Review

Childhood Thyroid Cancers and Radioactive Iodine Therapy: Necessity of Precautious Radiation Health Risk Management

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Abstract. One of the lessons from Chernobyl’s legacy on health impact beyond 20 years is not only how to detect and treat the patients with radiation-associated thyroid cancers but how to follow up those who received radioactive iodine treatment repetitively after surgery in order to monitor any recurrence/worsening and also how to predict the risk of secondary primary cancers for their lifetime period. To evaluate the possibility of second primary tumors after radioactive iodine treatment, we reviewed the reports on risks from both external and internal radiation exposure, especially at high doses during childhood through an internet service of the National Library of Medicine and the National Institutes of Health, PubMed by the end of June, 2007, together with our own experience of Chernobyl childhood thyroid cancers. Children who were internally exposed after Chernobyl accident have a long-term risk of well differentiated thyroid cancers. Once they have disease, ironically radioactive iodine ablation is one of the useful therapies after surgical treatment. Elevated risks of solid cancers and leukemia have been found in radiiodine-treated patients, however, so far precious few reports from Chernobyl thyroid cancer patient were published. To reduce the adverse effects of radioactive iodine therapy on non-target tissues, recombinant human TSH has been applied and proved effective. Period of latency of second primary cancers may be very long. Therefore patients treated with high activities of radioactive iodine, especially children cases, should be carefully followed up during their whole lifespan.

Key words: Chernobyl Nuclear Disaster, Radiation-Induced childhood thyroid cancer, Radioactive iodine therapy, Second cancer risk, Radiological protection

The past two decades have witnessed dramatic changes in the public health governance and international cooperation on Chernobyl Nuclear Power Plant Accident [1–3]. Apart from the dramatic increase in thyroid cancer incidence among those exposed at a young age around Chernobyl, there is no clear evidence of solid cancers or leukemia due to ionizing radiation in the most affected populations. There was, however, an increase in psychological problems compounded by insufficient communications about radiation effects and by the social disruption and economic depression that followed the break-up of the Soviet Union. Long-term risks for thyroid cancer for those exposed to radiation fallout are continuing around Chernobyl and so far more than 700 children have been operated in Belarus, among whom nearly 60% repeatedly received high-dose radioactive iodine therapy [4, 5]. The risks of second primary tumors in these patients have to be evaluated despite of relatively short follow-up period and are of particular important to be followed up carefully. Health effects of ionizing radiation exposure have been investigated mainly using data on atomic bomb survivors of Hiroshima and Nagasaki who had been exposed to external radiation [6–8]. There are also many reports on second primary
malignancies after external radiation therapy [9–13]. However there are very few reports about second primary tumors after internal radiation therapy for childhood thyroid cancers [14, 15]. Especially, there are no epidemiological studies about post-Chernobyl childhood thyroid cancers available except for reports by Demidchik et al. [4, 5]. Therefore, in this review article, in addition to a brief summary of second primary malignancies after external radiation therapy, risks of internal radiation exposure, especially Iodine 131 (\(^{131}\)I) therapy on second primary tumors will be evaluated. The possibility to reduce the risk of second primary tumors after \(^{131}\)I therapy will be also discussed.

**External radiation therapy**

Issues of various second primary malignancies after external radiation therapy have been well examined and reviewed. After radiation therapy for Hodgkin disease, second cancers are frequently observed in lung, digestive tract and mammary glands [9–13]. Increased rate of microsatellite alterations have been detected in the lung and breast cancers, second to Hodgkin disease [16], suggestive of an association between genomic instability of irradiated tissues and second malignancies. From the point of view of age, digestive tract and breast cancers are frequently observed in young irradiated patients with Hodgkin disease. Notably the risk of thyroid and respiratory cancers in patients with Hodgkin disease in under 10 years old was fifty-times higher than in the general population [17]. In patients who had undergone radiation therapy for childhood neuroblastoma as the first malignancy, risk of thyroid cancer after low dose irradiation was substantially higher than in groups as the first malignancies [18, 19]. Within in the group of the patients with childhood retinoblastoma, risk of second malignancy was increased after radiation therapy, whereas in patients with non-inherited retinoblastoma, second primary malignancies were not registered [20].

