UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS:
ENDOCRINOLOGIA

ALTERAÇÕES AGUDAS DA TIREOIDE APÓS RADIOTERAPIA NÃO DIRIGIDA À GLÂNDULA EM CRIANÇAS E ADOLESCENTES, E DOSIMETRIA IN VIVO PARA A TIREOIDE DE DIFERENTES REGIÕES CORPORAIS IRRADIADAS

TESE DE DOUTORADO

CASSIANE CARDOSO BONATO

Porto Alegre, agosto de 2012.

CIP - Catalogação na Publicação

Bonato, Cassiane Cardoso
Alterações agudas da tireoide após radioterapia não dirigida à glândula em crianças e adolescentes, e dosimetria in vivo para a tireoide de diferentes regiões corporais irradiadas / Cassiane Cardoso Bonato. -- 2012.
76 f.

Orientador: Regina Helena Elnecave.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2012.

1. Tireoide. 2. Radioterapia. 3. Dosimetria. 4. Crianças e adolescentes. 5. Neoplasia. I. Elnecave, Regina Helena, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

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Cassiane Cardoso Bonato

Orientadora: Regina Helena Elnecave

Tese de Doutorado apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) como requisito parcial para obtenção do título de Doutor em Endocrinologia.

Porto Alegre, agosto de 2012.

À minha família.

AGRADECIMENTOS

Aos meus pais pelo incentivo constante.

À minha querida orientadora, Dra. Regina Elnecave, pelos conhecimentos compartilhados e pela confiança.

Aos pacientes, que mesmo sofrendo com os efeitos de suas doenças e tratamentos, participaram bravamente deste estudo.

Ao meu colaborador, Henrique Dias, pela amizade e competência.

Aos físicos e médicos do Serviço de Radioterapia do HCPA pela infindável paciência.

Ao Programa de Qualidade em Radioterapia do INCA pela ajuda técnica.

À bibliotecária da Faculdade de Medicina da PUCRS, Rosaria Geremia, pelo carinho e pela valiosa ajuda nas pesquisas.

Aos amigos e ao Serviço de Endocrinologia da PUCRS pela tolerância.

Aos professores do Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul (UFRGS) pelos ensinamentos.

“ – Entre los pecados mayores que los hombres cometen, aunque algunos dicen que es la soberbia, yo digo que es el desagradecimiento, ateniéndome a lo que suele decirse: que de los desagradecidos está lleno el infierno. Este pecado, en cuanto me ha sido posible, he procurado yo huir desde el instante que tuve uso de razón; y si no puedo pagar las buenas obras que me hacen, con otras obras, pongo en su lugar los deseos de hacerlas, y cuanto éstos no bastan, las publico; porque quien dice y publica las buenas obras que recibe, también las recompensara con otras si pudiera; porque la mayor parte, los que reciben son inferiores a los que dan...”

Cervantes Saavedra, Miguel de – El ingenioso Hidalgo Don Quijote de La Mancha.
Barcelona: Ramon Sopena 1969. cap. 57, p. 685.

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LISTA DE ABREVIATURAS

95%LA	*95% limits of agreement*
ABD	*abdomen*
anti-TPO	*anti-thyroperoxidase*
BG	*background radiation*
CC	*calibration coefficient*
CCSS	*Childhood Cancer Survivor Study*
CLIA	*chemiluminescence immunoassay*
CT	*computed tomography*
$\mathbf{D_{ref}}$	*reference dose*
$\mathbf{D_{uncorr}}$	*uncorrected dose*
ECLIA	*electrochemiluminescence immunoassay*
fT4	*free thyroxine*
$\mathbf{k_{lin}}$	*dose linearity correction factor*
MDT	*mediastinum*
PAAF	punção por agulha fina
PLV	*pelvis*
QUANTEC	*Quantitative Analysis of Normal Tissue Effects in the Clinic*
SNC	sistema nervoso central
T3	*triiodothyronine*
T4	*thyroxine*
Tg	*thyroglobulin*
TL	*thermoluminescent*
TLDs	*thermoluminescent dosimeters*
TPS	*treatment planning system*
TPSskin	*TPS estimates of radiation scattered to the point of skin overlying the thyroid isthmus*
TPSthyroid	*TPS estimates of radiation scattered to the thyroid gland*
TSH	*thyroid-stimulating hormone*

Introdução

Logo após a descoberta dos raios X, em 1895, foi publicado um caso de dermatite grave induzida por radiação, e em 1902, foi recomendado o primeiro limite de dose de exposição, de 100 mSv por dia. No entanto, esse limite não se baseava em alterações biológicas, mas na menor quantidade capaz de produzir modificações visíveis em uma placa fotográfica. As primeiras considerações sobre dose de tolerância foram relatadas como dose-eritema, e grande parte dos conceitos da época advinha de observações clínicas do uso desastroso da radiação em tempos de ignorância do poder dessa energia. Em 1903, estudos em animais já haviam demonstrado que os raios X poderiam provocar câncer e matar tecidos vivos. Após esse período, as doses de tolerância foram sendo modificadas a partir da observação de indivíduos que trabalhavam com radiação (1). Os maiores avanços nas pesquisas sobre os efeitos biológicos da radiação, inclusive o conceito da modificação genética pela radiação, foram alcançados durante e após a II Guerra Mundial. As informações oriundas dos japoneses expostos às bombas atômicas de Hiroshima e Nagasaki são utilizadas como parâmetros até os dias de hoje (2).

O estudo das complicações endocrinológicas secundárias à toxicidade da radiação é de grande importância, sendo o tecido tireoidiano muito sensível (3). Os primeiros relatos dos efeitos da radiação na tireoide datam da década de 1920, quando pacientes desenvolveram tireotoxicose após radioterapia (4). Hipotireoidismo foi relatado na década de 1960 após o seguimento de pacientes submetidos à radioterapia de cânceres de cabeça e pescoço (5,6,7). No passado, a radioterapia também era utilizada no tratamento de diversas condições benignas, como no tratamento de tinea capitis do couro cabeludo, contribuindo para o risco aumentado de câncer de tireoide (8).

Atualmente, a radioterapia tem sido largamente utilizada no manejo de diversas neoplasias malignas. Vários estudos foram realizados com o objetivo de avaliar os efeitos crônicos da radioterapia sobre a tireoide (9,10,11), os quais demonstraram alta prevalência de disfunções hormonais e câncer, conforme revisado no primeiro artigo desta tese. No entanto, alguns fatores de risco e o momento real do início dessas alterações não estão totalmente elucidados. A maioria desses estudos apresenta um desenho retrospectivo, bem como os problemas inerentes à essa condição.

A avaliação das reações agudas da função tireoidiana através de estudos prospectivos, que levem em consideração o espalhamento de doses de radiação incidental à tireoide, poderá revelar estratégias de prevenção do dano. No segundo artigo, realizou-se uma avaliação das alterações tireoidianas agudas em crianças e adolescentes que receberam tratamento para diferentes tipos de cânceres, de diferentes regiões, levando-se em conta a dose de espalhamento para a tireoide.

Embora as técnicas de tratamento radioterápico apresentem-se cada vez mais direcionadas, órgãos e tecidos sadios ainda podem ser afetados. Além disso, as crianças apresentam proporções corporais menores, podendo receber doses consideráveis de espalhamento, mesmo para estruturas distantes do feixe primário de tratamento, conforme demonstrado no terceiro artigo, no qual foram comparadas duas técnicas de dosimetria, sendo uma delas *in vivo*.

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Parte I

Artigo de revisão

ALTERAÇÕES TIREOIDIANAS ASSOCIADAS À RADIAÇÃO EXTERNA EM CRIANÇAS E ADOLESCENTES

THYROID DISORDERS ASSOCIATED WITH EXTERNAL RADIATION IN CHILDREN AND ADOLESCENTS

ARTIGO DE REVISÃO

Título: Alterações tireoidianas associadas à radiação externa em crianças e adolescentes

Título inglês: Thyroid disorders associated with external radiation in children and adolescents

Autores: Cassiane Cardoso Bonato e Regina Helena Elnecave
Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre
Universidade Federal do Rio Grande do Sul
Porto Alegre, RS

Correspondência:
Regina Helena Elnecave
Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre
R. Ramiro Barcelos, 2350, prédio 12, 4° andar
CEP 90035-003 – Porto Alegre, RS
Fone/Fax: (51) 3359.8127
E-mail: rhelnecave@gmail.com

Título resumido: Tireoide e radiação

Este artigo foi publicado nos Arquivos Brasileiros de Endocrinologia e Metabologia. Referência: Bonato, Cassiane Cardoso and Elnecave, Regina Helena Alterações tireoidianas associadas à radiação externa em crianças e adolescentes. *Arq Bras Endocrinol Metab*, Ago 2011, vol.55, no.6, p.359-366. ISSN 0004-2730.

Sumário

O efeito da radiação ionizante sobre a tireoide vem sendo estudado há várias décadas, e os acidentes nucleares têm sido a maior fonte de informação. Existe associação de hipotireoidismo, hipertireoidismo, nódulos e câncer de tireoide com a radiação, mas os limiares de dose, mecanismos de lesão e alguns fatores de risco ainda não estão bem estabelecidos. Crianças são mais susceptíveis à lesão tireoidiana por radiação e necessitam de seguimento prolongado após a exposição. Este tema adquire maior relevância atualmente, pois um grande número de pessoas tratadas com radioterapia para câncer na infância sobrevive e poderá apresentar sequelas. Exames radiodiagnósticos também representam fonte de exposição à radiação na população pediátrica. Nesta revisão, analisamos as diferentes alterações clínico-patológicas e os mecanismos de lesões tireoidianas provocadas por tratamento radioterápico e tomografia computadorizada em crianças e adolescentes. É importante conhecer esses dados para a prevenção, detecção precoce e tratamento da disfunção tireoidiana.

