |
| 14 | 65-69 | 2.92 | 1.61 | 0.32 | 4 | 2.1 | 2.34 | 2.56 | 2.21 | 1.06 | 2.58 | 1.94 | 2.1 |
| 15 | 70-74 | 1.2 | 3.14 | 1.55 | 2.67 | 1.51 | 1.49 | 2.57 | 2.51 | 2.09 | 4.71 | 2.29 | 2.3 |
| 16 | 75-79 | 6.6 | 6 | 7.57 | 2.66 | 4.15 | 5.05 | 5.4 | 4.79 | 1.88 | 2.76 | 3.61 | 4.6 |
| 17 | 80-84 | 4.93 | 5.63 | 3.58 | 5.99 | 5.85 | 4.93 | 6.43 | 1.57 | 6.09 | 2.2 | 4.23 | 4.7 |
| 18 | 85-89 | 0 | 6.65 | 4.42 | 4.38 | 2.07 | 3.82 | 0 | 1.67 | 4.73 | 0 | 0 | 2.5 |
| 19 | 90-94 | 15.83 | 7.68 | 0 | 14.22 | 0 | 0 | 0 | 0 | 6.15 | 0 | 5.03 | 4.4 |
| 20 | 95-99 | 42.46 | 0 | 0 | 0 | 0 | 0 | 37.64 | 0 | 0 | 0 | 0 | 7.3 |
| Total | 0-99 | | | | | | | | | | | | 1.9 |

**Supplemental Table 3** – Incidence of Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in males per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Male | | Incidence Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | MDS/MPN |
| 1 | 0-4 | 0 | 0.19 | 0.38 | 0 | 0.39 | 0.2 | 0.82 | 0.62 | 0.63 | 0.21 | 0.21 | 0.3 |
| 2 | 5-9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 3 | 10-14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 4 | 15-19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.19 | 0 | 0.0 |
| 5 | 20-24 | 0 | 0 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 6 | 25-29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 7 | 30-34 | 0.15 | 0 | 0 | 0 | 0.34 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0.1 |
| 8 | 35-39 | 0 | 0 | 0 | 0.15 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 9 | 40-44 | 0 | 0 | 0 | 0.15 | 0 | 0.15 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 10 | 45-49 | 0 | 0.17 | 0.51 | 0 | 0.16 | 0 | 0.32 | 0 | 0 | 0.15 | 0.15 | 0.1 |
| 11 | 50-54 | 0.34 | 0.17 | 0.35 | 0.53 | 0.36 | 0 | 0 | 0.17 | 0 | 0 | 0 | 0.2 |
| 12 | 55-59 | 0.21 | 0.59 | 0.56 | 0.9 | 0.7 | 0.35 | 0.36 | 0.73 | 0.55 | 0.92 | 0.73 | 0.6 |
| 13 | 60-64 | 0.54 | 1.05 | 1.27 | 2.22 | 1.2 | 0.68 | 1.04 | 2.15 | 1.13 | 1.1 | 1.1 | 1.2 |
| 14 | 65-69 | 2.27 | 2.57 | 2.84 | 2.16 | 3.3 | 3.21 | 1.42 | 3.31 | 3.99 | 3.36 | 2.43 | 2.8 |
| 15 | 70-74 | 3.2 | 3.93 | 3.48 | 4.2 | 4.91 | 2.98 | 5.13 | 5.74 | 7.3 | 4.04 | 4.9 | 4.5 |
| 16 | 75-79 | 3.3 | 4.91 | 4.33 | 5.85 | 6.22 | 10.6 | 8.84 | 6.71 | 5.63 | 7.36 | 5.86 | 6.3 |
| 17 | 80-84 | 6.9 | 8.45 | 5.37 | 7.7 | 5.01 | 8.22 | 4.82 | 5.49 | 10.66 | 13.19 | 9.87 | 7.8 |
| 18 | 85-89 | 6.72 | 4.43 | 0 | 10.95 | 0 | 5.73 | 7.15 | 10.03 | 11.04 | 7.58 | 11.72 | 6.9 |
| 19 | 90-94 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 12.3 | 5.64 | 10.07 | 2.5 |
| 20 | 95-99 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| Total | 0-99 | | | | | | | | | | | | 1.7 |

