Assessment of Female Fertility and Carcinogenesis After Iodine-131 Therapy for Differentiated Thyroid Carcinoma

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The aim of this study was to evaluate female fertility, carcinogenic, and genetic effects after treatment with ^{131}I of differentiated thyroid carcinoma. **Methods:** A total of 814 females of child-bearing age were studied. The fertility of 627 females who received ^{131}I therapy was compared to 187 untreated females. Birth histories of the children born from these women were registered. The carcinogenic effect was evaluated by comparing the incidence of tumors in 730 patients treated with ^{131}I with an internal control group, as well as with local population incidence. **Results:** There was no significant difference in the fertility rate, birth weight and prematurity between the two groups. Only one case of a ventricular septal defect was observed in a child born to a woman treated with ^{131}I. The overall standardized incidence ratio (SIR) of second tumors was 1.19 (95% CI: 0.76–1.77) in patients treated with ^{131}I. An elevated SIR was registered for salivary gland tumors and melanoma. No case of leukemia was registered. **Conclusion:** The risk of long-term effects of ^{131}I treatment of differentiated thyroid carcinoma is quite low. Iodine-131 may be safely used in treating cases with a high risk of recurrence.

Key Words: differentiated thyroid carcinoma; radioiodine therapy; late effects

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Iodine-131 therapy for ablation of thyroid remnants after total thyroidectomy in differentiated thyroid carcinoma increases the sensitivity and specificity of ^{131}I whole-body scans and serum thyroglobulin assays in the diagnosis of local and distant recurrences and reduces frequency of recurrence (*1–4*). Furthermore, ^{131}I treatment of differentiated thyroid carcinoma lung and bone metastases prolongs survival and improves the quality of life in patients (*5–10*). Nevertheless, some groups limit the use of ^{131}I treatment in differentiated thyroid carcinoma in order to avoid possible long-term hazards (*11–13*) such as the effects in the possible induction of second tumors, subsequent offspring and the possible impairment of fertility. The aim of the present study was to evaluate these hazards, comparing the risk in differentiated thyroid carcinoma patients treated with ^{131}I and those not treated with ^{131}I.

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MATERIALS AND METHODS

From January 1960 to June 1993, 2361 patients (1653 female; 708 male; female-to-male ratio 2.49) were treated for differentiated thyroid carcinoma at the nuclear medicine department of the General Hospital in Busto Arsizio, Italy. About 40% of the patients were diagnosed and operated on at this hospital; treatment and follow-up on the remaining 60% was carried out in our center after patients underwent surgery in other hospitals. All patients were treated and followed-up by a limited group of physicians. The histotypes, according to the 1988 World Health Organization Classification (*14*), were as follows: 1753 (74.2%) papillary carcinoma and 608 (25.8%) follicular carcinoma. All the patients were treated with surgical and hormonal therapy. In particular cases, external radiotherapy and chemotherapy were also used, depending on the histotype, the stage and the year in which the patient was treated. Among the patients with differentiated thyroid carcinoma, 1,874 (79.4%) were treated with ^{131}I. The mean cumulative activity of ^{131}I administered was 5.38 GBq, the median cumulative activity was 3.7 GBq (range: 1.7–44.4 GBq). Indications for ^{131}I treatment changed in the period of the survey: in the first two decades, external radiotherapy was the first choice postsurgical therapy while ^{131}I therapy was added only occasionally, but increasingly. The lack of a presurgical pathology diagnosis (in this period) made less extensive surgery with large thyroid remnants relatively frequent. This rendered subsequent ^{131}I therapy either more complicated or generally inappropriate.

