Radiation Risk from Medical Exposure in Children

4

Michael Lassmann and Uta Eberlein

Contents

4.1 Introduction

Diagnostic nuclear medicine procedures imply the administration of activity levels that do not lead to the appearance of radiation deterministic effects. Effects to be expected, if at all, are stochastic effects of ionizing radiation. The assessment of adverse health effects from exposure of ionizing radiation in the dose range commonly encountered in clinical (and pediatric) diagnostic nuclear medicine is based on epidemiological and biological data. Most of the data on the effects on human health after exposure to ionizing radiation comes from the Life Span Study of the survivors of the bombings of Hiroshima and Nagasaki, as reported by the Radiation Effects Research Foundation [18, 22–24]. In addition, there are few data on the stochastic radiation risk after treatment of thyroid diseases with radioiodine [10, 21,

M. Lassmann (✉) • U. Eberlein
Klinik und Poliklinik für Nuklearmedizin, Universitätsklinikum Würzburg,
Oberdürrbacher Str. 6, Würzburg D - 97080, Germany
e-mail: lassmann_m@ukw.de

L. Mansi et al. (eds.), *Clinical Nuclear Medicine in Pediatrics*,
DOI 10.1007/978-3-319-21371-2_4

26, 31]. However, there is no clear evidence that there is an increase in cancer risk associated with I-131 therapy [31]. No such data are available concerning the potential cancer risk of diagnostic nuclear medicine.

For a risk assessment of medical diagnostic procedures involving ionizing radiation, the concept of the effective dose has been widely adapted. The risk associated with the effective dose is based on assumptions such as the concept of considering the risk to the general public or to workers. This does not reflect the situation for patients in nuclear medicine. Another aspect is the strong age and sex dependency of the radiation risk, which is not included in the effective dose. Therefore, the effective dose should not be used for risk-benefit assessments in patients; instead, the relevant quantity is the equivalent dose or the absorbed dose to irradiated organs. However, for comparing different medical procedures, effective dose is a useful quantity [17].

In addition, for obtaining reliable epidemiological data on low doses of ionizing radiation, it is mandatory to study very large sample sizes, as the required sample size increases approximately as the inverse square of the dose [3]. The size of the study cohort is important in order to distinguish the effect of the ionizing radiation statistically from the baseline cancer incidence rate. For example, if a sample size of 50,000 people would be needed to detect a significant cancer risk of 100 mGy, then one would need a study group of 5 million people for an absorbed dose of 10 mGy [3].

For the atomic bomb cohort in Japan (follow-up of 86,572 survivors with different age and different radiation exposure), the detection limit for radiation-induced cancer lies in between 50 and 100 mSv. However, for tumors with a very low baseline cancer risk, as thyroid cancer or childhood leukemia, the detection limit could be as low as 20 mSv [4].

For nuclear medicine, therefore, there are only epidemiologic studies on the diagnostic use of I-131, for which the thyroid absorbed dose is in the range of 1 Gy [7] corresponding to an equivalent dose of 1 Sv. Today, the use of I-131 is restricted to pre-therapeutic diagnostics, which is often followed by radioiodine therapies with activities exceeding the diagnostic activities at least tenfold. If patients are treated with I-131, the deterministic effects of radiation are predominant and, therefore, are not considered in this report.

The organ absorbed doses for other radiopharmaceuticals used in diagnostic nuclear medicine are much smaller than 1 Gy and therefore are considered to be below the detection limit for epidemiologic studies.

The aim of this chapter is to provide information, an overview, on epidemiological data available for nuclear medicine procedures and on the associated risk for children and adolescents.

4.2 Risk Definitions

4.2.1 LNT Model: Linear No-Threshold Model

Based on a comprehensive literature review, most national and international committees such as UNSCEAR, BEIR VII, and ICRP assume [6, 17, 29] that the

radiation cancer risk is proportional to the radiation dose with no threshold below which there is no cancer risk. The risk-dose response was mainly derived from the Japanese atomic bomb survivors, because all age groups and groups of persons with totally different radiation exposure were affected. This model fits very well for all solid cancers but, for example, for leukemia, a linear-quadratic model is assumed [19]. However, it is still discussed, controversially, whether there is a threshold or not [4, 19, 27].