**Supplemental Table 4** – Incidence of Myelodysplastic syndrome (MDS) in males per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Male | | Incidence Myelodysplastic syndrome (MDS) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | MDS |
| 1 | 0-4 | 0 | 0.38 | 0.38 | 0 | 0.2 | 0 | 0.41 | 0.42 | 0 | 0 | 0 | 0.2 |
| 2 | 5-9 | 0.2 | 0 | 0 | 0.4 | 0 | 0 | 0 | 0.39 | 0 | 0.2 | 0.4 | 0.1 |
| 3 | 10-14 | 0 | 0 | 0.58 | 0.97 | 0 | 0.2 | 0 | 0 | 0 | 0 | 0.58 | 0.2 |
| 4 | 15-19 | 0 | 0 | 0 | 1 | 0.2 | 0.2 | 0.39 | 0.39 | 0 | 0.39 | 0.19 | 0.3 |
| 5 | 20-24 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0.2 | 0.2 | 0.2 | 0 | 0 | 0.1 |
| 6 | 25-29 | 0 | 0.19 | 0.39 | 0.4 | 0.2 | 0 | 0.4 | 0 | 0.4 | 0.2 | 0.2 | 0.2 |
| 7 | 30-34 | 0.15 | 0.15 | 0.31 | 0.16 | 0.34 | 0.18 | 0.19 | 0 | 0 | 0.2 | 0.2 | 0.2 |
| 8 | 35-39 | 0.15 | 0.3 | 0.15 | 0.15 | 0.6 | 0.15 | 0 | 0.16 | 0.33 | 0.52 | 0.37 | 0.3 |
| 9 | 40-44 | 0 | 0.31 | 0.46 | 0.15 | 0.15 | 0.45 | 0.6 | 0.46 | 0.92 | 0.61 | 0.31 | 0.4 |
| 10 | 45-49 | 1.03 | 0.68 | 0.84 | 0.83 | 0.98 | 0.49 | 0.8 | 0.79 | 0.77 | 1.07 | 0.76 | 0.8 |
| 11 | 50-54 | 1.35 | 1.91 | 3.35 | 1.42 | 1.6 | 2.29 | 2.1 | 2.77 | 2.22 | 0.84 | 1.32 | 1.9 |
| 12 | 55-59 | 1.29 | 2.76 | 2.98 | 3.24 | 1.75 | 2.81 | 3.6 | 2.93 | 3.86 | 3.3 | 2.54 | 2.8 |
| 13 | 60-64 | 5.1 | 4.99 | 3.82 | 5.42 | 6.47 | 5.88 | 5.81 | 7.64 | 6.8 | 8.07 | 4.96 | 5.9 |
| 14 | 65-69 | 10.71 | 12.53 | 13.59 | 12.01 | 11.09 | 11.39 | 13.11 | 14.91 | 14.91 | 14.99 | 15.3 | 13.1 |
| 15 | 70-74 | 19.59 | 23.17 | 27.07 | 19.86 | 21.51 | 18.62 | 25.67 | 30.83 | 25.73 | 25.91 | 22.85 | 23.7 |
| 16 | 75-79 | 34.12 | 32.75 | 31.37 | 41.5 | 42.53 | 37.86 | 45.69 | 41.7 | 49.75 | 39.58 | 42.38 | 39.9 |
| 17 | 80-84 | 33.49 | 50.71 | 62.62 | 53.03 | 54.3 | 56.7 | 54.67 | 72.97 | 62.43 | 63.04 | 51.45 | 55.9 |
| 18 | 85-89 | 51.54 | 68.69 | 66.36 | 70.08 | 47.55 | 61.14 | 71.46 | 61.84 | 64.66 | 72.79 | 54.22 | 62.8 |
| 19 | 90-94 | 39.57 | 46.1 | 51.95 | 85.35 | 75.5 | 53.8 | 65.34 | 44.55 | 67.65 | 39.48 | 75.52 | 58.6 |
| 20 | 95-99 | 84.93 | 0 | 42.4 | 41.72 | 40.63 | 39.39 | 0 | 71.29 | 33.08 | 31.38 | 60.79 | 40.5 |
| Total | 0-99 | | | | | | | | | | | | 15.4 |

**Supplemental Table 5** – Incidence of Acute myeloid Leukemia (AML) in males per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Male | | Incidence Acute myeloid Leukemia (AML) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | AML |
| 1 | 0-4 | 1.75 | 1.54 | 1.15 | 1.15 | 1.76 | 1.2 | 1.23 | 1.67 | 1.05 | 1.27 | 1.06 | 1.3 |
| 2 | 5-9 | 0.2 | 0.59 | 0.6 | 0.4 | 0.59 | 0.39 | 0.19 | 0.97 | 0.58 | 0.59 | 0.4 | 0.5 |
| 3 | 10-14 | 0.99 | 1.57 | 1.36 | 0.58 | 0.97 | 0.79 | 0.99 | 0.4 | 0.6 | 0.59 | 0.39 | 0.8 |
| 4 | 15-19 | 0.83 | 1.03 | 1.41 | 0.6 | 0.99 | 0.59 | 0.59 | 0.39 | 0.58 | 0.39 | 0.58 | 0.7 |
| 5 | 20-24 | 0.2 | 0.41 | 1.22 | 0.82 | 0.2 | 0.61 | 1.22 | 0.2 | 0.39 | 1.16 | 1.14 | 0.7 |
| 6 | 25-29 | 1.09 | 1.32 | 1.75 | 0.8 | 1.21 | 1.01 | 0.61 | 1.41 | 0.8 | 1.59 | 0.99 | 1.1 |
| 7 | 30-34 | 1.49 | 1.06 | 0.78 | 0.65 | 1.2 | 0.91 | 0.76 | 1.57 | 1.39 | 1 | 0.99 | 1.1 |
| 8 | 35-39 | 1.18 | 1.33 | 1.34 | 1.2 | 1.5 | 1.06 | 0.62 | 0.79 | 0.99 | 2.26 | 1.46 | 1.2 |
| 9 | 40-44 | 1.27 | 1.4 | 1.69 | 1.52 | 1.2 | 1.65 | 1.06 | 0.91 | 2.44 | 1.22 | 1.54 | 1.4 |
| 10 | 45-49 | 2.41 | 3.91 | 2.7 | 2.99 | 1.48 | 2.59 | 2.55 | 2.99 | 2.01 | 2.3 | 2.44 | 2.6 |
| 11 | 50-54 | 4.06 | 4.17 | 3.35 | 4.44 | 2.84 | 2.29 | 3.15 | 4.15 | 2.73 | 3.36 | 3.14 | 3.4 |
| 12 | 55-59 | 5.36 | 5.32 | 6.7 | 5.03 | 5.42 | 5.44 | 6.12 | 4.94 | 6.61 | 6.41 | 4.72 | 5.6 |
| 13 | 60-64 | 6.99 | 7.35 | 9.69 | 7.39 | 8.39 | 8.14 | 5.6 | 7.44 | 8.88 | 8.25 | 10.28 | 8.0 |
| 14 | 65-69 | 15.25 | 13.17 | 13.27 | 13.86 | 9.89 | 14.02 | 13.11 | 10.49 | 11.98 | 11.63 | 12.14 | 12.6 |
| 15 | 70-74 | 15.19 | 22.38 | 17.4 | 17.57 | 18.12 | 15.64 | 16.5 | 20.08 | 15.99 | 14.8 | 19.91 | 17.6 |
| 16 | 75-79 | 31.92 | 23.47 | 20.01 | 16.49 | 27.49 | 22.72 | 23.09 | 27.32 | 22.53 | 18.87 | 29.3 | 23.9 |
| 17 | 80-84 | 32.51 | 19.72 | 27.73 | 33.36 | 29.24 | 17.26 | 28.94 | 29.03 | 34.26 | 31.52 | 28.9 | 28.4 |
| 18 | 85-89 | 29.13 | 24.37 | 19.91 | 32.85 | 14.47 | 26.75 | 17.86 | 16.71 | 20.5 | 18.2 | 27.84 | 22.6 |
| 19 | 90-94 | 15.83 | 23.05 | 29.69 | 35.56 | 13.73 | 20.18 | 19.6 | 6.36 | 43.05 | 22.56 | 15.1 | 22.2 |
| 20 | 95-99 | 42.46 | 42.46 | 0 | 0 | 81.27 | 39.39 | 0 | 0 | 33.08 | 0 | 0 | 21.7 |
| Total | 0-99 | | | | | | | | | | | | 8.9 |

