Stunning Is Not a Problem

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Introduction

To stun has been defined in several ways. The Webster dictionary provides synonyms of "to make senseless," "to daze or stupefy," or "to shock deeply." The adjective form also means excellent or attractive. None of these accurately represent what is meant by "stunning" in relation to treatment of thyroid cancer. In this context, stunning means that a diagnostic prescribed activity of radioiodine (^{131}I) can do sufficient damage to the thyroid that the follicular cells are incapable of trapping therapeutic prescribed activities of ^{131}I [1, 2]. It is true that some of us were "stunned" when the concept was first presented. The early reports implied that there would be no uptake of the therapeutic ^{131}I. Thus, when a pretreatment diagnostic scan was compared to a post-therapy scan, the latter would show the absence of uptake at one or more sites previously seen on the pretreatment diagnostic scan. Subsequently, the term was expanded to cover the possibility that the percentage of uptake of the therapeutic prescribed activity would be less than that of the prior diagnostic scintiscan, i.e., a quantitatively different finding. Lastly, the term "stunning" was expanded to include a worse outcome after treatment than when there was no diagnostic activity administered [3–6]. Whether or not stunning actually occurs has divided opinions into two perspectives, generating considerable debate [7–17]. This section presents data arguing against the concept of stunning. However, it might be considered superfluous since many clinicians are treating patients with ^{131}I without a prior diagnostic scan (although this is not the author's recommendation), and those who obtain a diagnostic scan are more frequently employing ^{123}I that theoretically should not cause stunning. We always use this radionuclide for diagnostic whole-body scanning. The author also exhorts the reader to study carefully the details of published reports with attention to the quantity of ^{131}I administered for the diagnostic scan, the percentage of uptake in thyroid tissue identified on scan (this is seldom available), and the delay between the administration of the diagnostic and therapeutic radioiodine (this also is often omitted in articles). Our group treats patients with a specified quantity of ^{131}I that is determined from the diagnostic images, pathology, and Tg value and that specified quantity of ^{131}I is ordered and administered on the same day as the diagnostic scan information is obtained. In several countries, there can be a delay of weeks or months between testing and treatment, and this alters the radiobiological effects of the former greatly. In a recent publication from Japan where patients treated with ^{131}I for thyroid cancer have to be admitted to hospital and where there is a shortage of appropriate rooms, about one half of patients are not treated within 180 days of thyroidectomy [18].

One additional comment is necessary. ^{131}I can ablate thyroid tissue, which has been known for more than 60 years. It is the basis of radioiodine treatment of hyperthyroidism and functioning thyroid cancer. This treatment is very successful provided thyroid tissues absorb sufficient radiation. Less absorbed radiation might fail to cure the patient, yet reduce the function and/or volume of thyroid tissue. This leads to the semantic debate whether the latter should be considered treatment or stunning. I review the data arguing against stunning and how it can be avoided recognizing that at high extremes of absorbed radiation doses there could be a therapeutic effect that might be judged to be stunning.

The first argument opposing stunning is self-evident. Diagnostic whole-body scanning with ^{131}I has been employed for five decades, and yet the treatment of thyroid cancer with ^{131}I has been remarkably successful [19]. The second argument is that it has been an accepted practice to obtain diagnostic and

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L. Wartofsky, D. Van Nostrand (eds.), *Thyroid Cancer*, DOI 10.1007/978-1-4939-3314-3_17

post-therapy scans for more than 30 years. There are a number of publications that demonstrate post-therapy scans show more lesions than the corresponding diagnostic images—not less lesions. Nemec et al. were probably the first to report on this in 1979 [20]. It is true that these investigators used a small diagnostic prescribed activity of 18.5 MBq (0.5 mCi) of ^{131}I; however, the post-therapy scan made after 3.7 GBq (100 mCi) showed an additional 25 % of lesions. Waxman et al. compared therapeutic scans with diagnostic images obtained with 370 MBq (10 mCi) ^{131}I [21]. When 1.1 GBq (30 mCi) ^{131}I was administered for treatment, 5/9 patients showed more lesions, and when 3.7 GBq (100 mCi) ^{131}I was the therapy prescribed activity, 5/10 patients showed more abnormalities on the post-therapy scintiscans. A third report, published as an abstract, also found 40 % more lesions were identified on the post-therapy scan [22]. The post-therapy scan can show the site of thyroglobulin production when the diagnostic scan is faintly positive and in some cases negative [23–25]. None of these reports provide evidence of reduced or absent uptake of therapeutic ^{131}I as a result of the diagnostic prescribed activity of ^{131}I.