After 1980, all patients with papillary or follicular carcinoma were treated with ^{131}I except for those with papillary carcinoma <1 cm in diameter and without node or distant metastases and patients younger than 45 yr with encapsulated follicular carcinoma of <2 cm in diameter. Iodine-131 treatment for ablation of thyroid remnants was usually performed 15–40 days after surgery and repeated at 6-mo intervals until the complete ablation of the remnants. Iodine-131 treatment of local recurrences and distant metastases was performed after demonstration of uptake in these sites on whole-body scans performed 48 hr after administration of 185–600 MBq of ^{131}I. Scans were done after a 20-day period of tri-iodothyronine withdrawal or a 35-day period of L-thyroxin withdrawal. A ^{131}I whole-body scan and an assay of thyroglobulin, both during hormonal therapy and after thyroid hormone stimulation, as well as a clinical examination were performed in all

TABLE 1
Age Distribution of the Patients Treated or (Group A) Not Treated (Group B) with ^{131}I and Studied for Carcinogenic Risk

Age groups (yr)	Group A		Group B	
	No. of patients	%	No. of patients	%
0–10	5	0.7	0	0
11–20	50	6.8	11	5.5
21–30	126	17.3	35	17.4
31–40	143	19.6	50	24.9
41–50	179	24.5	52	25.9
51–60	132	18.1	31	15.4
61–70	72	9.9	17	8.4
71–80	23	3.1	5	2.5

TABLE 2
Distribution of Cumulative Administered Activity of ^{131}I (Group A)

Cumulative administered activity of ^{131}I (GBq)	No. of patients
<2	26
2–3.9	313
4–5.9	180
6–9.9	98
10–13.9	38
14–17.9	36
18–21.9	18
22–29.9	15
30–44.4	6

patients treated. Neck echotomographies, chest x-rays, neck and chest computed tomographies, bone radionuclide scans and ^{201}Tl whole-body scintigraphies were used in selected cases.

Carcinogenic Risk Evaluation

The risk of induction of other tumors after therapeutic administration of ^{131}I was estimated by selecting all patients with a pathological diagnosis of differentiated thyroid carcinoma having a follow-up of at least 3 yr and without a diagnosis of other types of cancer in the years before and in the 2 yr following the diagnosis of thyroid cancer. Because their follow-up period had not reached 3 yr, 1401 (59.34%) patients were excluded; 455 were excluded because the diagnosis had been performed between 1990–1993, and 946 were excluded because they had dropped out before completing 3 yr of follow-up. Patients with cancers observed before diagnosis of thyroid cancer (n = 21) and during the first 2 yr after diagnosis (n = 8) were also excluded. Of the patients selected (931), 237 were male and 694 were female (female-to-male ratio: 2.93). These patients were divided into two groups: Group A, (n = 730), was made up of patients treated with surgical, hormonal and ^{131}I therapy and Group B, (n = 201), was made up of patients treated only with surgical and hormonal therapy and with no radiometabolic therapy. Papillary carcinoma was identified in 555 (76.0%) patients of Group A and in 163 (81.1%) of Group B; follicular carcinoma was found in 175 (24.0%) patients of Group A and in 38 (18.9%) of Group B. The mean age at diagnosis was 42.56 yr (s.d. 15.15) for Group A and 42.15 yr (s.d. 14.22) for Group B. The distribution of the ages at diagnosis in the two groups is shown in Table 1. Total thyroidectomy was performed in 460 patients (63.0%) of Group A and in 105 (52.2%) of Group B. In the other patients, either a subtotal thyroidectomy or a lobectomy was performed. External radiotherapy was performed in 42 (5.7%) patients of Group A and in 10 (5.0%) patients of Group B; chemotherapy in 16 (2.2%) patients of Group A and in 2 (1.0%) patients of Group B. The mean follow-up was 7.44 yr for the patients of Group A and 10.3 yr for the patients of Group B. The mean cumulative administered activity of ^{131}I was 6.5 GBq, median 4.6 GBq (range: 1.85–44.4 Gbq). The distribution of the cumulative administered activity of ^{131}I is shown in Table 2. The median interval of time from diagnosis to the first treatment with ^{131}I was 1 mo. The carcinogenic risk was evaluated in two ways: first by comparing the incidences of second tumors in the two groups and, second, by calculating standardized incidence ratios (SIRs) in the two groups, as well as the relative risks. The SIRs were calculated as the ratio of observed-to-expected numbers of cancers.