Descritores: Hipotireoidismo; criança; neoplasia; radioterapia.

Summary

The effects of ionizing radiation on the thyroid have been studied for several decades, and nuclear accidents are the major source of information. There is an association of hypothyroidism, hyperthyroidism, thyroid nodules and cancer with radiation, but the threshold dose, mechanism of injury, and some risk factors are not fully established. Children are more susceptible to thyroid injury from radiation and require prolonged follow-up after exposure. This issue is especially relevant nowadays, since a large number of people treated with radiation for childhood cancer survive and may have sequelae. Diagnostic radiology tests also represent a source of radiation exposure in the pediatric population. In this review we analyze different clinical and pathological changes and the mechanisms of thyroid lesions caused by radiotherapy and computed tomography in children and adolescents. It is important to understand these data for prevention, early detection, and treatment of thyroid dysfunction.

Keywords: Hypothyroidism; child; neoplasia; radiotherapy.

Introdução

A exposição à radiação externa ionizante apresenta diversas origens, como a exposição ambiental natural, um voo de avião, acidentes atômicos, exames diagnósticos e tratamentos médicos (Tabela 1). Exemplos de radiação ionizante incluem os raios X e gama, que não possuem massa, têm alta energia e são formas penetrantes de radiação eletromagnética. A dose de radiação absorvida é medida em Gray (Gy) (1 joule de energia para 1 kg de massa) – dose absorvida por um órgão ou tecido específico por unidade de massa. A lesão biológica provocada por uma unidade de radiação (dose efetiva) é expressa em Sievert (Sv) e varia conforme o tipo de radiação (alfa, beta ou gama). No caso de raios X e gama, 1 Gy é igual a 1 Sv. Os efeitos da radiação em seres humanos vêm sendo estudados há várias décadas, principalmente nos sobreviventes das bombas atômicas no Japão, quando se observou a associação entre câncer e radiação. Crianças são mais sensíveis às lesões causadas pela radiação devido à maior replicação celular e por apresentarem uma expectativa de vida maior para o aparecimento de alterações.

Tem-se observado um interesse crescente em identificar danos em tecidos biológicos sadios expostos à radiação médica (diagnóstica e terapêutica). O uso de exames radiodiagnósticos tem aumentado exponencialmente, especialmente o uso da tomografia computadorizada, e a dose de radiação não pode ser negligenciada (1). Na radioterapia, doses mais elevadas de radiação são dirigidas ao tumor ou tecido alvo, mas pode haver dispersão para tecidos normais próximos (2). Essa modalidade de tratamento do câncer encontra-se frequentemente associada a sequelas precoces ou tardias e tem sido alvo de diversos estudos.

A tireoide é particularmente suscetível aos efeitos da radiação e está frequentemente envolvida no campo de irradiação diagnóstica ou terapêutica, podendo apresentar alterações funcionais e estruturais. Nesta revisão serão abordados os efeitos da radiação ionizante externa sobre a tireoide e suas consequências clínicas em crianças e adolescentes submetidos a tomografia computadorizada ou a radioterapia.

Efeitos biológicos da radiação ionizante

Apesar de a radiação ionizante ser um agente terapêutico usado para diminuir ou parar o crescimento tumoral, a exposição de tecidos normais durante o tratamento pode resultar em câncer. O potencial carcinogênico dessa forma de radiação depende das mutações induzidas no DNA e da capacidade individual de reparo (3).

A radiação ionizante é liberada por átomos com excesso de energia, massa ou ambos. Esses átomos emitem o excedente de energia (p. ex. raios gama) ou massa (p. ex. partículas alfa) para tornarem-se estáveis. A radiação ionizante lesa os tecidos humanos de várias formas, e os efeitos diretos dessa radiação no microambiente tecidual são desencadeados pela deposição de energia nas macromoléculas, rompendo estruturas atômicas do tecido onde atua e produzindo modificações químicas e biológicas. Há interação direta com alvos como o RNAm, DNA e proteínas, rompendo suas ligações covalentes e quebrando sua estrutura irreversivelmente. Além disso, sessenta por cento do dano tecidual provocado por raios X e gama pode ser explicado pelos efeitos indiretos da radiação, que ocorrem devido à reação das partículas ionizadas com a água livre, produzindo espécies reativas de oxigênio e radicais livres, o que amplifica a lesão através da interação com lipídios, membranas e outras moléculas de oxigênio (4). Assim, as estruturas da arquitetura celular adjacente e a informação genômica são rompidas (Figura 1). A radiação ionizante causa uma ruptura celular que pode resultar na morte da célula. No entanto, a maioria dos tipos celulares não manifesta lesão até que muitas mitoses ocorram.

A lesão do DNA induz a uma resposta de *stress* do ambiente intracelular, com ativação de proteínas que facilitam o reparo e previnem a proliferação de células danificadas. De forma semelhante, citocinas e fatores de crescimento atuam no parênquima e estroma para modular o comportamento e fenótipos celulares. A radiação pode, também, ativar o TGF-β existente na matriz extracelular, que funciona como um supressor da tumorigênese e como um marcador de inflamação (5). Além disso, ocorre acúmulo de macrófagos que têm o fenótipo de fagócitos ativados, acompanhados por marginação e infiltração dos tecidos por neutrófilos, que são sinais clássicos da resposta inflamatória (6).

Na tireoide, a radiação pode inibir ou ativar funções específicas do epitélio folicular, reduzir o número de folículos funcionantes, alterar a vascularização ou a permeabilidade vascular e induzir reações imunológicas. Os achados histológicos de tireoides irradiadas variam substancialmente dependendo da dose de radiação e do intervalo que se segue à exposição. As alterações agudas, como as observadas em 3 a 6 semanas após a exposição a acidentes atômicos, incluem diminuição do tamanho dos folículos com afinamento do epitélio cuboidal dos tecidos. As modificações crônicas observadas em glândulas tireoidianas expostas durante a infância a baixas doses de irradiação externa incluem hiperplasia folicular focal, tireoidite linfocítica crônica, adenomas únicos ou múltiplos e carcinomas de tireoide papilares, foliculares ou mistos (7).

Um possível mecanismo de alteração da função tireoidiana induzida por radiação é a lesão celular direta, com exposição ao sistema imunológico, levando à produção de autoanticorpos ou à superativação de linfócitos T *helper* (8). Embora alguns estudos de sobreviventes de bombas atômicas e do acidente nuclear de Chernobyl tenham demonstrado maior prevalência de autoanticorpos tireoidianos, diretamente proporcional ao grau de exposição à radiação (9), outros não confirmaram esses resultados (10). Em pacientes submetidos a radioterapia externa, a frequência de doenças autoimunes da tireoide (tireoidite de Hashimoto, doença de Graves e oftalmopatia de Graves) é significativamente maior do que nos controles não tratados (11,12).

Tomografia computadorizada e tireoide

Sabe-se que altas doses de radiação ionizante (>100 mSv) levam a consequências deletérias em seres humanos, incluindo, mas não exclusivamente, a indução de câncer. Com doses mais baixas, os riscos são menos claros. Grande parte da informação que dispomos vem de estudos de sobreviventes da bomba atômica no Japão, observando-se um aumento global de câncer naqueles que receberam doses entre 5 e 150 mSv (13). No entanto, a dose de radiação resultante de exames radiológicos varia entre 3 e 30 mSv, sendo necessários estudos epidemiológicos com amostras maiores para quantificar com precisão os riscos para doses tão pequenas (14). A exposição à radiação de procedimentos médicos por imagem em geral não é monitorada e os dados de estudos longitudinais nessa área são escassos, apesar de alguns tipos de procedimentos serem realizados múltiplas vezes no mesmo paciente. A crescente utilização de exames radiológicos tem gerado preocupação com relação ao risco de lesão por órgão para diferentes doses. A tomografia computadorizada, por exemplo, utiliza vários cortes de raios X em múltiplos planos, sendo um dos exames que mais contribui para a dose efetiva total, conforme uma grande coorte retrospectiva norte-americana (1).

A tireoide é um órgão sensível à radiação e, com frequência, encontra-se incidentalmente exposta na área de estudos tomográficos de tórax, cabeça e pescoço. Mais de um terço de todas as tomografias computadorizadas realizadas envolvem a região da cabeça e pescoço (15). Um estudo de dosimetria realizado em crianças demonstrou que a tireoide pode receber doses de 15,2 a 52 mGy em tomografias da região cervical, o que poderia aumentar os casos de malignidade em mais de 390 por milhão de pessoas expostas (16). Nas tomografias de cabeça e tórax a tireoide também pode receber doses de espalhamento de até 8,7 e 21 mGy, respectivamente (16,17). Berrington de González et al. estimaram que haveria um excesso de 1200 casos futuros de câncer de tireoide resultantes de tomografias computadorizas realizadas nos Estados Unidos em 2007 (18). Não existem estudos, até o momento, sobre o risco de alterações funcionais e de autoimunidade da tireoide por uso de exames tomográficos.

Radioterapia externa e tireoide

Aproximadamente 70% das crianças com câncer ficam curadas ou apresentam remissão prolongada com os tratamentos atuais (19). A radioterapia é uma modalidade de tratamento do câncer frequentemente associada a sequelas precoces ou tardias, as quais requerem diagnóstico e intervenção. A tireoide pode estar direta ou indiretamente exposta à radiação quando outros órgãos são tratados. A principal disfunção tireoidiana após a irradiação direta ou incidental da glândula é o hipotireoidismo, mas também podem ocorrer tireoidite autoimune, doença de Graves, oftalmopatia de Graves, tireoidite silenciosa, cistos e nódulos benignos ou malignos (11).