Many authors writing on the topic of stunning cite the 1951 publication by Rawson et al. as the first to recognize this phenomenon [26]. Rawson et al. pointed out that ^{131}I can reduce the efficacy of subsequent therapeutic ^{131}I. However, they are reporting on this finding after a prescription of 925 MBq (25 mCi) of ^{131}I that was administered for treatment. There is no discussion of diagnostic or post-therapy rectilinear or scintiscan, and the response to treatment was judged by the percentage of radioactive iodine excreted in the urine. This does not fit the essence of stunning defined earlier. If stunning is a true finding, then it is more likely to occur after absorption of a large dose of radiation, and the factors that lead to that are the administration of a significant quantity of ^{131}I and a delay between conducting the diagnostic procedure and administering treatment.

In those publications that directly compare the pre- and post-therapy scans, several show little or no effect of the diagnostic prescribed activity. These reports cover a range of diagnostic prescribed activities of ^{131}I.

Park and colleagues were, as far as I can determine, the first to use the term *stunning* [1]. This was based on their review of post-therapy scans in patients who had preliminary diagnostic scans with 111 MBq (3 mCi), 185 MBq (5 mCi), or 370 MBq (10 mCi) ^{131}I. The numbers of patients were small, but there was a linear relationship of stunning and the quantity of ^{131}I administered. It is of considerable interest that the same investigators in a later publication found there was no statistical difference in successful ablation after the first or second application of therapy whether or not the patients had a diagnostic scan using ^{123}I or ^{131}I [1, 2]. In particular these investigators found no evidence of stunning when the diagnostic prescribed activity of ^{131}I was 111 MBq (3 mCi) or less.

A total of 122 patients were treated by Cholewinski et al. [27]. The investigators prescribed a diagnostic activity of 185 MBq (5 mCi) and scanned after a delay of 72 h. The treatment-prescribed activities covered a range from 1.1 to 7.4 GBq (30–200 mCi). However, 85 % of the patients received 5.5 GBq (150 mCi), and the treatment was administered on the same day as the diagnostic scan. There were no areas of absent uptake on the posttreatment scintiscans that were also obtained after 72 h. The authors then evaluated the outcome of the ^{131}I therapy by follow-up scan. In this analysis they separated the patients into two groups, the first where the operation had been a total thyroidectomy and the second where a lobectomy was conducted. In the first group consisting of 92 patients, 84 % were successfully ablated. The authors conclude "diagnostic whole-body scanning can be performed effectively with a 185 MBq (5 mCi) of ^{131}I 72 h before radioiodine ablation without concern for thyroid stunning."

Investigators from the Mayo Clinic compared diagnostic and post-therapy scans in a study designed to determine whether or not the latter provided additional information [28]. The data also allowed the question of stunning to be assessed. Diagnostic prescribed activities of ^{131}I ranged from 37 to 111 MBq (1–3 mCi) with a mean of 96 MBq (2.6 mCi), and imaging was conducted after 48 h. The authors did not note when the therapy was administered, but posttreatment scans were obtained after 3–5 days. They found reduced uptake on 4 % (5 of 117) of the post-therapy scans. In four of these five cases, they identified an alternative reason to stunning to explain the reduced uptake. With regard to these five patients, they comment "a stunning effect might have been the cause although it appears unlikely." Of their patients' scans, 96 % definitely showed no evidence of stunning.

One publication that is used by some to strengthen the argument for stunning I find supports the opposite. In the report by Bajen et al., the post-therapy scan showed less uptake in 78 (21 %) of 373 patients [29]. A prescribed activity of 185 MBq (5 mCi) was administered for the diagnostic scan, and patients were treated 7–8 weeks later. The average therapeutic prescribed activity of ^{131}I was 4 GBq (108 mCi). Follow-up scans were conducted in 76 of these 78 patients and were negative in 68 (89 %). Thyroglobulin (Tg) was <3 ng/ml in 61 of the 68 patients. Of the remaining eight patients (76–68), seven had improvement on the follow-up scan and had low values of Tg. Thus, although it appears that stunning occurred in 21 % of the patients, 89 % of the so-called stunned group had no functioning thyroid on follow-up, and in 88 % of the remainder, there was evidence of benefit from ^{131}I therapy. These investigators concluded "our data suggests that a stunning effect does not exist for prescribed activity of 185 MBq (5 mCi) ^{131}I."