The expected numbers of cancers for the two groups were calculated by indirect standardization; adjustment for the calendar year, sex and age, by applying specific incidence data obtained from the Cancer Register of the Province of Varese (*15*), the area where our hospital is located. This was one of the first registers to be set up in Italy (in 1976) and is still one of the few cancer registers operating in this country. It collects data only from the area of the Province of Varese, which is populated by a mean annual population of 790,000. The expected numbers for the patients diagnosed in the first 16 yr of the survey (1960–1975) were calculated by using the incidences of tumors in the first year (1976) covered by the Cancer Register of Province of Varese. The number of patients diagnosed before 1976 was 179 (19.2%), 98 (3.1%) of whom were diagnosed between 1971 and 1975. The 95% confidence interval (CI) of SIR was determined by assuming the observed number of cancers to be distributed as a Poisson variable. The relative risks (RR) were calculated as the ratio of SIRs of exposed and nonexposed patients. The 95% confidence interval for the population value of the relative risks was obtained using binomial statistics.

Evaluation of Fertility Impairment in Women

The risk of fertility impairment and of effects on the offspring was assessed by selecting all female patients with a pathologic diagnosis of differentiated thyroid carcinoma under the age of 43 at the time of diagnosis, who had been followed-up for at least 2 yr. The follow-up of these patients, for the purpose of this study, was limited to the fertile age and therefore was stopped if the patients had reached the age of 45. The 814 selected patients were then divided into two groups: Group I (n = 627) with the patients treated with surgical, hormonal and ^{131}I therapy and Group II (n = 187) made up of the patients treated only with surgical and hormonal therapy (without ^{131}I therapy). The number of patients who dropped out of the follow-up before reaching 45 yr of age was 97 (15.5%) in Group I and 26 (13.9%) in Group II. The patients who reached the age of 45 during the period of the study were 156 (24.88%) in Group I and 54 (28.9%) in Group II. In Group I, the mean age at diagnosis was 31.8 yr (s.d. = 8.2 ranging from 5 to 43 yr; median age 34 yr). In Group II, the mean age at diagnosis was 32.9 yr (s.d. 7.8, ranging from 11 to 43 yr; median age 35 yr). The distribution of the ages at diagnosis of the patients of the two groups are reported in Table 3. The mean follow-up duration was 4.58 yr (s.d. 4.35) in Group I and 6.4 yr (s.d. 4.98) in Group II. The cumulative number of years of observation of females in fertile

TABLE 3
Age Distribution at Initial Treatment

Age groups (yr)	Group I*		Group II†	
	No. of patients	%	No. of patients	%
0–10	1	0.4	0	0
11–20	52	8.3	13	6.9
21–30	184	29.3	47	25.1
31–40	297	47.4	94	50.3
41–45	92	14.7	33	17.6

*Patients treated with ^{131}I.
†Patients not treated with ^{131}I.

age (15–45 yr) was 2838 yr (71.1%) for Group I and 1151 yr (28.9%) for Group II. The fertility rate was then calculated as the ratio of live births per 1000 fertile females per year. The 95% confidence interval for the difference between the fertility rate of Group I and II was calculated by incorporating the Yates continuity correction. The p value for chi square distribution was also determined. The mean activity of ^{131}I administered to patients of Group I was 5.4 GBq, ranging from 2.2 to 22.2 GBq; median activity of 3.7 GBq. Clinical data about the children born from the females of each group were obtained by phone or during clinical examinations of the mothers. All other relevant clinical news was obtained directly during clinical examination or from family physicians of the patients.

RESULTS

Evaluation of Carcinogenic Risk

Twenty-four (5 males and 19 females) second primary cancers were observed in Group A and 7 (1 male and 6 females) in Group B. Details about treatment, histotypes of second tumors, and periods of latency from the first ^{131}I treatment are reported in Table 4. The mean age at diagnosis of the thyroid carcinoma of the patients with second malignancies was 49.4 yr (s.d. = 10.8) in Group A and 53.3 yr (s.d. = 8.6) in Group B. The median age was 47 yr (Group A) and 51.5 yr (Group B). The mean cumulative administered activity was 4.56 GBq (s.d. 2.66). The observed cancers, SIRs and 95% CI in the two groups are reported in Table 5.