**Supplemental Table 6** – Incidence of Myeloproliferative Neoplasms (MPN) in females per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Female | | Incidence Myeloproliferatieve Neoplasms (MPN) (excluding CML) per year | | | | | | | | | | | Average Incidence MPN |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | (excluding CML) |
| 1 | 0-4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 2 | 5-9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 3 | 10-14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 4 | 15-19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 5 | 20-24 | 0 | 0 | 0 | 0 | 0.21 | 0 | 0 | 0 | 0 | 0 | 0.19 | 0.0 |
| 6 | 25-29 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 7 | 30-34 | 0.31 | 0.16 | 0.16 | 0 | 0.17 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0.1 |
| 8 | 35-39 | 0 | 0 | 0.15 | 0 | 0.15 | 0 | 0 | 0 | 0.17 | 0 | 0.18 | 0.1 |
| 9 | 40-44 | 0 | 0.16 | 0 | 0 | 0.31 | 0 | 0 | 0.16 | 0 | 0.16 | 0.16 | 0.1 |
| 10 | 45-49 | 0.18 | 0.17 | 0 | 0.17 | 0.17 | 0 | 0 | 0.32 | 0 | 0 | 0.16 | 0.1 |
| 11 | 50-54 | 0.35 | 0 | 0.18 | 0.18 | 0 | 0.18 | 0 | 0.17 | 0.17 | 0.17 | 0.17 | 0.1 |
| 12 | 55-59 | 0.44 | 0.81 | 0.57 | 0.55 | 0.18 | 0.36 | 0.18 | 0.19 | 0.56 | 0.18 | 0.73 | 0.4 |
| 13 | 60-64 | 0.27 | 0.26 | 0.51 | 0.25 | 0.72 | 0.23 | 0.63 | 0.79 | 0.76 | 1.29 | 0.55 | 0.6 |
| 14 | 65-69 | 1.18 | 1.78 | 0.88 | 1.45 | 1.7 | 2.23 | 1.37 | 1.34 | 1.55 | 0.76 | 0.48 | 1.3 |
| 15 | 70-74 | 0.32 | 0.96 | 0.64 | 1.91 | 1.28 | 2.55 | 3.18 | 2.52 | 2.78 | 2.42 | 2.96 | 2.0 |
| 16 | 75-79 | 1.46 | 1.47 | 1.85 | 0.37 | 1.84 | 1.1 | 2.53 | 1.8 | 3.58 | 2.5 | 1.78 | 1.8 |
| 17 | 80-84 | 1.55 | 0 | 1.45 | 3.75 | 0.92 | 0.93 | 4.16 | 1.85 | 2.76 | 1.82 | 3.14 | 2.0 |
| 18 | 85-89 | 1.75 | 0 | 0 | 0.88 | 0.85 | 3.23 | 1.54 | 0.74 | 0 | 2.08 | 1.37 | 1.1 |
| 19 | 90-94 | 2.21 | 0 | 0 | 2.08 | 0 | 0 | 0 | 0 | 0 | 0 | 1.68 | 0.5 |
| 20 | 95-99 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| Total | 0-99 | | | | | | | | | | | | 0.5 |