Hipotireoidismo e radioterapia

O hipotireoidismo primário é a consequência clínica mais comum da irradiação externa para a região cervical, principalmente com altas doses (30-70 Gy) (8). Pacientes irradiados submetidos a *screening* bioquímico periódico frequentemente apresentam hipotireoidismo subclínico (11). A incidência de hipotireoidismo clínico e subclínico varia substancialmente (4-49%) conforme as técnicas, as doses e a frequência de radiação. Em uma população de adultos e crianças irradiadas na região cervical para tratamento de doença de Hodgkin, o hipotireoidismo clínico ou subclínico foi encontrado em 47% dos pacientes 27 anos após o tratamento. Aproximadamente metade desses casos se manifestou até cinco anos após a radioterapia (11). Dados do maior estudo de sobreviventes de câncer na infância, o Childhood Cancer Survivor Study (CCSS) (20), mostram que a incidência de hipotireoidismo em pacientes que tiveram doença de Hodgkin foi significativamente maior nos irradiados do que no grupo controle (irmãos hígidos) (RR=17,1; $p < 0,0001$) e a dose de radiação para a tireoide foi o fator de risco mais importante, sendo que o risco relativo aumentou em 1,06 por Gray ($p < 0,0001$). Aproximadamente metade dos pacientes manifestaram hipotireoidismo em 2 a 7 anos após a terapia, com um declínio da incidência após este período. O desenvolvimento de hipotireoidismo é diretamente proporcional à dose de radiação que atinge a tireoide, principalmente quando maior que 20 Gy (11,20).

Outros fatores associados ao maior risco de hipotireoidismo após irradiação cervical, como a idade do indivíduo no momento do tratamento radioterápico, o sexo e o uso associado de quimioterápicos, foram estudados. Embora a sensibilidade da tireoide à radiação pareça ser elevada em crianças pequenas, a incidência de hipotireoidismo mostrou-se maior nos pacientes tratados dos 15 aos 20 anos (39%) do que naqueles tratados antes dos 5 anos de idade (15%) (11). Um possível fator de confusão poderia ter sido o uso de doses menores de radiação nos mais jovens. No entanto, este achado foi confirmado, demonstrando a idade maior de 15 anos como um fator de risco independente (20). Em adultos, o sexo feminino foi identificado como um fator de risco (11), achado controverso em crianças e adolescentes (20). Os efeitos tardios do tratamento do câncer na infância são descritos predominantemente em relação à radioterapia. Na maioria dos estudos, a quimioterapia não tem demonstrado efeito adicional ou isolado sobre a função ou o aparecimento de nódulos de tireoide em indivíduos tratados para câncer na infância (21). No entanto, já foi observado efeito deletério adicional sobre a função tireoidiana em pacientes tratados com radioterapia para tumores cerebrais (22).

O hipotireoidismo também foi documentado após exposição incidental da tireoide à radiação, ou seja, quando a glândula está fora do campo de irradiação.

Crianças tratadas para tumores do sistema nervoso central (SNC) apresentaram hipotireoidismo em 20 a 68% dos casos (22). Em irradiação corporal total para o transplante de medula óssea a incidência de hipotireoidismo clínico ou subclínico foi de 25 a 73% (12,23), sendo menor quando fracionada do que após dose única para regimes preparatórios (12).

Em um estudo retrospectivo, hipotireoidismo bioquímico foi observado em 23/59 (39%) pacientes tratados com radiação externa para diferentes áreas corporais durante a infância (média de idade 7,6±3,4 anos). Essa foi uma alteração precoce, em média 3,5±1,9 anos após a radioterapia. O fator mais fortemente associado ao hipotireoidismo foi a proximidade da zona irradiada (área de risco) com o leito tireoidiano. Todos os pacientes apresentaram anticorpos antitireoperoxidase normais. O volume tireoidiano nos pacientes com hipotireoidismo foi significativamente menor do que naqueles com função tireoidiana normal ($p < 0{,}001$) (24).

Anticorpos antitireoidianos foram mais frequentemente encontrados em pacientes que receberam radiação externa na região cervical do que em pacientes não tratados (12), achado não confirmado por outros estudos, que atribuíram o hipotireoidismo à redução do número de células foliculares (24,25).

O hipotireoidismo secundário também pode ocorrer após irradiação da região hipotalâmico-hipofisária, de tumores cerebrais ou de alguns cânceres de cabeça e pescoço (22,26,27). O intervalo médio de tempo para a detecção de hipotireoidismo central é maior do que para o hipotireoidismo primário, chegando até 19 anos. Esse fato pode indicar que as avaliações feitas a curto prazo subestimem a incidência do problema. O risco de hipotireoidismo central está diretamente relacionado à dose de irradiação (22). Os outros eixos hipotalâmico-hipofisários são mais vulneráveis à radiação do que o eixo hipotálamo-hipófise-tireoide, afetado em 3 a 6% dos irradiados para tumores cerebrais não hipofisários e, em geral, associado a doses maiores do que 50 Gy (26,28).

O bloqueio da atividade metabólica e proliferativa da tireoide através do uso transitório de levotiroxina durante a radioterapia em crianças mostrou-se protetor contra a lesão funcional (hipotireoidismo primário) (29), mas deve ser comprovado por outros ensaios clínicos.

Hipertireoidismo e radioterapia

Diversos casos de tireoidite tireotóxica após irradiação externa, incluindo o leito tireoidiano, foram relatados de duas semanas a vários anos após o tratamento (30,31). O hipertireoidismo parece ser uma complicação precoce após a irradiação externa, mas permanece pouco diagnosticado. Não se sabe da história natural dessa disfunção, pois não se dispõe de estudos prospectivos maiores. Como o número de casos relatados na literatura é pequeno, é difícil determinar a verdadeira incidência do hipertireoidismo e estabelecer quais seriam os fatores de risco mais importantes. Até o momento, a variável associada ao maior risco foi a maior dose de radiação (11,20).

Em geral, o quadro clínico de hipertireoidismo é idêntico ao da doença de Graves e caracterizado pelo aumento da glândula tireoide, níveis elevados de hormônios tireoidianos, níveis suprimidos de TSH, aumento da captação tireoidiana de iodo e aumento de autoanticorpos para a tireoide. O risco de doença de Graves é 7 a 20 vezes maior em pacientes irradiados em região cervical para o tratamento de doença de Hodgkin do que na população geral (11). O desenvolvimento de autoanticorpos tireoidianos pode resultar da secreção de antígenos expostos após a lesão da tireoide induzida pela radiação. Apesar de ser menos frequente que o hipotireoidismo, a doença de Graves foi descrita em dois estudos maiores, que mostraram hipertireoidismo em média 5,3 a 8 anos após o tratamento radioterápico (11,20). Dos 30 pacientes com hipertireoidismo avaliados, 17 desenvolveram oftalmopatia infiltrativa. A dose de irradiação cervical e o tempo desde o tratamento da doença de Hodgkin foram preditores independentes de hipertireoidismo (20).

Neoplasias de tireoide e radioterapia

Nódulos benignos e malignos são encontrados com maior frequência em pacientes expostos à radiação ionizante terapêutica ou acidental. Nódulos benignos foram as lesões nodulares mais prevalentes nos grupos expostos a acidentes nucleares, sendo mais uninodulares no Japão (32) e multinodulares em Chernobyl (33). Há correlação direta entre a incidência de adenomas tireoidianos e a dose de radiação (34). Os pacientes submetidos a irradiação terapêutica de cabeça e pescoço podem apresentar nódulos adenomatosos (30-90%), bócio nodular (33-77%) e cistos coloides (6-11%) (35).

A associação entre radiação e carcinoma de tireoide foi inicialmente descrita por Duffy e Fitzgerald em 1950 (36). Foi observado que grande parte das crianças com carcinoma de tireoide tinha história de radioterapia. Vários estudos confirmaram essa associação (37). Em uma meta-análise realizada em 1995, incluindo sete estudos, demonstrou-se, pela primeira vez, que a exposição a doses baixas ou moderadas de raio X ou radiação gama está associada a um risco crescente de câncer de tireoide, proporcional à dose (38). Resultados comparáveis foram descritos em um estudo caso-controle (CCSS), sendo observado, também, que este risco diminui com a exposição a doses maiores que 30 Gy, corroborando a hipótese de morte celular com altas doses de radiação proposta por Louis Gray em 1964 (39).

O risco de câncer de tireoide é maior em crianças irradiadas antes dos cinco anos de idade (40). Há correlação negativa entre a idade do paciente no momento da irradiação e o risco de segundo câncer em tireoide (38). Em crianças mais jovens, o risco maior de câncer de tireoide após irradiação craniana é atribuído à menor distância craniofacial e à rápida proliferação das células da tireoide (27). A incidência de câncer de tireoide é maior 10 a 15 anos após a exposição à radiação externa, com um tempo de latência de aproximadamente cinco anos (37,41,42). O tempo de latência foi mais curto em vítimas do acidente nuclear de Chernobyl, em que o radioiodo foi um dos componentes (42).