The expected values for the incidence of other malignancies, as derived from sex- and age-specific rates obtained from the Cancer Register of Province of Varese were 20.14 (6.74 for males and 13.4 for females) for Group A and 7.39 (1.12 males and 6.27 females) for Group B. The overall SIRs were therefore 1.19 (95% CI: 0.76–1.77) for Group A

TABLE 4
Data for Patients Receiving ^{131}I Therapy Who Developed a Second Tumor

Patient no.	Site	Sex	DTC/DX Age/Yr	Latency period (yr)	ADM ACT (GBq)	No. of ADM	Surgical/additional therapy
4	Breast	F	44/1966	8	5.4	4	Hemi TX XRT
5	Breast	M	65/1966	14	3.5	2	Hemi TX XRT
7	Breast	F	39/1970	5	3.5	2	Total TX
10	Breast	F	71/1975	6	4.1	2	Subtotal TX XRT
11	Breast	F	55/1976	5	2.7	1	Total TX
13	Breast	F	44/1977	3	1.8	1	Subtotal TX
24	Breast	F	46/1988	4	2.7	1	Total TX
14	Salivary gland	F	41/1979	5	7.0	3	Hemi TX
15	Salivary gland	F	46/1980	11	7.6	3	Total TX
23	Salivary gland	M	66/1987	3	2.2	1	Total TX
9	Bladder	F	49/1975	4	7.4	3	Total TX
17	Bladder	M	46/1982	5	10.8	4	Total TX XRT, Chemo
16	Melanoma	F	53/1982	3	2.2	1	Total TX
19	Melanoma	F	28/1983	4	2.7	1	Total TX
6	Lung	F	54/1969	15	8.7	3	Hemi TX
2	Lung	M	27/1962	12	2.2	1	Subtotal TX
8	Colon	F	42/1974	3	1.8	1	Total TX XRT
21	Colon	F	48/1985	4	5.4	2	Total TX
3	Rectum	M	45/1964	24	5.1	3	Hemi TX XRT
1	Stomach	F	62/1962	8	2.6	2	Hemi TX
12	Maxillary sinus	F	58/1976	7	8.1	3	Subtotal TX
18	Larynx	F	63/1983	4	2.2	1	Total TX
20	Lymphoma	F	44/1984	6	8.1	3	Total TX
22	Neuroendocrine	F	50/1985	4	2.7	1	Total TX

TABLE 5
Observed Number of Second Primary Cancers, Standardized Incidence Ratio and 95% Confidence Interval for Patients Receiving (Group A) or Not Receiving (Group B) ^{131}I Therapy

	Group A			Group B		
Cancer site	Obs.	SIR	95% CI	Obs.	SIR	95% CI
Breast	7	2.08	0.84–4.29	3	1.9	0.39–5.55
Salivary glands	3	60	12.38–175.34	—	—	—
Colon-rectum	3	1.27	0.26–3.7	—	—	—
Melanoma	2	8	0.97–28.9	—	—	—
Head-neck	2	5	0.61–18.06	—	—	—
Bladder	2	2.6	0.31–9.38	—	—	—
Lung	2	1.05	0.13–3.78	—	—	—
Neuroendocrine tumors	1	33.3	0.83–185.73	—	—	—
Non-Hodgkin lymphoma	1	4.55	0.11–25.32	—	—	—
Stomach	1	0.52	0.01–2.92	1	1.12	0.03–6.26
Utherus	—	—	—	1	2.94	.07–16.38
Plasmocytoma	—	—	—	1	14.28	0.36–79.6
Pancreas	—	—	—	1	25	0.625–139.3

Obs. = Number of observed cancers; SIR = standardized incidence ratio; and 95% CI = 95% confidence interval of SIR.

and 0.95 (95% CI: 0.38–1.95) for Group B. The overall relative risk was 1.25 (95% CI: 0.53–3.46). An elevated SIR with the unity outside the confidence interval was found in the salivary gland cancers. Elevated SIRs were also found in the skin (melanoma) in Group A and in the breast in both groups, but the unity was comprised in the confidence interval. The relative risk of breast cancer was 1.9 (95% CI: 0.25–6.58). No case of leukemia was observed in either group. One case of non-Hodgkin lymphoma was registered in the patients treated. Overall SIR was 1.17 (C.I. 0.70–1.83) for the first 10 yr after exposure (86% of the overall person-years at risk) and 1.28 (C.I. 0.41–2.98) for the years after the first 10 yr from the exposure (14% of the overall person-years at risk).