For extrapolating the risk from high dose (dose-rate) exposure to low doses (dose-rates), a dose and dose-rate effectiveness factor (DDREF) of 2 was introduced in the ICRP 60 report [16]. The linear risk estimates derived from the Japanese atomic bomb survivors are reduced by this factor, based on the assumption of lower biological effectiveness of radiation exposure at low doses and low dose rates compared to exposures at high doses and high dose rates [17]. ICRP 103 and the UNSCEAR report 2006 [29] still use the factor 2, whereas BEIR VII [6] recommends the use of a factor 1.5. For comparing different risk assumptions, it is important to know which factor was used.

Another problem occurs, when transforming the risk of a particular exposed population to another, with different genetic and lifestyle characteristics. There are no simple solutions for this problem [6, 29]. There are approaches based on relative risk (risks resulting from radiation exposure are proportional to baseline risks) and absolute risk transport (in which it is assumed that radiation risks do not depend on baseline risk). The BEIR VII committee recommends a weighted estimate of both risk transport modalities. A weight of 0.7 is used for relative risk transport and 0.3 for absolute risk transport, respectively [6].

According to the models provided by the BEIR VII Phase 2 report, those exposed at an earlier age are in general at higher risk for cancer induction from ionizing radiation than adults. For example, a 1-year-old child and a 10-year-old child may have an approximately threefold and twofold higher risk, respectively, of cancer induction than a 40-year-old adult, respectively, for the same level of exposure. In addition, a young girl has a 30–40 % higher risk of cancer induction than a young boy with the same level of exposure, mostly due to the risk from breast cancer [9].

4.2.2 The Use of Effective Dose in Epidemiology

The term effective dose is, according to ICRP 103 [17], a protection quantity which provides a dose value that is related to the probability of health detriment to an adult reference person due to stochastic effects from exposure to low doses of ionizing radiation [16, 17, 20]. It is therefore a problematic quantity for the use in children. In particular, the effective dose reflects the risk of the nonuniform dose distribution in terms of a uniform or whole-body exposure. This is important for medical applications, as most medical exposures consist of nonuniform partial body irradiations.

For comparing different diagnostic procedures, or similar procedures in different hospitals and countries, the effective dose can be very useful. Furthermore, it is a good quantity to compare the use of different technologies for the same medical examination. But one has to keep in mind that this only holds for patient populations with the same age and sex distribution [17].

For this reason, the quantity effective dose should not be used for epidemiologic studies and for sex-specific or rather individual dose and risk assessment [14, 17].

4.3 Data on Radiation Risk in Nuclear Medicine

4.3.1 Thyroid Cancer Caused by Diagnostic Exposure of I-131

In a Swedish cohort, the excess cancer risk of diagnostic I-131 applications between 1952 and 1969 was investigated in different studies [7, 12, 15]. The patient follow-up started with the first administration of I-131 or on 1 January 1958 (since then, data have been available from the Swedish cancer registry) for the patients who received the examination before 1958 and was conducted until the end of 1984 [15], 1990 [12], and 1998 [7]. The studies of Holm et al. [15] and Hall et al. [12] on this cohort excluded the first 5 years after exposure for all patients. In order to further extend the time span and to include early cancer induction, Dickman et al. [7] included patients as early as 2 years after exposure and extended the follow-up to 1998 and furthermore included patients with previous external radiation therapy (XRT) to the head and neck.

The data of 36,792 mostly adult patients were included in the study; only 7 % of the patients were younger than 20 years at the time of the first administration of I-131. The patients were divided into two groups [7]: patients who reported previous external radiation therapy to the head and neck and patients who did not. These groups were further divided into two subgroups:

- Patients who referred for suspicion of a thyroid tumor
- Patients who referred for other reasons

Details on the patient population included in the study and mean total administered activities, 24-h uptake, and absorbed doses for the individual subgroups can be found in Table 4.1.

The authors did not find any evidence of an excess cancer risk for patients who were referred for a reason other than suspicion of a thyroid tumor and did not report external radiation therapy [7]. However, for the patient group suspicious for thyroid tumor, an excess risk was found.