Em um estudo recente, envolvendo 17.980 indivíduos sobreviventes de câncer na infância, o risco relativo para o aparecimento de segundo câncer em tireoide foi de 4,6 (intervalo de confiança de 95%: 1,4-15,1; P=0,003), quando comparados aos sobreviventes não tratados com radioterapia (43). A taxa padronizada de incidência por período de seguimento revelou ser maior de 0 a 9 anos em relação a períodos posteriores. Oitenta e oito por cento dessas lesões apareceram quando a tireoide estava próxima ou envolvida no campo de irradiação, sendo o risco maior nos pacientes que fizeram tratamento de linfomas Hodgkin e não Hodgkin, quando comparados aos tratados para leucemia e tumores do SNC. A taxa de câncer de tireoide observada sobre a esperada foi maior no sexo masculino do que no feminino após a radiação externa, embora essa relação seja o inverso na população geral, consistente com dados do CCSS (44).

O carcinoma papilar é a variante histológica mais comum após a irradiação, representando 78% dos casos de segundo câncer em tireoide nos pacientes tratados para outro câncer (41) e 93,8% em vítimas do acidente nuclear de Chernobyl (45). A prevalência de rearranjos RET/PTC é maior em carcinomas papilares de pacientes com história de exposição à radiação incidental (67-87%) ou à irradiação terapêutica externa (52-84%) do que em pacientes não irradiados (46,47). Nas crianças afetadas pelo acidente nuclear de Chernobyl, os tumores de aparecimento mais precoce foram associados à mutação RET/PTC3, enquanto aqueles com maior período de latência foram associados à RET/PTC1 (47). São conflitantes os dados quanto à agressividade dos tumores de tireoide após radiação externa (37,47,48).

Avaliação e seguimento pós-radioterapia

Tratando-se de crianças, o crescimento e o desenvolvimento neuropsicológico são fatores importantes. Portanto, recomenda-se que os pacientes que receberam radiação direta ou incidental na região tireoidiana ou hipotalâmico-hipofisária sejam seguidos e avaliados pelo menos anualmente para história de sintomas de disfunção tireoidiana, exame clínico e medida de T4 e TSH (49). Segundo o *guideline* escocês "Long term follow up of survivors of childhood cancer", a função tireoidiana deve ser aferida logo após o final da radioterapia e repetida pelo menos anualmente (50).

O diagnóstico de hipotireoidismo central é facilmente realizado em pacientes com nível baixo de T4 com concentração normal-baixa de TSH. Em alguns casos, no entanto, o TSH pode estar elevado. O teste do TRH pode não ser útil nesses casos, pois grande parte dos pacientes com hipotireoidismo central apresentam teste do TRH normal ou semelhante aos pacientes com hipotireoidismo primário (51). Assim, a única forma de diagnosticar essa condição seria través do decréscimo seriado dos níveis de T4 (52).

A ecografia pode revelar volume tireoidiano reduzido e alterações estruturais. Nódulos tireoidianos podem ser detectados em mais de 40% dos pacientes irradiados (53), sendo que um terço é maligno (54). O Children's Oncology Group recomenda palpação anual da tireoide, seguida por ultrassom e outros testes em caso de nódulo palpável. Devido ao alto risco de malignidade, alguns autores recomendam ultrassom periódico no primeiro ano e, posteriormente, a cada 2-3 anos (55,56). Embora a ecografia aumente a detecção de câncer de tireoide, também poderá induzir a cirurgias de alguns cânceres que nunca progrediriam e de alguns nódulos benignos que não seriam adequadamente avaliados por punção por agulha fina (PAAF) (57). Deve-se realizar a punção em nódulos tireoidianos palpáveis, embora a avaliação citológica possa ser difícil pela presença de atipias celulares induzidas pela radiação. Hatipoglu et al. demonstraram que a sensibilidade e especificidade da PAAF em pacientes irradiados é similar à encontrada na população geral (58). A Associação Americana de Tireoide recomenda que a PAAF seja realizada em nódulos menores do que o usual (menores que 1 cm no maior diâmetro) se houver história de exposição à radiação (59).

Conclusão

Na infância, a exposição da tireoide à radiação externa ionizante, mesmo com baixas doses, deve ser vista com preocupação. A tomografia computadorizada é um dos exames radiodiagnósticos que fornecem maior dose de exposição à radiação. A utilização crescente dessa técnica aplicada em larga escala, e por vezes repetidamente, torna-se um problema de saúde pública pelo risco potencial de câncer de tireoide. O uso responsável desse exame deve ser encorajado.

A lesão da tireoide também pode acontecer após o tratamento de neoplasias por radioterapia cervical ou em áreas próximas. Os sintomas de disfunção tireoidiana podem ser confundidos ou interpretados de forma errônea ao serem atribuídos à doença de base do paciente ou às medicações usadas para o tratamento da neoplasia, resultando em diagnóstico tardio da lesão glandular. Considerando-se o sucesso no tratamento do câncer da infância, os pacientes submetidos a radioterapia devem ter um seguimento adequado, possibilitando o diagnóstico correto e o tratamento precoce das eventuais sequelas sobre a tireoide.

Conflitos de interesse: Não há.

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Tabela 1. Magnitude da exposição à radiação de várias fontes*

Fonte de exposição	**Dose aproximada em mSievert (mSv)**
Voo de Nova York a Londres	0,037
Raio X de tórax (póstero-anterior e lateral)	0,14
Raio X panorâmico dentário	0,7
Radiação ambiental natural de base	3/ano
Mamografia (dose para mama)	2-4
Cateterismo cardíaco	12-40
Tomografia computadorizada de tórax	20-30
Tomografia computadorizada abdominal pediátrica (dose para o estômago)	25
Tomografia computadorizada de crânio	30-50
Sobreviventes da bomba atômica (Coorte Life-Span Study)	200
Terapia com irradiação corporal total (TBI)	8000

*Adaptado do *Low Dose Radiation Research Program*, coordenado por N. F. Metting (disponível em: http://lowdose.energy.gov/imagegallery.aspx).

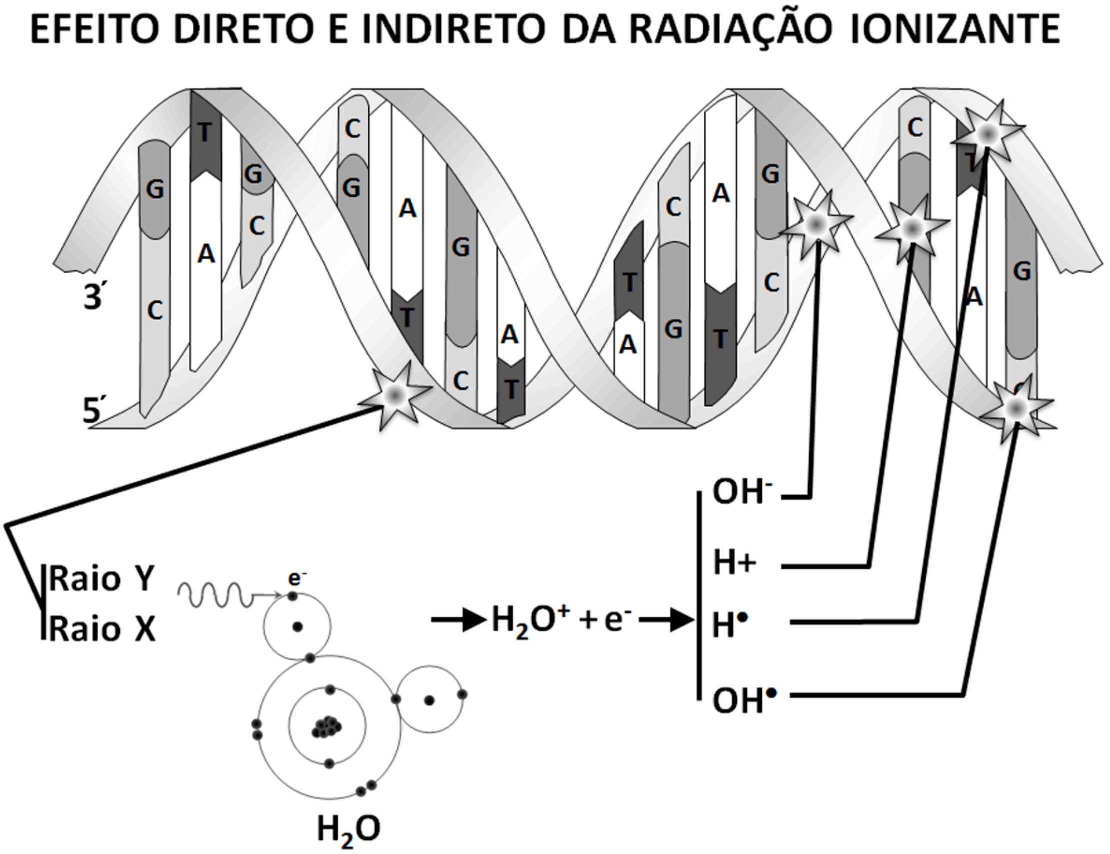

Figura 1. A lesão direta do DNA ocasiona a quebra de suas ligações estruturais. Na lesão indireta há deslocamento de elétron (e^-) da molécula de água (H_2O), que se torna um íon água positivo (H_2O^+). O elétron reagirá com outra molécula de água formando H_2O^-, que se dissocia em íon hidroxila (OH^-) e radical livre hidrogênio ($H^\bullet$). O íon água positivo (H_2O^+) se dissocia em íon hidrogênio positivo (H^+) e radical livre hidroxila ($OH^\bullet$). Os íons e radicais livres são altamente reativos com as estruturas celulares.