Evaluation of Fertility Impairment of Treated Females

Sixty-five children (45 males and 20 females) were born from 49 females of Group I and 19 children (12 males and 7 females) from 15 females of Group II. The 49 females of Group I who had pregnancies after administration of therapeutic activities of ^{131}I received a mean cumulative activity of ^{131}I prior to pregnancy of 6.5 GBq, range: 2.6–22.2 GBq and a median activity of 5.55 GBq. The mean activity of each single administration of ^{131}I given to the same patients prior to pregnancy was 2.6 GBq, range: 0.55–3.7 GBq, median activity: 2.96 GBq. The number of therapeutic administrations of ^{131}I given to these females prior to pregnancy ranged from 1 to 6. The mean interval between the last administration of ^{131}I and conception was 43.1 mo, s.d.: 39.6, range: 1–204 mo. The median interval was 36 mo. The distribution of the intervals between the last administration of ^{131}I and conception is shown in Table 6. The mean weight at birth of the infants born from the females of Group I was 3.348 kg, s.d. 0.5 kg and the median weight 3.400 kg, with a range from 1.750 to 4.350 kg. The mean weight at birth of the infants born to the females of Group II was 3.385 kg (s.d. 0.4), and the median weight 3.400 kg, with a range of 2.550 to 3.900 kg. Two premature births at the seventh month of pregnancy and three spontaneous abortions by the third month were registered in the females treated. One spontaneous abortion at the second month was registered in the group of females not treated with ^{131}I. Among the children born from treated females, only one case of ventricular septal defect and patent ductus arteriosus was registered. More details about the patients with abnormal pregnancies are reported in the Table 7. All other children, born from the females of Group I and Group II, were in good health and grew up regularly. The fertility rate was 23 for the females in Group I and 19 for those in Group II. A 95% confidence interval for the difference of fertility rates in the two groups ranged from 13.97 to −5.17, p value for chi square distribution was 0.39, NS.

DISCUSSION

Although ^{131}I has been used in medicine for over half a century (*16,17*), data about possible carcinogenic effects and damage to the female gonads after administration of ^{131}I for therapeutic purposes are not conclusive. The risk of induction of second tumors after exposure to ionizing ra-

TABLE 6
Intervals Between Last Administration of ^{131}I and Conception

Intervals (mo)	No. of patients
<12	13
13–36	16
37–60	10
61–84	5
85–204	3

TABLE 7
Data for Abnormal Pregnancies for Females Receiving ^{131}I Therapy

Anomaly	Sex of child	DTC DX Yr*	I-131 RX Age	Latency (mo)	ADM ACT	No. doses
VSD + PDA†	M	1981	27	60	2.2	1
Prematurity	M	1982	31	4	3.8	2
Prematurity	F	1972	22	3	4.05	2
Spontaneous abortion	—	1967	12	60	2.7	2
Spontaneous abortion	—	1979	29	25	12.2	5
Spontaneous abortion	—	1974	23	20	2.7	1

*All patients had Total TX preceding ^{131}I Rx.
†Ventricular septal defect and patent ductus arteriosus.

diation is low (*18*). The latency period for the clinical appearance of radioinduced malignancies is long, particularly for solid tumors (*19*). It would therefore be necessary to follow a great number of patients for decades to be able to show conclusively whether an excess of second tumors occurs in patients treated with ^{131}I compared to a control population. This is particularly difficult when dealing with low prevalence tumors such as thyroid carcinoma. Moreover, data obtained over long periods of time are heterogeneous due to the continuous evolution of diagnostic and therapeutic schedules and to the techniques available. Finally, exposure to other carcinogenic factors changes through time.