For the group with previous external radiation therapy, both subgroups showed an excess cancer risk, which was higher for the group with suspicious thyroid tumor.

Nevertheless, both factors – suspicion for thyroid cancer and external radiation therapy of the head and neck – were confounding factors.

The authors did not find a dose-response relationship or variation in risk with age, but it has to be mentioned that the cohort included only 7 % patients under the age of 20, so this is only a vague conclusion.

It is known [1, 13] that children are much more sensitive to radiation exposure than adults. Compared to the adult thyroid gland, the thyroid gland of children proliferates more rapidly and it is therefore believed that the fast growth of the

Table 4.1 Characteristics of patients exposed to I-131 classified according to prior exposure to external radiation therapy (XRT) to the head and neck and reason for referral [7]

	No prior exposure to XRT			Prior exposure to XRT		
	Reason for referral			Reason for referral		
	Suspicion of thyroid tumor	Other	All	Suspicion of thyroid tumor	Other	All
Number of patients at risk	11,015	24,010	35,025	608	1159	1767
Observed number of thyroid cancers	69	36	105	12	12	24
Percentage male	14	23	20	18	25	22
Mean age at first exposure (range, years)	44 (0–74)	43 (0–74)	43 (0–74)	53 (16–74)	51 (8–74)	52 (8–74)
Patients <20 years of age at exposure (%)	6	7	7	0	2	1
Mean follow-up period (range, years)	27 (2–47)	27 (2–47)	27 (2–47)	20 (2–44)	20 (2–47)	20 (2–47)
Mean number of administered doses (range)	1.3 (1–10)	1.3 (1–9)	1.3 (1–10)	–	–	–
Mean total administered activity (MBq)	2.5	1.6	1.9	3.5	3.1	3.2
Mean 24 h thyroid uptake (%)	39	38	39	36	36	36
Mean total absorbed I-131 dose to thyroid (Gy)	1.37	0.94	1.07	1.75	1.74	1.74

radiation-injured cells is the reason for the apparent effects in children. Furthermore, children have more years of cancer risk, because of their longer life expectancy.

A German multicenter retrospective cohort study investigating diagnostic administration of I-131 in children, with a median thyroid dose of 1 Gy, has not found any significantly increased risk of thyroid cancer in children [11]. A detailed characterization of the absorbed doses with age and initial diagnoses can be found in Table 4.2. However, in this study, the number of patients studied (789 exposed subjects and 1118 nonexposed subjects) and the follow-up time were limited and

Table 4.2 Median thyroid absorbed dose for different initial diagnoses and age [10]

Initial diagnosis	$n = 789$	Median thyroid dose, Gy (interquartile range)
Missing values	10	1.6 (0.8–1.9)
Uncertain diagnosis	13	1.5 (1.0–2.2)
Hyperthyroidism	34	1.5 (0.9–2.6)
Hypothyroidism	61	0.3 (0.2–0.7)
Goiter	385	1.1 (0.7–1.6)
Nodular goiter	77	1.0 (0.7–1.7)
Iodine metabolism disorder	10	1.8 (1.0–3.5)
No evidence of disease	199	0.8 (0.5–1.4)
Age at first administration		
0–5 years	62	0.6 (0.2–1.7)
6–10 years	85	0.8 (0.5–1.4)
11–15 years	366	1.2 (0.6–1.7)
16–17 years	276	1.0 (0.6–1.4)
All	789	1.0 (0.5–1.6)

furthermore, only a very small number of children under the age of 5 were part of the study. For this age group, the highest thyroid cancer rate was found in the most heavily contaminated areas after the Chernobyl accident [11].

According to these studies, there is no evidence that diagnostic exposure of I-131 causes excessive thyroid cancer cases [7, 11, 12, 15, 31].

4.3.2 Thyroid Cancer Caused by Radiation Exposure of the Japanese Atomic Bomb and the Chernobyl Accident

Cardis et al. [5] emphasized in their article about "Risk of thyroid cancer after exposure to I-131 in childhood" that the iodine deficiency and the iodine supplementation appear to be important and independent modifiers of the thyroid cancer risk after exposure of I-131 in childhood [5]. The authors carried out a case-control study of thyroid cancer in children younger than 15 years in 1986 and who lived in Belarus and the Russian Federation, taking account of environmental and host factors. They found that the relative risk of thyroid cancer in exposed children in iodine deficiency areas is three times higher than elsewhere and that an iodine supplemental diet (taken after exposure and even months after) reduced the relative risk by a factor of three.