Rubino et al. reported that second primary cancer risk in patients irradiated with more than 25 Gy was 6.7 times higher than in non-irradiated breast cancer patients [21]. Postmastectomy radiation therapy increased the risk of squamous cell esophageal cancer starting five years after exposure, which persisted after ten years, with no increase in the risk of adenocarcinoma [22]. In the report of Salminen et al. the standardized incidence ratio for esophageal cancer was 2.3 among patients followed for 15 years and treated with radiotherapy. However, there was no increased risk in patients who had not received radiotherapy [23].

In the field of diagnostic medical radiation, Andrieu et al. reported that chest X-ray increased risk of breast cancer in women who carry germline mutations in the BRCA1 and BRCA2 genes [24]. That study also demonstrated that this risk was particularly high in carrier women aged 40 years and younger. These findings suggest that genetic predisposition may modulate susceptibility to radiation effects, and that genetic alteration might also have impact on outcome in different people after same radiation therapy. Genetic diagnosis will be necessary to better determine the therapeutic strategy in the future.

**\(^{131}\)I therapy for adult thyroid cancer**

Primary treatment of differentiated thyroid cancer is generally total or sub-total thyroidectomy with or without radioiodine ablation [25]. Although radioiodine therapy was mainly applied to adult patients in the past, most of childhood thyroid cancer patients have been treated by surgery and radioiodine therapy after Chernobyl accident. Petrich et al. reported radioiodine therapy offered a fair chance of cure without pronounced side-effects in patients with bone metastases younger than 45 years old patients in comparison with older patients. Remission could be achieved in younger patients after a relatively low dose of radiation [26]. The study also documented minor blood count alterations in the younger group.

Berthe et al. analyzed 875 cases of French thyroid cancer patients, and they did not observe any significant correlation between \(^{131}\)I therapy or external neck irradiation and second primary malignancy [27]. This study concluded that only female gender, age and medical history of primary malignancy before thyroid cancer were risk factors for second cancer.

Chuang et al. identified 26,639 patients with first primary thyroid malignancy in U.S [28], among whom there were 1,896 second primary malignancies. The group reported a significance association between external radiation and digestive tract cancers, usage of radioactive implants and male genital cancers, radioisotopes and myeloid malignancies. Additionally,
combined external beam therapy with radioactive implants or radioisotopes increased the risk of respiratory system cancers. Especially, high risk was found for head and neck cancer 5–9 years after diagnosis, but risk for second thyroid cancer was reduced.

Durante et al. did not describe recurrence and second primary malignancy in the follow-up study of 444 patients with distant metastases of thyroid cancer who had received radioactive iodine therapy [29]. Also in a Swedish cohort study of consequences of $^{131}$I medical diagnostic examination, thyroid cancer risk was not increased [30].

According to large scale investigation of 6,841 cases in Europe, an increased risk of both solid cancers and leukemia was found with increasing cumulative activity of $^{131}$I administered. A relationship was found between $^{131}$I usage and occurrence of bone and soft tissue, colorectal, and salivary gland malignancies [15].

In addition, some earlier reports suggested no impact of $^{131}$I therapy and the risk for second malignancies [31–35]. Tsang et al. investigated 382 Canadian cases of well-differentiated thyroid cancer. They demonstrated that combination of total thyroidectomy with radioactive ablation reduced local recurrence, however it did not influence survival rate [36].