Parte II

Artigo original

ACUTE EFFECTS ON THE THYROID GLAND AFTER NON-DIRECTED RADIATION THERAPY IN CHILDREN AND ADOLESCENTS

Acute effects on the thyroid gland after non-directed radiation therapy in children and adolescents

Cassiane Cardoso Bonato, MD, MSc,[1] Henrique Bregolin Dias,[1] Michele da Silva Alves,[2] Lucas Ost Duarte,[2] Telpo Martins Dias,[2] Maiara Oliveira Dalenogare,[2] Claudio C B Viegas, MSc,[3] Regina Helena Elnecave, MD, PhD[1]

[1]Graduate Program in Internal Medicine, Endocrinology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.
[2]Radiation Therapy Center, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil.
[3]Ionizing Radiation Quality Program, Brazilian National Cancer Institute (INCA) José de Alencar Gomes da Silva, Ministério da Saúde, Rio de Janeiro, RJ, Brazil.

Corresponding author:
Regina Helena Elnecave
Endocrinology Service, HCPA - Rua Ramiro Barcelos, 2350/12, 4th floor
CEP 90035-003 – Porto Alegre, RS
Phone/Fax: +55 51 3359.8127
E-mail: rhelnecave@gmail.com

Running title: Early effects of incidental radiation on the thyroid

Acknowledgements: The authors would like to thank the Nuclear Medicine Service of HCPA, Dr. Ilza Vasques de Moraes for ^{131}I uptake, Dr. Alvaro Porto Alegre Furtado for the thyroid ultrasound examinations and Dr. Günther Alex Schneider for the precious assistance in radiotherapy.

Conflict of interest notification: All authors declare that they have no conflicts of interest

Summary

This is a prospective analysis of the acute effects on the thyroid of radiotherapy aimed at different sites in children and adolescents. TSH, T4, fT4, T3, anti-TPO antibodies and thyroglobulin were measured before, on the last day, and 1 and 3 months after completion of radiation therapy. Ultrasound and ^{131}I uptake were performed immediately before and after treatment. There were no differences in the analyzed parameters with different radiation doses scattered to the thyroid.

Abstract

Purpose: To assess acute changes in thyroid function and volume in children and adolescents undergoing external radiation therapy for a variety of non-thyroid cancers.

Methods and Materials: The study sample comprised 31 children and adolescents undergoing radiation therapy of various body areas in which the thyroid was outside the main beam. Thyroid-stimulating hormone (TSH), thyroxine (T4), free thyroxine (fT4), triiodothyronine (T3), anti-thyroperoxidase (anti-TPO) antibodies and thyroglobulin (Tg) were measured before radiation therapy, on the last day of irradiation, and 1 month and 3 months after the end of radiation therapy. Ultrasound and 6-hour and 24-hour ^{131}I uptake were also performed before and after treatment. The scattered dose to the thyroid region was estimated with a treatment planning system (TPS) or measured with thermoluminescent dosimeters (TLDs).

Results: The median radiation dose scattered to the thyroid was 296.6 cGy (IQR 16.7–1709.0). Levels of TSH (P=0.575), T4 (P=0.950), fT4 (P=0.510), T3 (P=0.842), Tg (P=0.620), and anti-TPO antibodies (P=0.546) were statistically similar at all four points in time. Younger subjects had higher T4, T3 and Tg levels, and T4 was highest in girls. There were no differences between pre- and post radiotherapy thyroid volume and ^{131}I uptake (P=0.692 and 0.92, respectively).

Conclusion: The radiation doses scattered to the thyroid in this sample were not associated with acute changes in thyroid function or volume. More sensitive methods may be required to ascertain whether acute injury to the follicular epithelium occurs with lower radiation doses.

Introduction

Approximately 1 in every 350 individuals living in the United States will develop cancer before the age of 20 (1). Since the 1960s, a variety of treatment modalities have been used against cancer, including combinations of surgery, chemotherapy, and radiation. Currently, over 70% of children diagnosed with cancer will survive for years, when not decades, after treatment (2). However, cancer therapy carries a high morbidity rate, and may affect organs not targeted during treatment (3).

During radiation therapy, the highest radiation doses are directed to the tumor or target tissues, but radiation may scatter to nearby healthy tissue (4). Children are more sensitive to radiation injury, perhaps due to higher cell replication rates and to their longer life expectancy (5). The thyroid gland is particularly susceptible to the effects of radiation and is often encompassed by or near the target field of radiation therapy (6). Hypothyroidism is the most common consequence of thyroid radiation injury, and early detection is paramount to the prevention of changes in growth and development (7,8). Although several studies have focused on this topic, the exact timing of these changes is still unknown, as is their potential correlation with radiation doses.

This study consisted of a prospective assessment of children and adolescents who underwent radiation therapy directed to a variety of organs and structures other than the thyroid to evaluate the occurrence of any functional and structural changes in this gland within 3 months of treatment.

Materials and methods

The study sample comprised 31 children and adolescents, with a median age of 7.0 years (IQR: 3.6–16; range: 1.3–20.0), treated between January 2009 and December 2011. Patients were consecutively enrolled into a contemporary cohort for early diagnosis of acute functional or volumetric thyroid changes (the latter diagnosed by ultrasonography) after external radiation therapy not directed to the thyroid gland. The exclusion criteria were: glucocorticoid therapy, history of thyroid dysfunction, history of radiation therapy, a planned radiation therapy regimen in which the thyroid gland fell within the main beam, or a planned radiation therapy regimen involving total body irradiation (TBI). The irradiated sites encompassed several different body segments, for the treatment of a wide range of cancers. Radiation was administered with one of two linear accelerators (Siemens Mevatron MDE, S/N 3054, nominal photon energy 6 MV, or Varian 23EX, S/N 3595, nominal photon energies 6 and 15 MV) at the Hospital de Clínicas de Porto Alegre (HCPA), Radiation Therapy Center.

Thyroid-stimulating hormone (TSH), thyroxine (T4), free thyroxine (fT4), triiodothyronine (T3), anti-thyroperoxidase antibodies (anti-TPO) and thyroglobulin (Tg) levels were measured before radiation therapy, on the last day of radiation therapy, and 1 month and 3 months after the end of radiation therapy. Measurements were obtained by electrochemiluminescence immunoassay (ECLIA) or chemiluminescence immunoassay (CLIA). Both methods exhibited good correlation and agreement on analysis at the HCPA Clinical Pathology Laboratory. All ECLIA assays were performed on Roche equipment (Roche Diagnostics GmbH, Mannheim, Germany) and reference ranges were as follows: TSH, 0.27–4.2 μUI/mL; T4, 5.1–14.1 μg/dL; free T4, 0.93–1.7 ng/dL; T3, 80–200 ng/dL; anti-TPO antibodies, <34 UI/mL; and Tg, 1.4–78 ng/mL. CLIA assays were performed on Siemens equipment (Siemens Healthcare Diagnostics, Erlangen, Germany) and reference ranges were as follows: TSH, 0.35–5.50 μUI/mL; T4, 3.2–12.6 μg/dL; fT4, 0.70–1.90 ng/dL; T3, 60–181 ng/dL; anti-TPO antibodies, <35 UI/mL; and Tg, <55 ng/mL.

Thyroid volume was measured by ultrasound before and shortly after the completion of radiation therapy by a staff radiologist at the HCPA Radiology Service, using an ALOKA ProSound 4000 ultrasonography system (Hitachi-Aloka, Japan) with a 15 Hz linear transducer.

Six-hour and 24-hour ^{131}I uptake (10 μCi) were also performed at baseline and after the last radiation therapy session. The testes were performed at the HCPA Nuclear Medicine Service using a GE Millennium gamma camera (GE Healthcare, Milwaukee, WI, USA).

Patients' chemotherapy regimens were recorded, but not analyzed, as there is controversy regarding the potential isolated or add-on effect of chemotherapy on thyroid dysfunction (9,10,11,12).

In patients who underwent computerized planning of 3D conformal radiation therapy, a radiologist singled out the thyroid gland in their planning CT scans. The estimated scattered dose to the thyroid during radiation therapy was then calculated with the Eclipse 10.0 TPS (VARIAN Medical Systems, USA). This software package uses pencil beam convolution and anisotropic analytical algorithms for dose calculation.

The linear accelerator was calibrated with a Farmer-type ionization chamber (PTW TN30004, S/N 244) and a PTW Unidos E electrometer (S/N T10010-00055), in accordance with the IAEA TRS-398 protocol.

Scattered doses to the thyroid gland and to the skin overlying the thyroid isthmus, where TLDs were placed, were estimated in the TPS. Field and total radiation doses were calculated. Dose-volume histograms were used to determine the mean dose to the gland.

During treatment, TLDs were placed onto the skin overlying the thyroid isthmus to measure the radiation dose from each treatment field that reached the thyroid gland. As the thyroid is located only a few millimeters from the surface (skin), one may estimate that the entrance dose (by definition, the absorbed dose at depth of maximum ionization) is the dose absorbed by the gland. Therefore, doses measured by TLDs during treatment provide reliable estimates of the radiation dose deposited in the region of the gland. At least two measurements were obtained for each treatment field in some sessions.

TLDs were provided and analyzed by the Radiation Therapy Quality Program of the José de Alencar Gomes da Silva National Cancer Institute (INCA), affiliated with and operated by the Brazilian Ministry of Health, in Rio de Janeiro. The dosimeters were Harshaw TLD-100 (Thermo RMP) chips (lithium fluoride doped with magnesium and titanium [LiF:MgTi], dimensions: $3x3x0.9mm^3$). One pair of TLDs was used for each treatment field, and the mean of two measured values calculated for analysis. The pair of TLDs was placed into a chrome-nickel steel hemispherical build-up cap (radius 15 mm) to accomplish electronic equilibrium and to ensure maximal readings.