**Supplemental Table 7** – Incidence of Chronic Myeloid Leukemia (CML) in females per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Female | | Incidence Chronic Myeloid Leukemia (CML) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | CML |
| 1 | 0-4 | 0.2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 2 | 5-9 | 0.21 | 0 | 0 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0 | 0 | 0.0 |
| 3 | 10-14 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.21 | 0 | 0.21 | 0.41 | 0.1 |
| 4 | 15-19 | 0 | 0 | 0 | 0 | 0.21 | 0 | 0 | 0.2 | 0.2 | 0 | 0.2 | 0.1 |
| 5 | 20-24 | 0.21 | 0.21 | 0.21 | 0 | 0.42 | 0 | 0 | 0 | 0.4 | 0.2 | 0 | 0.2 |
| 6 | 25-29 | 0.37 | 0.77 | 0.39 | 0.2 | 0 | 0 | 0.61 | 0.41 | 0.2 | 0.2 | 0.4 | 0.3 |
| 7 | 30-34 | 0.15 | 0.31 | 0.48 | 0.33 | 0.35 | 0 | 0.76 | 0.59 | 1 | 0 | 0.6 | 0.4 |
| 8 | 35-39 | 0.61 | 0.77 | 0.62 | 0.31 | 0.46 | 0.47 | 1.1 | 1.44 | 0.66 | 0.52 | 0.91 | 0.7 |
| 9 | 40-44 | 0.98 | 0.96 | 0.16 | 0.47 | 0.77 | 0.77 | 0.47 | 0.47 | 0.78 | 0.94 | 0.62 | 0.7 |
| 10 | 45-49 | 1.41 | 1.04 | 0.86 | 1.01 | 1.33 | 0.99 | 1.46 | 0.64 | 0.63 | 0.94 | 0.47 | 1.0 |
| 11 | 50-54 | 0.87 | 1.43 | 0.18 | 1.45 | 1.08 | 1.25 | 1.59 | 2.1 | 0.34 | 0.68 | 1.17 | 1.1 |
| 12 | 55-59 | 0.44 | 0.2 | 1.53 | 2.21 | 1.97 | 1.07 | 1.65 | 1.11 | 1.3 | 0.92 | 2.19 | 1.3 |
| 13 | 60-64 | 0.53 | 2.09 | 1.02 | 1.49 | 2.41 | 1.37 | 1.05 | 1.18 | 1.52 | 0.37 | 2.03 | 1.4 |
| 14 | 65-69 | 1.78 | 3.55 | 1.47 | 2.31 | 1.42 | 1.95 | 0.82 | 0.8 | 2.07 | 1.26 | 1.66 | 1.7 |
| 15 | 70-74 | 2.89 | 2.55 | 2.55 | 1.59 | 1.28 | 2.55 | 2.23 | 0.63 | 2.47 | 1.21 | 2.08 | 2.0 |
| 16 | 75-79 | 2.92 | 1.47 | 3.7 | 2.22 | 4.06 | 2.56 | 1.81 | 2.51 | 1.43 | 3.21 | 1.78 | 2.5 |
| 17 | 80-84 | 3.63 | 4.51 | 2.42 | 2.81 | 2.31 | 3.24 | 3.7 | 2.31 | 2.3 | 0.91 | 0.9 | 2.6 |
| 18 | 85-89 | 3.5 | 1.74 | 3.51 | 5.28 | 4.26 | 2.42 | 1.54 | 4.43 | 1.42 | 2.77 | 1.37 | 2.9 |
| 19 | 90-94 | 2.21 | 6.55 | 0 | 2.08 | 4.06 | 0 | 1.95 | 0 | 0 | 0 | 1.68 | 1.7 |
| 20 | 95-99 | 0 | 0 | 0 | 8.6 | 0 | 0 | 7.69 | 0 | 0 | 0 | 0 | 1.5 |
| Total | 0-99 | | | | | | | | | | | | 1.1 |

**Supplemental Table 8** – Incidence of Myelodysplastic/Myeloproliferative Neoplasms (MDS/MPN) in females per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Female | | Incidence Myelodysplastic/myeloproliferative neoplasms (MDS/MPN) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | MDS/MPN |
| 1 | 0-4 | 0 | 0 | 0.2 | 0.2 | 0.2 | 0.21 | 0.21 | 0.44 | 0 | 0.22 | 0.22 | 0.2 |
| 2 | 5-9 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 3 | 10-14 | 0 | 0 | 0 | 0 | 0.2 | 0 | 0.21 | 0 | 0 | 0 | 0 | 0.0 |
| 4 | 15-19 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 5 | 20-24 | 0.21 | 0 | 0 | 0 | 0 | 0.21 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 6 | 25-29 | 0 | 0 | 0 | 0 | 0 | 0.2 | 0 | 0 | 0 | 0 | 0.2 | 0.0 |
| 7 | 30-34 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0.0 |
| 8 | 35-39 | 0 | 0 | 0 | 0.15 | 0 | 0 | 0 | 0.16 | 0 | 0 | 0 | 0.0 |
| 9 | 40-44 | 0.16 | 0 | 0 | 0 | 0 | 0 | 0.16 | 0.31 | 0 | 0.16 | 0 | 0.1 |
| 10 | 45-49 | 0 | 0 | 0 | 0 | 0 | 0.49 | 0 | 0.16 | 0 | 0.16 | 0 | 0.1 |
| 11 | 50-54 | 0.35 | 0 | 0.36 | 0.18 | 0 | 0 | 0.18 | 0.52 | 0.69 | 0.34 | 0.17 | 0.3 |
| 12 | 55-59 | 0.22 | 0 | 0.19 | 0.18 | 0.36 | 0.18 | 1.1 | 0.19 | 0.37 | 0.37 | 0.18 | 0.3 |
| 13 | 60-64 | 0.53 | 0.78 | 0.26 | 0.5 | 0.72 | 0.68 | 0.84 | 0.39 | 0.38 | 0.37 | 0.37 | 0.5 |
| 14 | 65-69 | 0.89 | 1.48 | 1.47 | 1.45 | 1.98 | 0.83 | 0.27 | 1.07 | 1.55 | 1.26 | 1.66 | 1.3 |
| 15 | 70-74 | 0.32 | 0.64 | 1.91 | 2.55 | 2.87 | 2.23 | 2.23 | 0.95 | 3.09 | 2.12 | 2.96 | 2.0 |
| 16 | 75-79 | 2.56 | 1.1 | 2.59 | 2.22 | 1.48 | 3.29 | 3.62 | 3.23 | 1.07 | 3.57 | 2.85 | 2.5 |
| 17 | 80-84 | 2.07 | 2.51 | 2.91 | 3.28 | 2.31 | 3.24 | 3.24 | 6.01 | 2.76 | 4.55 | 4.04 | 3.4 |
| 18 | 85-89 | 3.5 | 1.74 | 1.75 | 1.76 | 5.11 | 6.46 | 2.32 | 4.43 | 4.95 | 3.46 | 2.06 | 3.4 |
| 19 | 90-94 | 0 | 2.18 | 0 | 0 | 2.03 | 3.99 | 0 | 0 | 0 | 3.62 | 0 | 1.1 |
| 20 | 95-99 | 0 | 0 | 0 | 0 | 0 | 0 | 7.69 | 7.32 | 0 | 0 | 0 | 1.4 |
| Total | 0-99 | | | | | | | | | | | | 0.8 |