**$^{131}$I therapy for childhood thyroid cancer**

Incidence of childhood thyroid cancers has been increased in children and adolescents exposed to irradiation by the Chernobyl nuclear plant accident. The majority of patients underwent a high dose $^{131}$I therapy with fairly good therapeutic response clinically. Compared to the adult cases, the patients with childhood thyroid cancers have to be followed up for their lifetime because $^{131}$I therapy may potentially be a risk factor of second primary malignancy. Besides, childhood thyroid cancers have a higher risk for relapses in comparison with adult cases. Reports on follow-up studies in patients after $^{131}$I therapy for childhood thyroid cancer are summarized in Table 1. Dottorini et al. reported 2 cases of second primary breast and gastric cancers, approx. 10 years after $^{131}$I therapy among 99 patients with childhood differentiated thyroid carcinomas [14]. Chow et al. had not observed second primary cancers by their follow-up of 60 cases of childhood thyroid cancer for 14 years after $^{131}$I therapy [37].

Rubino et al. detected 13 cases with second primary cancers among 344 thyroid cancer patients aged less than 20 years old with thyroid cancer. The overall risk of second primary malignancies and the risk of breast cancer were significantly increased in comparison with the general population. However, comparing the subgroups of those young patients with (61%) and without (39%) radioiodine treatment, no carcinogenic effect of $^{131}$I was found [15].

The radiation dose to pediatric or young adult female breast tissue associated with a 5.6 GBq ablation treatment ranges from 0.35 to 0.55 Gy, resulting in a lifetime risk of breast cancer ranging from 2 to 4 cases per 100 females exposed [38, 39]. According to published data on risk assessment, the risk for developing breast cancer has to be expected to increase after $^{131}$I therapy. Epidemiologic studies, however, failed to prove this hypothesis. Because these risk assessments in very young patients are not well established, strategies for the lifetime follow-up and monitoring of the young Chernobyl victims have to be developed and implemented, considering that breast cancer risk per se may increase in Belarus and Ukraine with time [39].

Hod et al. observed a high prevalence of lung metastases in 31 young patients (aged less than 20 years old) with thyroid cancer. Although a complete remission of lung metastases after $^{131}$I therapy was difficult to achieve, most of patients had a good quality of life with no further disease progression and a low mortality rate [40]. However, in this series, there was one case refractive to $^{131}$I therapy with a fatal outcome.

Recently, Shapiro reported from a cross-sectional analysis of the SEER-database, that $^{131}$I therapy did not significantly influence excellent overall survival in 291 patients [41]. Collini et al. reported 13 childhood papillary cancers with relapses after $^{131}$I therapy but there was no description of second primary malignancies [42]. Demidchik et al. summarized their results of treatment of 464 childhood Chernobyl thyroid cancers and also reported many cases with relapses and metastases but no second primary malignancies were observed among patients followed-up for one to seventeen years [4, 5].

In June 2007, one of the important data has been reported. Drozd et al. have followed up 245 Belarusian

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1 It has to be supposed, that radioactive implants in this large cohort have not been used for treatment of thyroid cancer but of other malignancies e.g. prostate cancer.
childhood operated cases (42% distant metastases, 97% cervical lymph node metastases) with thyroid cancer for 10 years after $^{131}$I therapy [43]. Among 228 cases analyzed, they have detected 2 cases of second primary tumors (salivary gland cancer and syringoepithelioma). They also reported that there were relatively many cases with general concomitant disorders (11 cases with cardiac dysfunction and 11 cases with gastro-intestinal disorders).

Therefore, especially in young patients, only one report has so far demonstrated the risk of second primary malignancy caused by $^{131}$I therapy in the Chernobyl patients with thyroid cancers. In view of the high incidence of metastases and relapses in childhood thyroid cancers in comparison with adult cases, these observations advocate $^{131}$I therapy against childhood thyroid cancer as an effective and relatively safe therapeutic procedure. However, the follow-up periods up to now with 15 years at maximum are much too short to allow definitive conclusions. It is very important to organize thorough follow-up and support them with early diagnosis or preventive management of second tumors.