TLD readouts were performed in a PCL3 (Fimel) reader at the Radiation Therapy Quality Program, INCA, Rio de Janeiro. Annealing was performed with an EDG1800 oven (EDG Equipamentos, Brazil) and a Fanem 315SE drying oven (Fanem, Brazil).

The supplementary material (Appendix e1 and Figure e1) includes calculations and corrections for TLD dosimetry.

The procedures carried out on the patients of this study were reviewed and approved by the Research Ethics Committee of the institution where the study was conducted, and were performed in accordance with standards set by the committee and in compliance with the 1975 Helsinki Declaration and its 2000 revision. Assent from patients and informed consent from their legal guardians was obtained before the study.

Statistical analysis

Based on Nishiyama *et al.* (13), who estimated an effect size (E/S) of 1.23 standard deviation units (which is considered a large effect), we chose to use a smaller effect. Thus, for a 40% smaller effect size (E/S=0.74), a significance level of $\alpha=0.05$ and a statistical power of 90% to detect TSH changes before and after radiotherapy, the required sample size was estimated at 21 patients. Considering a maximum loss to follow-up of 20%, the sample size was expanded to 27 patients.

Quantitative laboratory test values (TSH, T4, fT4, T3, Tg and anti-TPO antibodies) were skewed and thus log-transformed prior to analysis. A mixed-effects model for repeated measures was used, with comparison across all four time points of assessment. A similar model was used to assess the effects of sex, age (as a continuous variable and as a dichotomous variable, with the cutoff set at 15 years), the interaction between sex and age, and the total radiation dose scattered to the thyroid. Values were expressed as the mean antilog of log-transformed values (i.e., the geometric mean), with their respective 95% confidence intervals.

Thyroid volumes were expressed as medians, interquartile ranges (P_{25}–P_{75}) and ranges (minimum–maximum). The Wilcoxon signed rank test was used for between-group comparisons of this variable.

Six-hour and 24-hour ^{131}I uptake values, before and after radiation therapy, were expressed as means and standard deviations and subjected to mixed-effects repeated measures analysis.

The significance level was set at $\alpha=0.05$ for all analyses. However, for multivariable analyses, values of $0.10 > P > 0.05$ were considered borderline significant (14). Data were processed and analyzed with SPSS version 18.0 and R version 2.14.1 softwares.

Results

Table 1 describes the overall sample profile.

There were no statistically significant differences across the four time points of assessment with regard to levels of TSH (P=0.575), T4 (P=0.950), fT4 (P=0.510), T3 (P=0.842), Tg (P=0.620) (Figure 1), or anti-TPO antibodies (P=0.546).

Age and sex had no significant impact on TSH (P=0.853 and 0.526, respectively), fT4 (P=0.596 and 0.697, respectively) or anti-TPO antibodies (P=0.620 and 0.907, respectively). However, patients who were younger at the time of radiation therapy exhibited higher levels of T4 (P=0.006), T3 (P=0.032) and Tg (P=0.001). Furthermore, T4 levels were slightly higher in girls than in boys, although the significance of this difference was borderline (P=0.07). There was no such trend toward a gender difference in levels of T3 (P=0.432) or Tg (P=0.435).

Stratification of patients into two age groups (<15 years and >15 years) failed to show any differences in levels of TSH (P=0.390), fT4 (P=0.552) or anti-TPO antibodies (P=0.699). However, there were significant between-group differences in T4 values, which were 9.68 μg/dL (95%CI: 9.00–10.45) in the under-15 group and 8.00 μg/dL (95%CI: 7.23–8.85) in the over-15 group (P=0.003). Considering the effect of sex on T4, female subjects had a higher geometric mean (9.44 μg/dL; 95%CI: 8.47–10.47) than males (8.20 μg/dL; 95%CI: 7.66–8.79) (P=0.03). Furthermore, a potential interaction effect between age and sex on T4 levels was detected, which suggests that younger girls would have the highest levels and older boys, the lowest. However, this finding was only borderline significant (P=0.086) (Figure 2).

When the total radiation dose scattered to the thyroid was added to the T4 model, which already included age and sex, the effect of sex presented no significance (P=0.371), the dose effect was borderline significant (P=0.092), and age remained statistically significant (P=0.009), as in the previous models.

Age had a significant effect on T3, with subjects under the age of 15 years exhibiting higher geometric mean T3 levels (158.12 ng/dL; 95%CI: 131.52–190.55) as compared with older subjects (118.03 ng/dL; 95%CI: 93.54–148.99) (P=0.036). However, in a model adjusting for the combined effects of age (<15 years or >15 years), sex, and total radiation dose scattered to the thyroid, none of the factors was significantly associated with T3.

Geometric mean thyroglobulin levels were higher in under-15s (23.44 ng/mL; 95%CI: 17.86–30.76) than in older subjects (12.25 ng/mL; 95%CI: 8.47–17.70) (P=0.005).

Median thyroid volumes were 3.50 cm^3 (IQR: 1.60–4.41; range: 1.14–12.78) before radiation therapy and 3.87 cm^3 (IQR: 2.06–4.56; range: 1.25–15.83) shortly thereafter. There was no significant difference between these values (P=0.692).

Mean ^{131}I uptake at 6 and 24 hours was 25.4±10.2% and 25.1±8.9% respectively before radiation therapy and 27.2±12.0% and 25.1±8.6% respectively after radiation therapy. There were no statistically significant differences among these four values (P=0.92).

Discussion

Most studies of the effects of radiation on the thyroid are retrospective, which hinders assessment of the dose–injury relationship. In children the distance between the thyroid gland and other organs is shorter due to body size, and cell replication is greater. These factors might increase the susceptibility of the gland even if scattered radiation doses were lower.

In this study, there were no differences in TSH, T4, fT4, total T3, Tg or anti-TPO values over the 3-month assessment period. The radiation dose scattered to the thyroid may have been too low for detection of any changes within this period, which does not rule out the possibility of such changes surfacing during long-term follow-up. Furthermore, the sample size may have been too small to demonstrate changes. Nishiyama *et al.* (13) and Bakhshandeh *et al.* (15) reported decreased TSH and increased T4 levels, the former occurring shortly after radiation therapy and the latter during treatment. In these studies, radiation was directed to the neck or head and neck respectively, and the dose scattered to the thyroid was higher. The median dose scattered to the thyroid in the present study was 296.6 cGy, at the end of treatment, whereas the first changes in the Bakhshandeh *et al.* study (15) were only detected at 1200 Gy.

In the Childhood Cancer Survivor Study (CCSS) (8), the incidence of hypothyroidism was higher in children receiving radiation therapy after the age of 15 than in younger patients. In our study, using the same stratification strategy, detectable difference were observed in T4, T3 and Tg levels, which were higher in patients under the age of 15. T4 levels were also higher in females. These differences may correspond to physiological behavior (16,17).

In our sample, there were no differences in thyroid volume before and shortly after radiation therapy. This may have been due to the rather short study interval. In a prior, retrospective study assessing late effects of non directed radiation therapy on the thyroid, we detected hypothyroidism and smaller thyroid volume, and we inferred this two findings were associated (7).

In this study, ^{131}I uptake was performed to detect cell injury, which could not be observed by this method. However, the optimal timing for scans was unknown, and there was no evidence as to whether radiation scattered to the thyroid would produce any significant changes. This technique was previously used in patients who received radiation therapy to the neck and presented with clinical signs and symptoms of thyrotoxicosis within 2 weeks of treatment, and were thus diagnosed with thyrotoxic thyroiditis (18,19).

This was the first prospective study assessing early effects of scattered radiation on the thyroid in children and adolescents undergoing radiation therapy targeted to different sites. Perhaps a more sensitive method would be required to detect radiation injury induced by the low doses to which patients were exposed in this study—a method such as color Doppler ultrasonography, which is capable of demonstrating vascular changes and changes in echogenicity (15). It is important that such early changes be known so that prophylactic measures can be instituted in an attempt to prevent the development of hypothyroidism. We plan to continue follow-up of the patients included in this study so as to observe the long-term incidence of functional and structural changes and their correlation with the dose of radiation scattered to the thyroid gland.

Conclusion

Despite the increasingly targeted nature of radiation therapy and ever-greater care concerning protection of tissues and organs outside the target field, incidental radiation exposure still occurs. This may produce delayed sequelae that must be known ahead, so they can be prevented and treated. In this study, the scattered doses measured had no acute effect on thyroid function or volume in children and adolescents. Larger studies using more sensitive methods are required to confirm these findings.

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Table 1. Sample profile

Variable	n = 31
Age, years (interquartile range)	7.0 (3.6–16.0)
Sex, n (%)	
Male	22 (72)
Female	9 (29)
Cancer type, n (%)	
Abdominal neuroblastoma	7 (22.6)
Acute lymphoblastic leukemia	6 (19.4)
Hodgkin’s lymphoma	4 (12.9)
Retinoblastoma	2 (6.5)
Wilms’ tumor	2 (6.5)
Thoracic neuroblastoma	2 (6.5)
CNS tumor	2 (6.5)
Acute myeloid leukemia	1 (3.2)
Non-Hodgkin lymphoma	1 (3.2)
Medulloblastoma	1 (3.2)
Rhabdomyosarcoma	1 (3.2)
Synovial sarcoma	1 (3.2)
Primitive neuroectodermal tumor	1 (3.2)
Irradiated region, n (%)	
Abdomen	7 (22.6)
Thoracic	7 (22.6)
Head	6 (19.4)
Head and spine	3 (9.7)
Orbit	2 (6.5)
Lower extremity	1 (3.2)
Pelvis	1 (3.2)
Testicle	1 (3.2)
Lateral cervical	1 (3.2)
Upper extremity	1 (3.2)
Suprascapular	1 (3.2)
Total prescribed dose, cGy	3060 (2160 – 4140)

Scattered dose to the thyroid, cGy	296.6 (16.7 – 1709.02)
Post chemotherapy	23 (74.1)
Concomitant chemotherapy	7 (22.5)
Without chemotherapy	1(3.2)

Data are expressed as n (%) or median (interquartile range).