**Supplemental Table 9** – Incidence of Myelodysplastic syndrome (MDS) in females per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Female | | Incidence Myelodysplastic syndrome (MDS) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | MDS |
| 1 | 0-4 | 0.2 | 0.2 | 0 | 0 | 0.2 | 0.21 | 0 | 0 | 0 | 0 | 0.22 | 0.1 |
| 2 | 5-9 | 0 | 0.41 | 0 | 0 | 0.21 | 0 | 0 | 0.41 | 0.2 | 0.21 | 0 | 0.1 |
| 3 | 10-14 | 0 | 0 | 0 | 0 | 0 | 0.21 | 0.42 | 0.21 | 0 | 0.21 | 0 | 0.1 |
| 4 | 15-19 | 0 | 0.43 | 0 | 0 | 0 | 0.21 | 0 | 0.61 | 0.2 | 0.2 | 0.2 | 0.2 |
| 5 | 20-24 | 0.42 | 0 | 0.62 | 0 | 0 | 0.21 | 0.21 | 0 | 0.2 | 0.2 | 0.19 | 0.2 |
| 6 | 25-29 | 0.37 | 0.38 | 0.39 | 0.2 | 0.2 | 0.4 | 0.2 | 0 | 0.4 | 0.2 | 0 | 0.2 |
| 7 | 30-34 | 0 | 0.31 | 0.32 | 0.33 | 0.17 | 0.18 | 0.19 | 0 | 0 | 0 | 0 | 0.1 |
| 8 | 35-39 | 0.61 | 0.15 | 0.46 | 0.15 | 0.31 | 0.16 | 0.16 | 0.32 | 0.5 | 0.35 | 0.18 | 0.3 |
| 9 | 40-44 | 0.49 | 0.64 | 0.47 | 0.62 | 0.62 | 0.31 | 0.62 | 0.47 | 0.62 | 0.78 | 0.31 | 0.5 |
| 10 | 45-49 | 0.53 | 1.04 | 0.69 | 0.51 | 0.33 | 0.33 | 0.65 | 0.96 | 0.79 | 1.4 | 1.09 | 0.8 |
| 11 | 50-54 | 1.22 | 1.25 | 1.09 | 0.73 | 0.72 | 1.07 | 1.06 | 1.05 | 1.03 | 1.18 | 1 | 1.0 |
| 12 | 55-59 | 1.76 | 2.23 | 1.91 | 1.47 | 3.4 | 2.5 | 1.83 | 2.04 | 2.05 | 1.85 | 2.56 | 2.1 |
| 13 | 60-64 | 3.45 | 2.35 | 4.34 | 3.47 | 3.86 | 5.01 | 6.07 | 4.14 | 3.8 | 3.88 | 2.77 | 3.9 |
| 14 | 65-69 | 4.74 | 9.18 | 8.23 | 7.23 | 4.53 | 8.07 | 8.48 | 5.87 | 7.25 | 6.81 | 8.56 | 7.2 |
| 15 | 70-74 | 10.29 | 13.73 | 10.19 | 13.38 | 8.93 | 11.48 | 11.45 | 13.86 | 10.51 | 15.11 | 12.75 | 12.0 |
| 16 | 75-79 | 16.8 | 12.13 | 24.03 | 15.93 | 20.29 | 12.79 | 18.09 | 17.6 | 28.26 | 22.12 | 22.41 | 19.1 |
| 17 | 80-84 | 18.14 | 21.57 | 25.68 | 19.21 | 25.89 | 29.62 | 33.77 | 24.49 | 30.84 | 25.04 | 23.34 | 25.2 |
| 18 | 85-89 | 24.52 | 20.93 | 29.82 | 24.62 | 34.9 | 30.7 | 29.34 | 24.35 | 26.18 | 28.37 | 26.07 | 27.3 |
| 19 | 90-94 | 17.69 | 17.47 | 17.12 | 16.64 | 22.33 | 21.94 | 15.64 | 32.75 | 15.19 | 25.31 | 16.84 | 19.9 |
| 20 | 95-99 | 0 | 9.12 | 17.82 | 8.6 | 8.24 | 0 | 15.38 | 0 | 6.95 | 6.65 | 19.26 | 8.4 |
| Total | 0-99 | | | | | | | | | | | | 6.4 |

**Supplemental Table 10** – Incidence of Acute Myeloid Leukemia (AML) in females per age category from 2001-2011 in The Netherlands, obtained from the Netherlands Cancer Registry (www.cijfersoverkanker.nl).