It is important to consider, that a low expression level of Na-I symporter in the papillary thyroid cancer tissue with $BRAF$ gene point mutation ($BRAF^{T796A}$) has been demonstrated [44]. On the other hand, frequency of $BRAF^{T796A}$ mutation in childhood papillary thyroid cancer is very low [45–47]. This molecular biological finding also advocates radioiodine therapy. Therefore, it seems to be promising that genetic analysis will contribute in future to predict the effect of $^{131}$I therapy. Extensive further investigations are needed to identify unknown genetic factors, such as gene polymorphisms which also may affect iodine uptake and metabolism.

By radiation dosimetry, cumulative radiation dose was correlated with risk of second leukemia below 18.5 GBq, and 3.7 GBq may double the risk [48]. 3.7 GBq of $^{131}$I therapy induces an excess of 53 solid cancers and 3 leukemias in 10,000 adult patients during 10 years follow-up [15].

From the viewpoint of environmental radiation exposure with $^{131}$I, Cardis et al. analyzed the risk of thyroid cancer [49]. However, this is not applicable to the patients with high radiation doses from radioactive iodine therapy.

In summary, $^{131}$I exposure of children after the Chernobyl accident and $^{131}$I therapy in adults can increase the risk of primary thyroid cancer and radiation-induced second primary malignancy, respectively. Yet, $^{131}$I therapy did not increase the risk of second primary cancers in children and adolescents but this observation is hampered by short follow-up periods.

### Table 1.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of Subjects of $^{131}$I Treated</th>
<th>Age Range at Diagnosis</th>
<th>Mean Follow-Up Period</th>
<th>Second Primary Tumors</th>
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<tr>
<td>Dottorini et al.</td>
<td>59</td>
<td>&lt;18 y.o.</td>
<td>111 month (1–324 months)</td>
<td>2 cases (Breast, Stomach)</td>
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| Rubino et al.     | 344*                                   | <20 y.o.               | Not described         | 13 cases (Both adult and Childhood)$^1$
| Chow et al.       | 36                                     | <21 y.o.               | 14 years              | Not described         |
| Hod et al.        | 31                                     | <25 y.o.               | 60 months (16–150 months) | Not described         |
| Shapiro et al.    | 291†                                   | <18 y.o.               | –155 months           | Not described         |
| Collini et al.    | 13                                     | <17 y.o.               | 189 months (39–368 months) | Not described         |
| Demidchik et al.  | 464                                    | <15 y.o.               | 115.8 months (1.5–236.4 months) | Not described         |
| Drozd et al.      | 228                                    | <12 y.o.               | 10 years              | 2 cases (Salivary gland, Syringoepithelioma) |

* Both of external radiotherapy and $^{131}$I therapy
† There was no significant association between the risk of second primary malignancy and $^{131}$I therapy
†† The number of subjects was described as 51.4% of 566 cases.
Reduction of radiation effect to bone marrow during $^{131}$I therapy

As mentioned above, leukemia may be one of the major second primary malignancies after $^{131}$I administration. Reduction of bone marrow absorbed dose is, therefore, the most important issue. Surgical resection and thyroid hormone suppressive therapy with levothyroxin (L-T$_4$) has been a standard therapy of differentiated thyroid cancer for a long time [50]. Increased serum TSH levels are necessary for effective and selective $^{131}$I uptake. Traditionally, increased serum TSH levels have been induced by withdrawal of L-T$_4$ for 4 weeks or more. However this procedure frequently induced clinical hypothyroidism including cognitive impairment, emotional dysfunction and physical discomfort in thyroidectomized patients [51]. Besides, L-T$_4$ withdrawal also might induce cardiac, cerebrovascular, or neurological complication in fragile patients. In addition, L-T$_4$ withdrawal has not always been effective, especially in patients with large residual thyroid tissue. Because of these problems, recombinant human TSH (rhTSH) has been developed as an alternative means. rhTSH could stimulate target tissues (thyroid remnants and/or thyroid cancer) through TSH receptor without hypothyroidism. After development of rhTSH, its clinical safety and efficacy have been verified [52–54], giving an opportunity to conclude that rhTSH would contribute to approve quality of patient life in comparison with L-T$_4$ withdrawal [55].