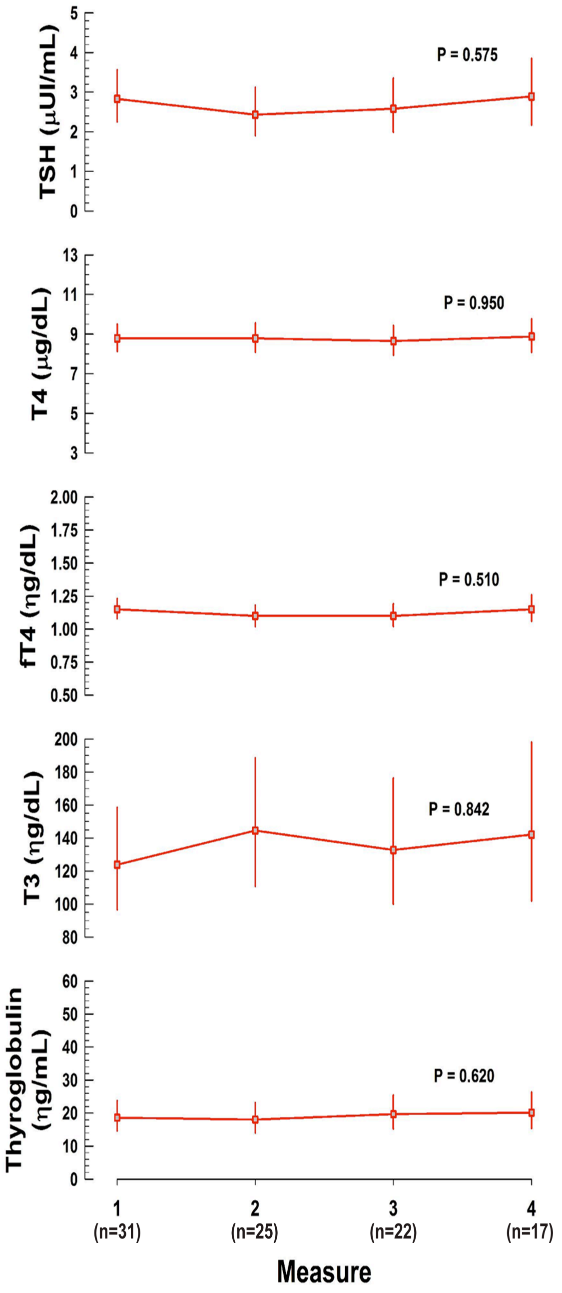

Figure 1. Line plots with geometric means and 95% confidence intervals representing the variation observed along four measurements for selected variables.

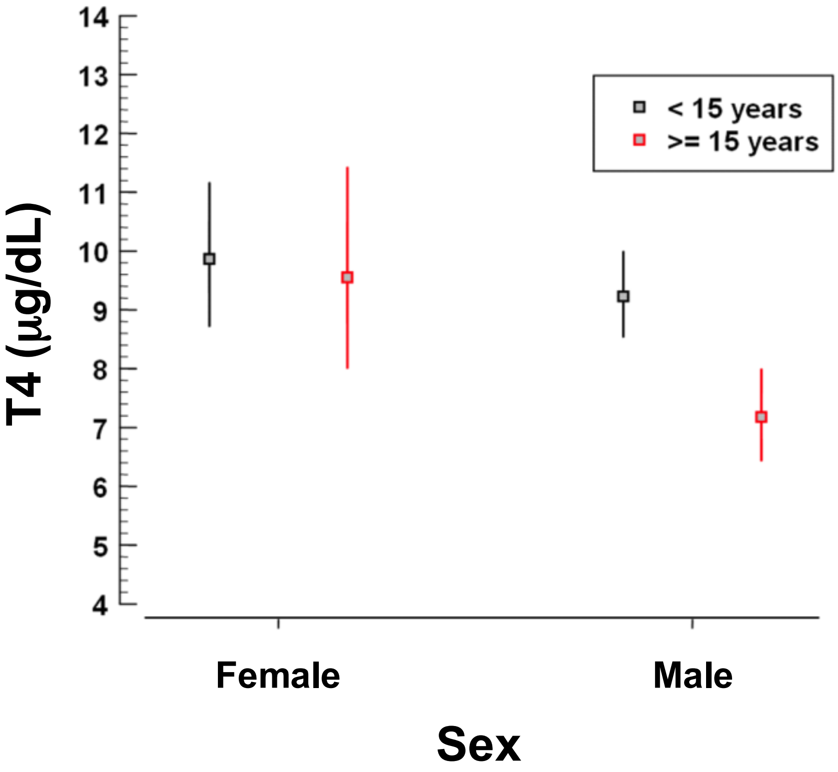

Figure 2. Geometric mean T4 levels, stratified by sex and age (cutoff value: 15 years), with 95% confidence intervals.

Appendix e1

Determination of the dose absorbed into TLDs took into account background radiation (BG), the dose linearity correction factor (klin), and the calibration coefficient (CC) of the TLDs employed, as this was a relative dosimetry system—i.e. doses were obtained by comparison between the TLD and a TLD exposed to a known radiation dose under reference conditions. Although the energy dependence of TLDs is well known, it was not taken into account, as all measurements were obtained at the same energy of dosimeter calibration. The fading effect was also not taken into account, as all dosimeters were irradiated and read together on the same day.

Under reference conditions for TLD irradiation, the absorbed dose used in the experimental array was 40 cGy. TLDs were placed on the surface of a 5 cm-thick acrylic slab phantom (to simulate body mass), at center beam, with a distance of 100 cm between the radiation source and the surface, a 10x10cm2 field, a dose rate of 200 MU/min, and a nominal energy of 6 MV.

TLDs were calibrated by adjusting the measurements in thermoluminescent (TL) signal with the doses provided by the linear accelerator, taking into account a dose of 40 cGy (the reference dose, Dref), which was that expected for the majority of patients. To deliver this dose, the accelerator was set to 164 MU.

Dose counts are shown in the reader as a TL signal and then converted to an absorbed dose unit (cGy). This value is then multiplied by the calibration coefficient (CC) after subtracting the background dose (BG).

The calibration coefficient (CC) was calculated with Equation 1:

Equation 1

$$\boxed{\mathrm{CC} = \frac{\mathrm{D_{ref}}}{\mathrm{TL} - \mathrm{BG}}}$$

The uncorrected dose (D_{uncorr}) is the uncorrected dose at the measurement TLD, as per Equation 2:

Equation 2

$$\boxed{D_{uncorr} = CC(TL - BG)}$$

Finally, the patient, or corrected, dose was calculated by correction of Duncorr by the aforementioned factors (Equation 3):

Equation 3

$$D_{corr} = D_{uncorr}.k_{lin}$$

To correct for nonlinear dose-response, a linearity correction curve was plotted for the radiation beam (Figure 1), using 15 pairs of TLDs in the same experimental array used for irradiation of the calibration TLDs.

Three pairs of TLDs were used for each of the five known doses: 10, 20, 35, 50, and 85 cGy. These doses were chosen in view of the expected doses for the type of treatment used in the study sample. The vertical axis in Figure e1 is the correction factor due to nonlinearity (klin).

The determining points (klin) of the best-fit curve for correction of nonlinearity were calculated using Equation 4, where M is the TLD readout (or TL signal), D is the absorbed dose, and parameters with an index of zero represent reference values or normalization points.

Equation 4

$$\boxed{\mathrm{k}_{\mathrm{lin}} = \frac{\left[\dfrac{\mathrm{M}_{\mathrm{D}_0}}{\mathrm{D}_0}\right]}{\left[\dfrac{\mathrm{M}_{\mathrm{D}}}{\mathrm{D}}\right]}}$$