Carcinogenic risk was evaluated in a similar way to the study by Hall et al. (*20*), i.e., comparing the incidence of second tumors in patients treated with ^{131}I with the incidence in an internal control group, as well as in a standardized reference population from a Cancer Register of our area. Our study considered a lower number of thyroid cancer patients than that of Hall's study, with a shorter duration of the follow-up period. The patients were all treated and followed in our center by a limited group of physicians. Thus these data are as homogeneous as possible over a period of three decades. The percentage of the patients not treated with ^{131}I is much lower than that of the Swedish survey. This may be due to different criteria in patient selection since patients with more advanced disease are sent to our center to be treated with ^{131}I. The diagnosis of a subsequent tumor was obtained during the periodical clinical examinations performed in our center or by the patients' family physician. The overall SIR of second tumors in our series is lower than that of the Swedish survey. This could be related to the shorter follow-up duration in our series, as well as to differences in the features of the two populations or even to statistic imprecision. The 95% confidence intervals of SIRs of our series were quite wide, particularly for single sites of cancers, due to the limited number of the cancers observed. This shortcoming could be overcome by longer followup, as well as recovering information on patients lost to followup. The increased risk observed for salivary gland carcinoma is consistent with the observation in the Swedish survey. Slightly elevated SIRs were also registered for melanoma and breast cancer. Although one case of melanoma after 24 GBq of ^{131}I was reported by Edmonds (*21*), there is no evidence in the literature of an increased risk of melanoma after ^{131}I therapy. In our series, an elevated number of patients with breast cancer were seen both in the group of the patients treated, and in the internal control group. An increased risk of breast cancer in patients affected by differentiated thyroid carcinoma and other thyroid diseases has been reported, and no increased risk is reported in hyperthyroid females treated with ^{131}I (*22,23*).

The possible role played by hormonal replacement therapy in increasing the risk for breast cancer is controversial (*22–24*). The fact that the breast carcinoma incidences were higher than expected in our series could be related to a closer medical surveillance of cancer patients. It should be noted that no case of leukemia was registered in our series although an increased risk of leukemia was reported by Brinker and Edmonds (*21,25*). More recently, Hall reported leukemia in patients treated with over 30 GBq of ^{131}I (*26*). Most reported cases of leukemia after ^{131}I therapy occur in series with higher mean administered activities of ^{131}I.

In our series, 126 (17.3%) patients received over 9.25 GBq of ^{131}I, and only 6 patients received over 30 GBq. In this study, only indirect data concerning the possible link of the induction of second tumors with the age at the moment of treatment or with the absorbed dose are available. The mean age of the patients with a second tumor was slightly lower (but not in a statistically significant way), in the group of the patients treated (49.42 yr) than in the control group (53.33 yr). Among the patients treated with ^{131}I, the age at the time of the treatment of patients who developed a second tumor was higher than in the patients who did not, probably reflecting the higher cancer incidence of the more advanced age groups. Thyroid remnants of the patients with a second tumor and the cumulative administered activities of ^{131}I were not significantly higher compared to the other patients treated with ^{131}I, thus suggesting the lack of a relationship between SIR and absorbed dose. Seven out of 24 patients with second tumors were treated using external radiotherapy, a fraction higher

than that of the overall Group A. Only one patient underwent chemotherapy. This could be explained by the fact that 14 of the 25 patients with second tumors were diagnosed before 1980, when external radiotherapy was used more frequently. Even if statistical error is high for the paucity of the data, SIR does not seem to increase over time (SIR was 1.17 for the first 10 yr of follow-up and 1.28 for the subsequent years).

Even if possible damage to the gonads of females treated with ^{131}I is not an uncommon problem for a nuclear medicine physician, there are only a few reports on this issue in the literature (*27,28*). In our caselist, 4 out of 10 females with differentiated thyroid carcinoma were of child-bearing age and 3 of them were treated with ^{131}I. Precluding these females from becoming mothers severely reduces the quality of life of these patients, who usually have a long life expectancy.

The dose to the gonads after therapeutic administration of 3.7 GBq of ^{131}I is about 20 cGy and increases as the uptake in the tumor or the thyroid increases (*21*). Raymond reported a temporary ovarian failure in 18 out of 66 females treated with activities of ^{131}I ranging from 4 to 12.1 GBq. No quantitative link was found between the appearance of ovarian failure and the absorbed dose (*29*). Temporary ovarian dysfunction in these females may be due to other factors such as hypothyroidism and perturbation of the pituitary-gonadal axis rather than ^{131}I therapy.

The purpose of this study was to evaluate in a clinical setting whether ^{131}I therapy could promote an impairment in fertility. It was preferable to compare the fertility rate of patients treated with ^{131}I with the fertility rate of an internal control group rather than with the fertility rate of the population at large. The fertility rate varied significantly over time and with different geographic areas making standardization impractical. Moreover, fertility rates can be lower in cancer patients, who often refrain from having children for psychological reasons.