Richardson [25] analyzed the cancer incidences among the atomic bomb survivors of Hiroshima and Nagasaki who were 20 years and older at the time of the bombing. He used Poisson regression methods for data analyzing and deriving associations between thyroid absorbed dose and thyroid cancer incidence by sex, age at exposure, and time-since-exposure [25].

In most reviews [2, 28], people conclude that there is only little evidence of radiation-induced thyroid cancer in adult atomic bomb survivors. Richardson

concludes in his article that there is evidence of an increased thyroid cancer rate among female A-bomb survivors as compared to male survivors. Nevertheless, these studies of atomic bomb survivors do not provide information on internal intake of radioactive iodine [2].

4.3.3 Radiation Risk in Children

According to a recent review by Fahey et al [8] a recent reevaluation of data from the Life Span Study of the survivors of the bombings of Hiroshima and Nagasaki indicated an increased risk of cancers of the stomach, lung, liver, colon, breast, gallbladder, esophagus, bladder, and ovary. No increased risk was found for cancers of the rectum, pancreas, uterus, prostate gland, and kidney. A total of 86,600 subjects were followed up for solid tumors from 1950 to 2003, and it was estimated that there were 527 excess deaths in that population [8].

A review of the data from the Life Span Study indicates a clear relationship between induction of solid cancer and absorbed dose at levels of more than 0.5 Gy [8]. However, as has been shown before, the limitations of epidemiological approaches make a risk estimate at the dose range associated with clinical nuclear medicine (i.e., 0.01–0.1 Gy) difficult. Differences in biokinetics, dose rate, or the fractionation of dose between the subjects considered in the epidemiological studies and nuclear medicine patients can also affect the accuracy of the estimation.

In 2013, the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) issued a report titled "Sources, Effects and Risks of Ionizing Radiation" (Volume II, Annex B) on the effects of radiation exposure in children [30]. The report included a review of data for 23 types of tumors in regard to the evidence as to whether there was an association with ionizing radiation and whether there was an effect based on the age of exposure (i.e., whether younger patients were at higher or lower risk with the same level of exposure). According to the review article by Fahey et al. [8], the report indicated that a quarter of the types of tumors (including leukemia as well as thyroid, skin, breast, and brain) clearly demonstrated higher radiation sensitivity in younger subjects. In 15 % of the types of tumors (including bladder), children had the same level of radiosensitivity as adults. For another 10 % of the types of tumors (most notably lung), the risk in younger subjects was lower than that in adults. In the other 50 % of types of tumors, the association was either too weak to draw a conclusion regarding the relationship between risk and age (e.g., for esophagus) or no evidence that there was a relationship between radiation and tumor induction at any age (Hodgkin's lymphoma, prostate, rectum, or uterus). For two types of tumors (leukemia and lung), associations of risk with age were notably different between the BEIR VII Phase 2 report and the 2013 UNSCEAR report. There was little variation in risk at different ages in the BEIR VII Phase 2 report, whereas there was a markedly higher risk for younger patients in the 2013 UNSCEAR report. Conversely, the BEIR VII Phase 2 report indicated a higher risk and the 2013 UNSCEAR report reported a slightly lower risk of lung cancer in children [6, 9, 30].