For several decades physicians at the Memorial Sloan Kettering Cancer Center have employed dosimetric

measurements prior to treatment with ^{131}I. The aim is to ensure the bone marrow does not receive 2 Gy (200 rad) or more radiation-absorbed dose. The measurements require scans and blood measurements over 4 or 5 days, which can only be achieved with ^{131}I since the half-life of ^{123}I is too short. They used 1–5 mCi (37–185 MBq) of ^{131}I for diagnostic measurements. The researchers compared the uptake of the therapeutic prescribed activity to the diagnostic one and concluded "we did not observe a strong correlation between administered activity and the magnitude of stunning" [30].

This author has compared diagnostic and post-therapy scans in 305 patients. The diagnostic scans were usually obtained 66–72 h after 74 MBq (2 mCi) of ^{131}I (the patients received the test prescribed activity on a Friday and were scanned on the following Monday). Treatment was administered as soon as possible after the information from the diagnostic scan was reviewed. Forty percent were treated on the same day and a further 34 % by 24 h. Post-therapy scans were obtained after an average of 8 days. Reduced uptake was identified on ten (3.3 %) of these scans. Follow-up scan and Tg measurements were negative in eight of these ten patients. Earlier results from this investigation have been published [31].

Several years ago our group stopped using ^{131}I for diagnostic scanning in favor of ^{123}I. The change was not because of concern of stunning but the better quality of ^{123}I images and reduced total radiation to the patient. It was a surprise when we found post-therapy scans that showed reduced uptake in 4 (13 %) of 30 patients who were treated with ^{131}I shortly after the diagnostic scan [32]. It is not probable, and indeed it is not possible that the prescribed activity of 74 MBq (2 mCi) ^{123}I that was employed at that time could deliver sufficient radiation to cause stunning over 24 h. We have demonstrated that post-therapy scans can vary with less lesions being identified with the passage of time from administration of the diagnostic activity. Therapeutic ^{131}I can be released from various sites of uptake at different rates, so all lesions seen on an early image might not be seen after many days. This has been demonstrated in a publication by the author [33]. Lee et al. compared post-therapy scans conducted 3 and 10 days after therapy [34]. The lesion to background ratio fell from 10.8 + 7.6 to 5.4 + 5.2 ($p < 0.001$), and ratio in the thyroid remnant to background fell from 12.0 + 10.8 to 8.0 + 7.6 ($p < 0.02$). When a region shows absent or reduced uptake on delayed scan, this should not immediately be blamed on stunning. It has long been recognized that cancerous thyroid cells may trap and organify iodine less efficiently than normal thyroid and there may be more rapid turnover. This is a likely explanation for reports of stunning in some patients. Because of an increasing body of information that ^{123}I is a better radionuclide for whole-body scanning, our group and others now routinely use 148–185 MBq (4–5 mCi) of ^{123}I [3]. Van Nostrand et al. established the importance of the information obtained from the diagnostic scan on determining appropriate therapy [5].

Returning to the discussion of diagnostic whole-body scan and stunning, the articles discussed above demonstrate no evidence of stunning, and several also demonstrate no loss of therapeutic efficacy. One criticism of most of these publications is the lack of quantitative comparisons. In defense of this missing information, the question remains of the reliability of uptake measurement of large therapeutic prescribed activities and the relevance of a difference between a 24–72 h diagnostic result and a 7–8 day post-therapy result.

Because there has been a movement away from obtaining a diagnostic scan for fear of stunning, some physicians proceed directly to therapy [35]. The goal of this presentation is not only to argue against stunning but also to promote the value of technically high-quality diagnostic scan that aids the physician to select the most appropriate therapeutic prescribed activity of ^{131}I [5]. Morris et al. were able to compare the outcome in two well-matched groups of patients. One group had a diagnostic scan using prescribed activities of 111–185 MBq (3–5 mCi) ^{131}I and the other did not [36]. There was no difference in outcome with 65 % of the former group being ablated versus 67 % of the latter. Treatment was administered 2–5 days after the diagnostic scan.

Rosario et al. compared outcome after ^{131}I treatment in 145 patients who had a preliminary diagnostic scan using 185 MBq (5 mCi) ^{131}I [37]. Seventy-six patients were treated without a diagnostic scan. There was no difference in the rates of ablation whether the patients were treated for residual thyroid tissue or for pulmonary metastases. A similar investigation compared the therapeutic outcome in 20 patients who had a diagnostic scan with 185 MBq (5 mCi) ^{131}I versus 20 matched patients who had no scan. Follow-up whole-body scan, ultrasound, and Tg measurements were used to determine therapeutic success. There was no difference ($p = 0.6$) [38].

A retrospective multivariate analysis of factors that influence the success of ^{131}I ablation in 389 patients found the most important factor was the size of the therapeutic prescribed activities [39]. They concluded with the statement "higher diagnostic doses were not associated with higher rates of ablation failure."