The features of the two groups of patients compared were quite homogeneous, except for the administration of ^{131}I given only to females in Group I. The follow-up period of the patients of Group I is shorter, because, in recent years, the number of the patients treated with ^{131}I has been increasing; therefore, patients were diagnosed more recently in Group I than in Group II. Our clinical data suggest that the use of ^{131}I for therapeutic purposes does not reduce fertility in females.

We usually did not have data concerning the partners of our patients and did not perform extensive interviews about their sexual behavior. We could not perform complete studies on ovarian function after ^{131}I therapy because the majority of our patients live far from our area and usually leave our center a few days after treatment. Genetic damage has been demonstrated in irradiated animal oocytes (*30*) and is due to gene mutations or to aberration of the chromosomal number or structure (*31–33*). The spontaneous mutation rate is 0.5×10^{-6} per gene per generation. The increased risk of birth defects is 3 per 10^4 live births, 20 cGy over the background (*34*). The spontaneous risk is 80 per 10^4 live births. Thus, it is difficult to see the effects of this risk in small groups of patients exposed to quite low doses, as in this series. Only in a few cases did we administer activities over 9 GBq. Very low activities of ^{131}I were given in some cases, in the first years of the survey. The range of intervals from the last administration of ^{131}I and conception is quite wide. The patients who became pregnant only 1 mo after therapy did so against our advice.

In our center, females treated with ^{131}I are not discouraged from becoming pregnant at 1 yr after the completion of radioiodine therapy. Only one case of ventricular septal defect and patent ductus arteriosus was observed, although cardiac malformations are the most frequent congenital defects observed in Europe (44.3 per 10^4 births) (*35*). A significant difference in the number of abortions or premature births in the two groups was not registered. All females had normal pregnancies and delivered children who were normal on follow-up. A curious item is the prevalence of the male sex in the children born in each group. This may be a statistical fluctuation due to the small numbers involved.

CONCLUSION

The risk of a second tumor or of damage to the gonads of females treated with ^{131}I is low and lacks clinical impact. Thus, radioiodine ablation of thyroid remnants and treatment of distant metastases is a safe procedure and can be performed in all cases of differentiated thyroid carcinoma at high risk for recurrence, without significant effect.

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EDITORIAL

How Safe for the Patient Is Iodine-131 Therapy for Differentiated Thyroid Carcinoma?

Radioactive ^{131}I has been used in the treatment of well-differentiated thyroid carcinoma over the past fifty years with general agreement from published reports of the safety and efficacy of this treatment, although considerable difference of opinion exists regarding the methodology employed and appropriate restrictions necessary to ensure safety for the patient and others involved (*1*). In the early years of its employment, wide variations in dose from very low to very high provided the experience upon which, in more recent years, dose ranges have been narrowed and techniques have been employed to optimize results.

Because well-differentiated thyroid carcinoma is not uncommon in children and young women in childbearing years, the possibility that this treatment may affect fertility has generated discussion, and these effects have been the subject of several reports (*2,3*). In general, there has been no observable effect based on studies of offspring, although at least one report of ovarian dysfunction after ^{131}I treatment in humans was described (*4*).

Carcinogenesis is also an issue in younger patients. In the early years when larger doses were employed, Brincher et al. described an increase of leukemia in ^{131}I-treated carcinoma patients in Denmark (*5*). However, Hall et al. in Sweden more recently concluded that "no specific cancer or groups of cancers could be convincingly linked to high-dose ^{131}I exposures . . ." (*6*), and that "excess leukemia risks of more than 25% could thus be excluded with high reassurance in this population of mainly adults" (*7*). However, conflicting data have come from Edmonds and Smith in England who found "a small, significant excess of deaths from cancer of the bladder and from leukemia . . ." (*8*). Because most case series are small, it has been difficult to establish the statistical validity of these observations.

With this background, we have in this issue of the *Journal* a paper on the subject of long-term hazards of ^{131}I therapy. Dottorini et al. review the outcome of women with carcinoma of the thyroid treated with ^{131}I to deter-

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