Conclusions

- For comparing different diagnostic procedures or similar procedures in different hospitals and countries, the effective dose can be very useful. Furthermore, this quantity is suited for a comparison of the use of different technologies for the same medical examination. One has to keep in mind, however, that this only holds for patient populations with the same age and sex distribution. For this reason, the quantity effective dose should not be used for epidemiologic studies and for sex-specific or individual risk assessment and is, therefore, a problematic quantity for the use in radiation risk estimates in children.
- As very large sample sizes are needed to statistically distinguish radiation-induced cancers from the baseline cancer incidence rate at very low absorbed doses, there exist only epidemiologic studies on the diagnostic use of I-131, for which the thyroid absorbed dose is in the range of 1 Gy. Especially for children and adolescents, only few data on I-131 with limited patient numbers can be found. Therefore, it is not possible to make a reliable risk assumption for children and adolescents.
  According to these epidemiologic studies, there is no evidence that diagnostic exposure of I-131 causes excessive thyroid cancer cases.
- For other radiopharmaceuticals used in diagnostic nuclear medicine, the absorbed doses to the organs are too small and are therefore below the detection limit for epidemiologic studies. In this case, theoretical assumptions have to be taken into account. The data for low doses are primarily based on the long-term follow-up of the atomic bomb cohort and are linear extrapolations from high-dose exposure (linear no-threshold model).
- As seen from the epidemiological data, children may be considered in general to be at higher risk for adverse health effects from ionizing radiation than adults. Across many types of tumors, children may be two to three times more sensitive than adults. However, this is not true for all types of tumors; some may demonstrate higher radiosensitivity, some less radiosensitivity, and some similar radiosensitivity to that of adults. More data are necessary to provide reliable, tumor-specific risk estimates.

References

1. Boice JD (2005) Radiation-induced thyroid cancer–what's new? J Natl Cancer Inst 97:703–705. doi:10.1093/jnci/dji151
2. Boice JD (2006) Thyroid disease 60 years after Hiroshima and 20 years after Chernobyl. JAMA 295:1060–1062. doi:10.1001/jama.295.9.1060
3. Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little JB, Lubin JH, Preston DL, Preston RJ, Puskin JS, Ron E, Sachs RK, Samet JM, Setlow RB, Zaider M (2003) Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc Natl Acad Sci USA 100:13761–13766. doi:10.1073/pnas.2235592100
4. Bundesamt für Strahlenschutz (1999) Jahresbericht 1999: Wirkung kleiner Strahlendosen, accessed at: http://www.bfs.de/de/bfs/druck/jahresberichte/jb1999_kompl.pdf
5. Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassov O, Bouville A, Goulko G, Hoshi M, Abrosimov A, Anoshko J,

Astakhova L, Chekin S, Demidchik E, Galanti R, Ito M, Korobova E, Lushnikov E, Maksioutov M, Masyakin V, Nerovnia A, Parshin V, Parshkov E, Piliptsevich N, Pinchera A, Polyakov S, Shabeka N, Suonio E, Tenet V, Tsyb A, Yamashita S, Williams D (2005) Risk of thyroid cancer after exposure to ^{131}I in childhood. J Natl Cancer Inst 97:724–732. doi:10.1093/jnci/dji129

6. Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, National Research Council (2006) Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2. The National Academies Press, Washington, D.C.
7. Dickman PW, Holm L-E, Lundell G, Boice JD, Hall P (2003) Thyroid cancer risk after thyroid examination with ^{131}I: a population-based cohort study in Sweden. Int J Cancer 106:580–587. doi:10.1002/ijc.11258
8. Fahey FH, Hee-Seong Bom, Henry, Chiti, Arturo, Young Choi, Yun, Huang, Gang, Lassmann, Michael, Laurin, Norman, Mut, Fernando (2015) Standardization of Administered Activities in Pediatric Nuclear Medicine: A Report of the First Nuclear Medicine Global Initiative Project, Part 1: Statement of the Issue and a Review of Available Resources. J Nucl Med 56(4):646–651. doi:10.2967/jnumed.114.152249
9. Fahey FH, Treves ST, Adelstein SJ (2011) Minimizing and communicating radiation risk in pediatric nuclear medicine. J Nucl Med 52:1240–1251. doi:10.2967/jnumed.109.069609
10. Franklyn JA, Maisonneuve P, Sheppard M, Betteridge J, Boyle P (1999) Cancer incidence and mortality after radioiodine treatment for hyperthyroidism: a population-based cohort study. Lancet 353:2111–2115. doi:10.1016/S0140-6736(98)12295-X
11. Hahn K, Schnell-Inderst P, Grosche B, Holm LE (2001) Thyroid cancer after diagnostic administration of iodine-131 in childhood. Radiat Res 156:61–70
12. Hall P, Mattsson A, Boice JD (1996) Thyroid cancer after diagnostic administration of iodine-131. Radiat Res 145:86–92
13. Hempelmann LH (1968) Risk of thyroid neoplasms after irradiation in childhood. Studies of populations exposed to radiation in childhood show a dose response over a wide dose range. Science 160:159–163
14. Hendrick RE (2010) Radiation doses and cancer risks from breast imaging studies. Radiology 257:246–253. doi:10.1148/radiol.10100570
15. Holm L-E, Wiklund KE, Lundell GE, Bergman NA¨, Bjelkengren G, Cederquist ES, Ericsson U-BC, Larsson L-G, Lidberg ME, Lindberg RS, Wicklund HV, Boice JD (1988) Thyroid cancer after diagnostic doses of iodine-131: a retrospective cohort study. Journal of the National Cancer Institute 80:1132–1138. doi:10.1093/jnci/80.14.1132
16. ICRP (1991) Publication 60: 1990 recommendations of the International Commission on Radiological Protection. Ann ICRP 21(1–3)
17. ICRP (2007) Publication 103: the 2007 recommendations of the International Commission of Radiological Protection. Ann ICRP 37(2–4):1–332
18. Little MP (2009) Heterogeneity of variation of relative risk by age at exposure in the Japanese atomic bomb survivors. Radiat Environ Biophys 48:253–262. doi:10.1007/s00411-009-0228-x
19. Little MP, Wakeford R, Tawn EJ, Bouffler SD, Berrington de Gonzalez A (2009) Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology 251:6–12. doi:10.1148/radiol.2511081686
20. Martin CJ (2007) Effective dose: how should it be applied to medical exposures? Br J Radiol 80:639–647. doi:10.1259/bjr/25922439
21. Metso S, Jaatinen P, Huhtala H, Auvinen A, Oksala H, Salmi J (2007) Increased cardiovascular and cancer mortality after radioiodine treatment for hyperthyroidism. J Clin Endocrinol Metab 92:2190–2196. doi:10.1210/jc.2006-2321
22. Preston DL, Cullings H, Suyama A, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K, Kasagi F, Shore RE (2008) Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. J Natl Cancer Inst 100:428–436. doi:10.1093/jnci/djn045
23. Preston DL, Pierce DA, Shimizu Y, Cullings HM, Fujita S, Funamoto S, Kodama K (2004) Effect of recent changes in atomic bomb survivor dosimetry on cancer mortality risk estimates. Radiat Res 162:377–389

24. Preston DL, Shimizu Y, Pierce DA, Suyama A, Mabuchi K (2003) Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950-1997. Radiat Res 160:381–407
25. Richardson DB (2009) Exposure to ionizing radiation in adulthood and thyroid cancer incidence. Epidemiology 20:181–187. doi:10.1097/EDE.0b013e318196ac1c
26. Ron E, Doody M, Becker DV et al (1998) Cancer mortality following treatment for adult hyperthyroidism. JAMA 280:347–355. doi:10.1001/jama.280.4.347
27. Tubiana M, Feinendegen LE, Yang C, Kaminski JM (2009) The linear no-threshold relationship is inconsistent with radiation biologic and experimental data1. Radiology 251:13–22. doi:10.1148/radiol.2511080671
28. United Nations Scientific Committee on the Effects of Atomic Radiation (2000) UNSCEAR 2000 report – Vol. II: sources and effects of ionizing radiation. United Nations. New York, NY
29. United Nations Scientific Committee on the Effects of Atomic Radiation (2008) UNSCEAR 2006 report – Vol. I: Effects of ionizing radiation. United Nations. New York, NY
30. United Nations Scientific Committee on the Effects of Atomic Radiation (2013) UNSCEAR 2013 report – Vol. II: Sources, effects and risks of Ionizing radiation, scientific annex B: effects of radiation exposure of children. United Nations. New York, NY
31. Verburg FA, Luster M, Lassmann M, Reiners C (2010) ^{131}I therapy in patients with benign thyroid disease does not conclusively lead to a higher risk of subsequent malignancies. Nuklearmedizin. doi:10.3413/Nukmed-0341-10-08