| Female | | Incidence Acute myeloid Leukemia (AML) per year | | | | | | | | | | | Average Incidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cat | Age | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | AML |
| 1 | 0-4 | 1.02 | 1.21 | 1 | 1.41 | 1.64 | 1.26 | 1.07 | 1.09 | 0.88 | 0.44 | 1.33 | 1.1 |
| 2 | 5-9 | 0.21 | 0.41 | 0 | 0.62 | 0.21 | 0.41 | 0.2 | 0.2 | 0.41 | 0.21 | 0.21 | 0.3 |
| 3 | 10-14 | 0.41 | 0.82 | 0.61 | 0.61 | 0.41 | 0.41 | 0.42 | 0.84 | 0.42 | 0 | 0.41 | 0.5 |
| 4 | 15-19 | 0.22 | 0.86 | 0 | 0 | 2.28 | 1.23 | 1.23 | 0.41 | 0.4 | 1.01 | 0.61 | 0.8 |
| 5 | 20-24 | 1.26 | 1.04 | 0.62 | 1.04 | 0.42 | 0.42 | 1.67 | 0.61 | 0.4 | 1.18 | 0.78 | 0.9 |
| 6 | 25-29 | 0.74 | 0.96 | 1.58 | 0.6 | 1.62 | 1.01 | 0.81 | 1.42 | 2.02 | 0.6 | 1 | 1.1 |
| 7 | 30-34 | 1.24 | 1.09 | 1.11 | 1.15 | 0.35 | 1.83 | 0.76 | 1.38 | 1.99 | 1.2 | 0.99 | 1.2 |
| 8 | 35-39 | 1.69 | 1.38 | 1.54 | 1.86 | 1.24 | 2.17 | 2.04 | 1.76 | 1 | 2.09 | 2 | 1.7 |
| 9 | 40-44 | 2.11 | 1.6 | 1.58 | 3.12 | 3.4 | 2.16 | 1.86 | 1.87 | 2.19 | 1.71 | 1.56 | 2.1 |
| 10 | 45-49 | 2.11 | 3.48 | 1.72 | 3.72 | 2.33 | 2.46 | 2.91 | 2.24 | 2.36 | 2.65 | 3.27 | 2.7 |
| 11 | 50-54 | 3.49 | 1.97 | 2.17 | 2.54 | 1.63 | 4.83 | 2.3 | 3.15 | 2.92 | 3.39 | 2.5 | 2.8 |
| 12 | 55-59 | 3.53 | 5.67 | 5.34 | 4.97 | 3.93 | 4.83 | 4.77 | 4.46 | 4.28 | 4.99 | 3.29 | 4.6 |
| 13 | 60-64 | 3.99 | 6.27 | 7.65 | 4.95 | 6.52 | 3.65 | 3.35 | 5.72 | 5.9 | 4.43 | 4.61 | 5.2 |
| 14 | 65-69 | 4.15 | 6.52 | 9.41 | 10.41 | 5.95 | 8.35 | 6.57 | 7.48 | 8.8 | 9.33 | 9.75 | 7.9 |
| 15 | 70-74 | 9.97 | 12.45 | 10.5 | 12.42 | 9.56 | 8.61 | 7 | 9.45 | 9.89 | 14.81 | 10.97 | 10.5 |
| 16 | 75-79 | 9.86 | 13.24 | 15.9 | 13.34 | 12.17 | 14.26 | 13.39 | 13.65 | 16.81 | 14.98 | 13.87 | 13.8 |
| 17 | 80-84 | 12.96 | 16.55 | 16.48 | 18.27 | 12.48 | 17.58 | 15.27 | 15.25 | 13.35 | 18.21 | 19.75 | 16.0 |
| 18 | 85-89 | 10.51 | 11.34 | 14.04 | 14.07 | 14.47 | 10.5 | 15.44 | 20.66 | 21.94 | 13.15 | 19.21 | 15.0 |
| 19 | 90-94 | 8.84 | 6.55 | 4.28 | 16.64 | 10.15 | 15.96 | 9.77 | 9.63 | 9.5 | 9.04 | 10.1 | 10.0 |
| 20 | 95-99 | 9.4 | 0 | 8.91 | 0 | 8.24 | 0 | 7.69 | 0 | 0 | 0 | 0 | 3.1 |
| Total | 0-99 | | | | | | | | | | | | 5.1 |

**Supplemental Table 11** – Patient age, sex and follow-up characteristics in 367 patients. Age category (Age-Cat), Follow-up (FU)

| Age-Cat | Age | Total no. | Male | Female | FU in yrs. | FU-Male | FU-Female |
|---|---|---|---|---|---|---|---|
| 1 | 0-4 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 2 | 5-9 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 3 | 10-14 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 4 | 15-19 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 5 | 20-24 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 6 | 25-29 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 7 | 30-34 | 14 | 7 | 7 | 20.6 | 7.1 | 13.4 |
| 8 | 35-39 | 12 | 2 | 10 | 28.2 | 7.0 | 21.3 |
| 9 | 40-44 | 29 | 14 | 15 | 53.9 | 15.3 | 38.5 |
| 10 | 45-49 | 38 | 20 | 18 | 228.2 | 59.9 | 168.3 |
| 11 | 50-54 | 44 | 23 | 21 | 135.8 | 68.0 | 67.8 |
| 12 | 55-59 | 66 | 33 | 33 | 173.6 | 85.3 | 88.3 |
| 13 | 60-64 | 62 | 34 | 28 | 317.7 | 108.3 | 209.4 |
| 14 | 65-69 | 34 | 14 | 20 | 145.2 | 73.5 | 71.7 |
| 15 | 70-74 | 39 | 19 | 20 | 104.2 | 51.2 | 53.0 |
| 16 | 75-79 | 22 | 13 | 9 | 73.5 | 42.9 | 30.6 |
| 17 | 80-84 | 6 | 4 | 2 | 20.9 | 11.9 | 9.0 |
| 18 | 85-89 | 1 | 0 | 1 | 7.0 | 4.3 | 2.7 |
| 19 | 90-94 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 20 | 95-99 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| **Total** | **0-99** | 367 | 183 | 184 | 1308.8 | 534.7 | 774.1 |

**Supplemental Table 12** - Expected number of hematological malignancies in 367 patients; Myeloproliferative Neoplasms (MPN), Chronic Myeloid Leukemia (CML), Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN). Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML).