Recent reports clearly demonstrate that rhTSH contributes considerably to reduce the dose to blood and bone marrow by shortening blood and whole-body residence times of $^{131}$I [56–58].

Reduction of radiation effect to salivary glands, digestive and urinary tract

Salivary gland tissues express Na-I symporter [59, 60]. Therefore, $^{131}$I therapy can bring about sialadenitis, taste loss, dry mouth and salivary gland cancer [28, 61, 62]. Several studies have shown that S-2-(3-aminopropylamino)-ethylphosphorothioic acid (Amifostine) could reduce the absorbed dose to salivary glands [63, 64]. Although Amifostine appears beneficial, it is not accepted by many patients because of its side effects such as nausea/vomiting, hypotension and allergic reactions (www.drugs.com/cdi/ethyol.html).

Tempol (4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl) is a stable nitroxide shown to be a radioprotector [65, 66]. Tempol treatment alone significantly reduced radiation-induced salivary hypofunction in a mouse model [67].

The other countermeasures, salivation-inducing measures, such as lemon candy, lemon juice and chewing gum, have been also found to be helpful in prevention of salivary side effect of $^{131}$I therapy [68, 69]. However, Nakada et al. reported that an early start of sucking lemon candy might induce a significant increase in salivary gland damage. They recommended lemon candy should not be given until 24 hours after radioiodine therapy [70]. Salivary gland flow also can be stimulated by hydration. The administration of larger amounts of fluid to patients after radioiodine treatment for thyroid cancer so may contribute to reduce deterministic and stochastic side effects of $^{131}$I therapy to the salivary glands and — in addition — the risk of cancers of the urinary tract.

As described above, digestive tract cancers have been described as a possible second primary cancer after radioactive iodine therapy. Laxation with large quantity of water has been recommended to prevent this type of complication [48]. Besides this, laxative drugs usually are administered to patients after $^{131}$I therapy for reduction of background activity in post-therapeutic radioiodine whole-body scans.

Summary

The most common setting in which it is necessary to consider radiation induced cancers is in children who have been irradiated either externally or internally. Particularly the children who were exposed after the Chernobyl accident have a long-term risk of thyroid cancers. Once some of them develop well differentiated thyroid cancer, thyroid surgery and radioactive iodine therapy are most effective in terms of risk and benefits. In those patients, second primary cancers may develop, and such individuals should be carefully followed up for their lifetime. In adults, leukemia and salivary gland cancer have been determined as high risk diseases due to radioiodine therapy. Besides, recently, first case of childhood secondary salivary tumor after post-Chernobyl radioiodine therapy was observed. From the viewpoint of the reduction of non-
targeted radiation exposure with selective uptake of radioactive iodine to thyroid gland remnants and cancer tissues, rhTSH has been introduced and its usage will be also recommended in future. At present the peak of incidence of thyroid cancers around Chernobyl shifted clearly from children to young adults. It is necessary to consider and prepare for the most appropriate countermeasures against primary thyroid cancer as well as second primary cancers after exposure to radioactive iodine. To improve or mitigate deterministic effects of radioactive iodine therapy is also needed. One of the lessons from Chernobyl legacy is that we need to monitor continuously these patients establishing a precautious risk management for any kind of radioactive iodine induced cancers.

Acknowledgements of Research Support

This review was performed when the correspondent author was at the Department of Public Health, WHO, Geneva, together with Dr. Shunichi Yamashita in 2006 and also supported by the 21st Century COE Program, “International Consortium of Medical Care for Hibakusha and Radiation Life Sciences” and subsequently by the Global COE Program, “Global Strategic Center for Radiation Health Risk Control” in Nagasaki University.

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