In Vitro Data

Postgard et al. conducted an experiment using thyroid cells in culture in a chamber [40]. They incubated the cells with ^{131}I for 48 h and then 3 days later studied the ability of the cells to transport iodine. 3 Gy (300 rad) reduced transport by 50 % and 30 Gy (3,000 rad) by approximately 90 %. In a later study they demonstrated that provided there was no delay between testing and treatment, trapping actually

increased over 72 h, thus supporting the benefit of treating soon after a diagnostic scan employing ^{131}I. Researchers from the same center also studied the effects of ^{131}I, ^{123}I, ^{99m}Tc, and ^{211}At [41]. Thyroid cells in culture were exposed to radiation for 48 h. They found that ^{131}I caused no reduction in mRNA NIS expression 24 h after radiation, but by 5 days it had fallen to 80 %. Paradoxically, ^{123}I produced a 55 % drop in NIS mRNA expression at 24 h, but this returned to normal by 5 days. The paradox is explained by the fact they used the same absorbed dose of radiation and the absorbed dose per unit of activity is about 100 times greater for ^{131}I than ^{123}I. Thus, the probability of stunning with 148–185 MBq (4–5 mCi) ^{123}I would be about 1/100th that of 148–185 MBq (4–5 mCi) of ^{131}I.

Another Possible Example of Stunning

In patients with negative radioiodine scans but measurable Tgs, there is a body of data supporting the use of ^{18}F fluorodeoxyglucose (^{18}F FDG) positron emission tomography/computer tomography (PET/CT) scans to identify the site(s) of Tg production. A meta-analysis provides data on sensitivity and specificity and a comprehensive list of references, and this subject has been reviewed elsewhere in this book (see Chaps. 43, 47, and 76) [42]. In several non-thyroidal cancers, ^{18}F FDG PET/CT scans can be falsely negative after external radiation, i.e., a form of stunning. This raised concern that ^{131}I might cause stunning on ^{18}F FDG PET/CT scans. Hung et al. compared six patients who had PET/CT scans within 4 months of ^{131}I therapy to ten patients who had not been treated. The standardized uptake values (SUVs) were lower in the treated patients. However, the two groups were not equivalent with regard to age and TSH values. This area needs clarification.

Dosimetric evidence against stunning can be derived from knowledge of how much radiation is required to ablate thyroid tissue. Maxon et al. calculated that 300 Gy (30,000 rad) has to be delivered for reliable success [43, 44]. Some authorities suggest a similar dose could be required for 100 % success in treating hyperthyroidism caused by hyperfunctioning nodules [45]. Therefore, it seems reasonable that the prescribed activity required to cause stunning would be significant. Let us consider two reasonable examples. First, consider a patient with remnant tissue of 1 g who has an uptake of 1 % and is scanned 72 h after a prescribed activity of 74 MBq (2 mCi) of ^{131}I administered for diagnostic scanning and treatment performed shortly after the diagnostic scan. Assuming almost instantaneous uptake of the tracer, the absorbed radiation dose to the thyroid from the diagnostic prescribed activity would be approximately 6 Gy (600 rad). Second, a patient with a 1 g remnant tissue and uptake of 4 % receives a diagnostic prescribed activity of 370 MBq (10 mCi) ^{131}I and treatment delayed for 1 week. The thyroid could receive 160 Gy (16,000 rad) assuming an effective half-life of 100 h. The former's absorbed dose would not be enough to cause ablation but the latter could. These numbers make the obvious point that larger diagnostic amounts of prescribed activity and **longer** delays between diagnosis and therapy result in thyroid tissue receiving more radiation, in fact enough to cause ablation or certainly a significant reduction in function, and could be interpreted as stunning when a post-therapy scan made some time later shows reduced uptake. Therefore, when ^{131}I is used for a diagnostic whole-body scan, it is prudent to use 37–111 MBq (1–3 mCi) and be prepared to treat as soon as possible after the test. Although several studies indicate that prescribed activities of 185 MBq (5 mCi) of ^{131}I do not cause stunning, it would be more important that treatment should certainly not be delayed.

In summary, there are several studies involving large numbers of patients that do not support the concept of stunning whether this means absent uptake on the post-therapy scan or reduced efficacy of ^{131}I treatment. Is it possible to state stunning never occurs? No. When a large diagnostic prescribed activity of ^{131}I is administered and there is a significant delay before therapy is given, stunning can be anticipated. These facts argue in favor of diagnostic imaging with ^{123}I and treating as soon as possible with an administered prescribed activity determined by the clinical risk and scan and Tg findings.

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