| Age-Cat | Age | MPN (without CML) | CML | MDS/MPN | MDS | AML |
|---|---|---|---|---|---|---|
| 1 | 0-4 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 2 | 5-9 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 3 | 10-14 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 4 | 15-19 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 5 | 20-24 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 6 | 25-29 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 7 | 30-34 | 0.000 | 0.001 | 0.000 | 0.000 | 0.002 |
| 8 | 35-39 | 0.000 | 0.002 | 0.000 | 0.000 | 0.004 |
| 9 | 40-44 | 0.001 | 0.006 | 0.000 | 0.002 | 0.015 |
| 10 | 45-49 | 0.005 | 0.043 | 0.004 | 0.042 | 0.111 |
| 11 | 50-54 | 0.010 | 0.033 | 0.006 | 0.035 | 0.094 |
| 12 | 55-59 | 0.044 | 0.078 | 0.026 | 0.146 | 0.291 |
| 13 | 60-64 | 0.080 | 0.137 | 0.076 | 0.345 | 0.600 |
| 14 | 65-69 | 0.044 | 0.047 | 0.047 | 0.280 | 0.243 |
| 15 | 70-74 | 0.051 | 0.044 | 0.065 | 0.358 | 0.283 |
| 16 | 75-79 | 0.028 | 0.033 | 0.042 | 0.298 | 0.171 |
| 17 | 80-84 | 0.002 | 0.003 | 0.004 | 0.029 | 0.016 |
| 18 | 85-89 | 0.000 | 0.000 | 0.000 | 0.001 | 0.000 |
| 19 | 90-94 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 20 | 95-99 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| **Total** | **0-99** | **0.265** | **0.425** | **0.271** | **1.536** | **1.831** |

**Supplemental Table 13** – Patient age, sex and follow-up characteristics in 274 Gastroenteropancreatic Neuroendocrine tumors (GEP-NETs) patients.

| Patient Characteristics | | | | | | | | | Expected number of hematopoietic neoplasms | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Age-Cat** | **Age** | **Total no.** | **Male** | **Female** | **FU in yrs** | **FUMale** | **FUFemale** | | **MPN (without CML)** | **CML** | **MDS/MPN** | **MDS** | **AML** |
| 1 | 0-4 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 2 | 5-9 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 3 | 10-14 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 4 | 15-19 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 5 | 20-24 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 6 | 25-29 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 7 | 30-34 | 6 | 3 | 3 | 9.4 | 5.8 | 3.6 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 8 | 35-39 | 7 | 1 | 6 | 23.1 | 6.3 | 16.8 | | 0.000 | 0.001 | 0.000 | 0.000 | 0.002 |
| 9 | 40-44 | 19 | 10 | 9 | 38.3 | 9.7 | 28.6 | | 0.000 | 0.003 | 0.000 | 0.002 | 0.007 |
| 10 | 45-49 | 26 | 13 | 13 | 203.2 | 45.7 | 157.5 | | 0.003 | 0.027 | 0.002 | 0.020 | 0.070 |
| 11 | 50-54 | 36 | 19 | 17 | 108.2 | 49.4 | 58.8 | | 0.006 | 0.021 | 0.004 | 0.028 | 0.060 |
| 12 | 55-59 | 47 | 23 | 24 | 144.6 | 75.5 | 69.1 | | 0.026 | 0.046 | 0.015 | 0.085 | 0.173 |
| 13 | 60-64 | 53 | 29 | 24 | 298.0 | 94.8 | 203.2 | | 0.063 | 0.109 | 0.060 | 0.354 | 0.474 |
| 14 | 65-69 | 28 | 12 | 16 | 125.9 | 63.6 | 62.4 | | 0.031 | 0.034 | 0.034 | 0.172 | 0.175 |
| 15 | 70-74 | 29 | 15 | 14 | 87.8 | 46.9 | 40.9 | | 0.033 | 0.028 | 0.043 | 0.235 | 0.184 |
| 16 | 75-79 | 18 | 11 | 7 | 54.1 | 36.5 | 17.6 | | 0.019 | 0.022 | 0.028 | 0.184 | 0.113 |
| 17 | 80-84 | 5 | 3 | 2 | 16.2 | 9.5 | 6.8 | | 0.001 | 0.002 | 0.003 | 0.019 | 0.010 |
| 18 | 85-89 | 0 | 0 | 0 | 4.3 | 3.8 | 0.5 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 19 | 90-94 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 20 | 95-99 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 | | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| **Total** | **0-99** | 274 | 139 | 135 | 1113.2 | 447.3 | 665.8 | | **0.183** | **0.292** | **0.190** | **1.100** | **1.268** |

**Supplemental Table 14** – Expected number of hematological malignancies in 274 patients; Myeloproliferative Neoplasms (MPN), Chronic Myeloid Leukemia (CML), Myelodysplastic/Myeloproliferative neoplasms (MDS/MPN). Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML).

| Age-Cat | Age | MPN (without CML) | CML | MDS/MPN | MDS | AML |
|---|---|---|---|---|---|---|
| 1 | 0-4 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 2 | 5-9 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 3 | 10-14 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 4 | 15-19 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 5 | 20-24 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 6 | 25-29 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 7 | 30-34 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 8 | 35-39 | 0.000 | 0.001 | 0.000 | 0.000 | 0.002 |
| 9 | 40-44 | 0.000 | 0.003 | 0.000 | 0.002 | 0.007 |
| 10 | 45-49 | 0.003 | 0.027 | 0.002 | 0.020 | 0.070 |
| 11 | 50-54 | 0.006 | 0.021 | 0.004 | 0.028 | 0.060 |
| 12 | 55-59 | 0.026 | 0.046 | 0.015 | 0.085 | 0.173 |
| 13 | 60-64 | 0.063 | 0.109 | 0.060 | 0.354 | 0.474 |
| 14 | 65-69 | 0.031 | 0.034 | 0.034 | 0.172 | 0.175 |
| 15 | 70-74 | 0.033 | 0.028 | 0.043 | 0.235 | 0.184 |
| 16 | 75-79 | 0.019 | 0.022 | 0.028 | 0.184 | 0.113 |
| 17 | 80-84 | 0.001 | 0.002 | 0.003 | 0.019 | 0.010 |
| 18 | 85-89 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 19 | 90-94 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| 20 | 95-99 | 0.000 | 0.000 | 0.000 | 0.000 | 0.000 |
| **Total** | **0-99** | **0.183** | **0.292** | **0.190** | **1.100** | **1.268** |

**Supplemental Table 15** - 43 out of 367 off-protocol with reason:

| **Reason:** | **Number of patients** |
|---|---|
| Low uptake (on first post therapy scan) | 14 |
| Concomitant Radiotherapy | 6 |
| Diagnostic | 4 |
| Previous $^{111}$In-PRRT | 3 |
| Low Karnofsky score | 3 |
| Poor renal function | 3 |
| Low baseline Hb, platelets or WBC | 3 |
| Previous $^{90}$Y-PRRT | 2 |
| No pathology available | 2 |
| Hb tranfusion prior to PRRT | 1 |
| Previous $^{131}$I-therapy | 1 |
| Patient was not able to give fully consent | 1 |
| | |
| **Totaal** | **43** |

**Supplemental Table 16** - 93 out of 367 patients with Non GEP-NETs:

| **Type of tumor** | **Number of patients** |
|---|---|
| NET - thorax/chest | 2 |
| NET - unknown primary | 28 |
| NET - other locations | 4 |
| | |
| Tyroid carcinoma | 19 |
| Paraganglioma | 14 |
| Feochromocytoma | 2 |
| Meningioma | 4 |
| Hurthecell carcinoma | 6 |
| SCLC | 1 |
| Grawitz pancreas | 1 |
| Mamma carcinoma | 3 |
| Erdheim chester | 1 |
| HCC | 2 |
| Prostaat carcinoma | 1 |
| Esthesioneuroblastoom | 1 |
| Melanoma | 2 |
| Meduloblastoma | 1 |
| Rectum carcinoma | 1 |
| | |
| **Totaal** | **93** |

**Supplemental Table 17** – Characteristics of 13 patients with persistent hematological dysfunction (PHD) after peptide receptor radiotherapy (PRRT) with $^{177}$Lu-DOTATATE ($^{177}$Lu). Neuroendocrine tumor (NET), Neuroendocrine tumor of the pancreas (PNET), Radioactive iodine I-131 therapy ($^{131}$I), cold Octreotide (Octreotide), External beam radiotherapy (EBRT), PRRT with 177Lu-Hemoglobin (Hb), Platelets (PLT), White Blood Cells (WBC).

| Patient | | | | Previous | Administered Activity | PRRT | | Blood work | Bone marrow | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| no. | sex | Age | Diagnosis | therapy | (GBq) | interrupted | Reason | Cytopenia | 1. Aspirate | 2. Flow | 3. Cytogenetics | 4. Biopsy | Diagnosis |
| 359 | f | 70 | NET | Octreotide | 30.0 | no | - | Hb | yes | no | no | yes | MDS, RARS |
| 297 | f | 60 | NET | Octreotide | 18.6 | yes | Maximum kidney dose | Hb, PLT, WBC | yes | no | no | yes | Hypoplasia |
| 293 | m | 61 | PNET | chemo-embolisation | 29.3 | no | - | Hb, PLT | yes | yes | 46,XY, t(9;22) | yes | CML |
| 284 | m | 57 | PNET | - | 29.7 | no | - | Hb | yes | no | -5,-7,del(12p), +mar | yes | MDS, RAEB-II |
| 252 | f | 64 | NET | Octreotide | 30.0 | no | - | Hb, WBC | no | no | no | no | Pancytopenia |
| 241 | f | 41 | PNET | - | 26.3 | yes | Hematological toxicity | Hb, PLT, WBC | yes | no | no | yes | Aplasia |
| 185 | m | 74 | PNET | - | 26.4 | no | | Hb, PLT | yes | yes | 45,XY,-7 [20] | yes | MDS/MPN: CMML-1 |
| 158 | m | 62 | NET | Octreotide | 22.2 | yes | Maximum kidney dose | Hb, PLT, WBC | yes | yes | no | yes | MDS, RAEB-II |
| 105 | v | 67 | NET | - | 22.3 | yes | Hematological toxicity | WBC | yes | no | no | yes | Hypoplasia |
| 102 | m | 68 | NET | - | 30.0 | no | - | Hb, PLT, WBC | yes | yes | no | yes | MDS, Hypocellular |
| 91 | f | 59 | NET | Octreotide, local EBRT | 22.7 | yes | Maximum kidney dose | Hb, PLT, WBC | yes | yes | 46,XX | yes | AML |
| 81 | f | 58 | NET | Octreotide | 22.3 | yes | Maximum kidney dose | Hb, PLT, WBC | yes | no | no, JAK2 neg | yes | Myelofibrosis/ MPN |
| 45 | f | 58 | Thyroid cancer | Radioactive iodine therapy | 16.7 ($^{131}$I) & 15.2 ($^{177}$Lu) | no | - | Hb, PLT | yes | no | no | yes | Hypoplasia |

**Supplemental Table 18** – Calculations for the relative risk (RR) in all 367 patients and 274 Neuroendocrine gastroenteropancreatic tumors (GEP-NETs).

| | **All 367 patients** | **274 GEP-NET patients** |
|---|---|---|
| Exposed group | | |
| Number with positive (bad) outcome (a): | 8 | 8 |
| Number with negative (good) outcome (b): | 359 | 266 |
| Control group | | |
| Number with positive (bad) outcome (c): | 4.4 | 3 |
| Number with negative (good) outcome (d): | 362.6 | 271 |
| | | |
| Relative Risk | 1.82 | 2.67 |
| 95% Confidence Interval | 1.26 to 2.62 | 0.72 to 9.95 |
| Z statistic | 3.22 | 1.46 |
| Significance level | P = 0.0013 | P = 0.1442 |
| NNT (Harm) | 101.81 | 54.800 |
| 95% Confidence Interval | 254.25 (Harm) to 63.65 (Harm) | 23.99 (Harm) to ∞ to 192.77 (Harm) |