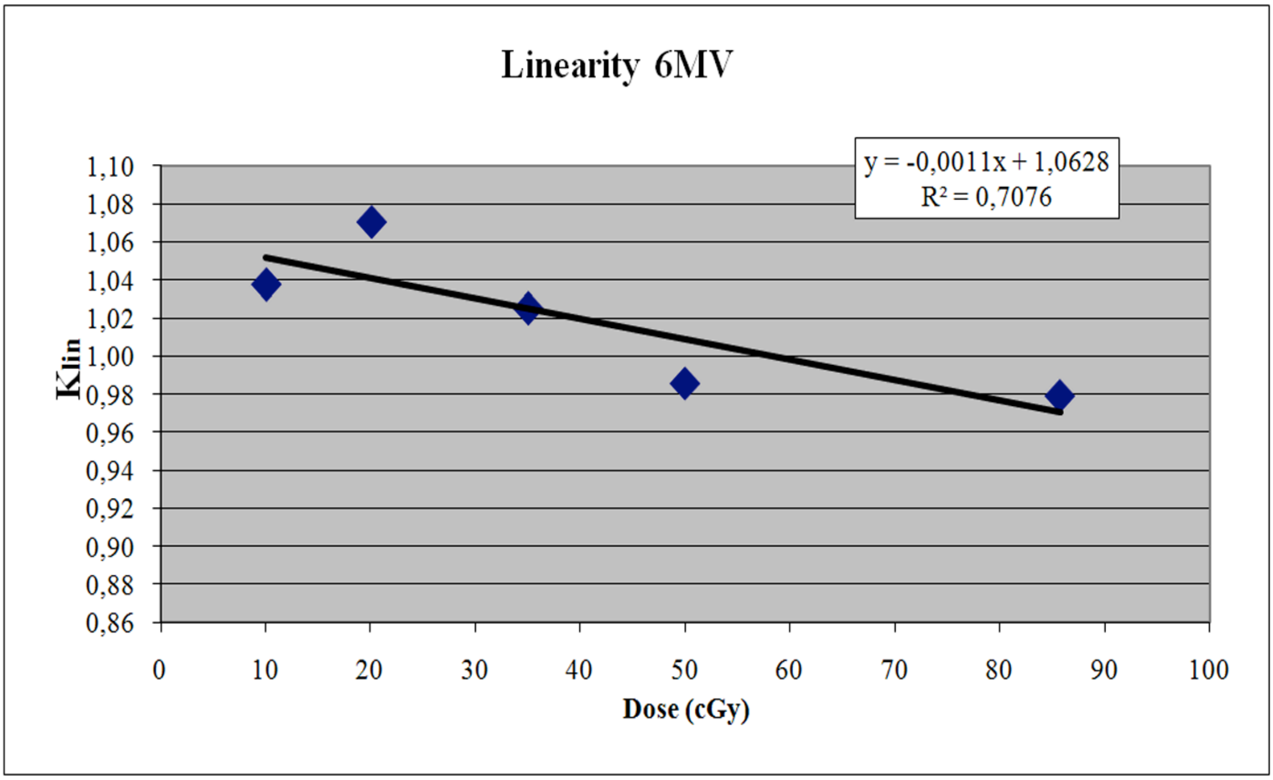

Figure e1. Plot and trendline of the linearity coefficient of TLD values as a function of absorbed dose in the acrylic phantom.

Parte III

Artigo original

IN VIVO DOSIMETRY OF THYROID DOSES FROM DIFFERENT IRRADIATED SITES IN CHILDREN AND ADOLESCENTS

In vivo dosimetry of thyroid doses from different irradiated sites in children and adolescents

Running title: Dosimetry of thyroid doses from different irradiated sites

Cassiane Cardoso Bonato, MD, MSc,[1] Henrique Bregolin Dias,[1] Michele da Silva Alves,[2] Lucas Ost Duarte,[2] Telpo Martins Dias,[2] Maiara Oliveira Dalenogare,[2] Claudio C B Viegas, MSc,[3] Regina Helena Elnecave, MD, PhD[1]

[1]Graduate Program in Internal Medicine, Endocrinology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil.

[2]Radiation Therapy Center, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS, Brazil.

[3]Ionizing Radiation Quality Program, Brazilian National Cancer Institute (INCA) José de Alencar Gomes da Silva, Ministério da Saúde, Rio de Janeiro, RJ, Brazil.

Corresponding author

Regina Helena Elnecave

Endocrinology Service, HCPA

Ramiro Barcelos, 2350, 12, 4º floor

CEP 90035-003 – Porto Alegre, RS

Phone/Fax: (51) 3359.8127

E-mail: rhelnecave@gmail.com

Funding: Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundo de Incentivo à Pesquisa (FIPE) of Hospital de Clínicas de Porto Alegre (HCPA).

Conflicts of Interest: The authors have nothing to declare.

Acknowledgement: The authors would like to thank Paul Clivland Oliveira for his major contribution to the dosimetry portion of this study.

Summary

This study used thermoluminescent dosimeters (TLDs) to measure, in vivo, the scattered dose to the thyroid region in children receiving radiation therapy for a variety of non-thyroid cancers. Results were then compared with treatment planning system (TPS) estimated doses. Differences were detected between TLD-measured and TPS-estimated doses. *In vivo* dosimetry enables measurement of radiation scatter to the thyroid, regardless of the site of irradiation.

Abstract

Purpose: *In vivo* dosimetry assesses the quality of radiotherapy and enables measurement of radiation scattered to locations outside the target field. Thyroid tissue is sensitive to radiation, even at doses <10 cGy. In this study, thermoluminescent dosimeters (TLDs) were used *in vivo* to measure the scattered dose to the thyroid region in children and adolescents treated for various types of non-thyroid cancer. Results were then compared with the dose estimated by the treatment planning system (TPS).

Methods and Materials: During radiation therapy of 16 children and adolescents, 102 measurements of radiation scattered to the thyroid region were obtained. Seventy-two measurements were valid for comparison with TPS-estimated doses. The biases and 95% limits of agreement (95%LA) of the TPS/TLD ratios in relation to TLD measurement were calculated by the Bland-Altman method.

Results: The overall TPS/TLD bias was 1.02 (95%LA 0.05 to 21.09). When bias was stratified by treatment field, the TPS overestimated TLD values at doses <1 cGy and overestimated them at doses >10 cGy. However, these disagreements depend on anatomical location. The greatest bias was found in pelvic and abdominal measurements: 15.01 (95%LA 9.16 to 24.61) and 5.12 (95%LA 3.04 to 8.63) respectively. There was good agreement in orbit, head, and spine measurements: bias 1.52 (95%LA 0.48 to 4.79), 0.44 (95%LA 0.11 to 1.82) and 0.83 (0.39 to 1.76) respectively. There was small agreement with broad limits for lung and mediastinal measurements: 1.13 (95%LA 0.03 to 40.90) and 0.39 (95%LA 0.02 to 7.14) respectively.

Conclusion: Even in radiation treatment of organs remote from the thyroid, the gland absorbs ionizing radiation due to scattering, and this exposure should not be neglected. The scattered dose can be measured with TLDs, and TPS algorithms for outside structures should be improved.

Introduction

The effects of ionizing radiation on the thyroid gland have been studied for decades (1,2). The association between hypothyroidism, hyperthyroidism, thyroid nodules, thyroid cancer and radiation is often reported (3,4), but the thresholds of absorbed dose, the mechanism of injury, and some risk factors have not been clearly established. The thyroid is particularly sensitive to radiation and may be directly or indirectly exposed to it during radiation therapy of other organs (5). Doses as low as 10 cGy are known to be associated with an increased incidence of thyroid nodules and thyroid cancer (6,7).

Children are more sensitive to injury caused by ionizing radiation, due to their greater rate of cell replication and to their longer life expectancy. Furthermore, the distances between body segments in relation to the site of irradiation are smaller in children. Despite the concern with the use of more targeted radiation therapy techniques, dosimetry studies have shown that radiation scatters to the thyroid gland (8,9).

Knowing the radiation dose that reaches healthy tissues plays a key role in determining clinical effects over time (tolerance doses). Older data on damage to normal tissues by radiation therapy were based on retrospective studies or on the clinical experience of radiation therapists (10). Modern computed tomography (CT)-assisted techniques for planning of three-dimensional conformal radiation therapy enable mathematical estimation of the radiation dose scattered to healthy tissues near the target field during treatment, by means of absorbed radiation dose and volume of the irradiated organ. The Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) study provided information on dose, volume, and prognosis for different organs, including, more recently, the thyroid gland, taking into account the development of hypothyroidism (11,12). A retrospective study of patients with Hodgkin’s lymphoma showed that, thyroid volume percentages in excess of 10, 20, and 30 Gy (V10, V20, and V30) were significantly associated with hypothyroidism at mean doses of 32 Gy. Thyroid V30 was an independent predictor of the risk of hypothyroidism (13).

The quality of radiation therapy can be measured by means of in phantom or *in vivo* dosimetry (14). Among the various techniques available for absolute dosimetry, thermoluminescent dosimeters (TLDs) have been widely used for their simplicity, excellent spatial resolution, and ability to integrate the dose absorbed over a certain period of time (15). TLDs can be used on the body surface or within body cavities. Most studies that use TLDs focus on quantification of the main beam dose, and scattered dose studies are usually performed in phantoms, not *in vivo* (16). In the present study, we evaluated the agreement between scattered radiation dose to the thyroid as predicted by a treatment planning system (TPS) for three-dimensional conformal radiation therapy and that measured by TLDs placed on the skin overlying the thyroid region in a sample of children treated for a variety of non-thyroid cancers.

Materials and methods

Sample

Sixteen patients with a mean age of 6.99 years (range 1.3–17.7 years) received radiation therapy for a variety of non-thyroid cancers in several regions of the body. Treatments were administered with two linear accelerators: a Siemens Mevatron MD (SN 3054, nominal photon energy 6 MV) and a Varian 23EX (SN 3595, nominal energy 6 and 15 MV) at the radiation therapy center of a large tertiary care hospital.

Skin entrance radiation doses at the thyroid region were measured with TLDs. Eleven patients also underwent three-dimensional radiation therapy planning in which the thyroid region was included in the planning CT scan volume, thus enabling estimation of doses scattered to the gland during treatment. Doses measured by the TLDs were then compared with the estimates produced by the TPS mathematical model.

A total of 72 measurements were used in this comparison, as five patients either did not undergo CT-based treatment planning or did not have the thyroid gland included in their scans.

In vivo dosimetry

During treatment, TLDs were placed onto the skin overlying the thyroid isthmus measured those of radiation from each treatment field that reached the thyroid gland. As the thyroid is located only a few millimeters from the surface (skin), one may estimate that the entrance dose (by definition, the absorbed dose at depth of maximum ionization) is the dose absorbed by the gland. Therefore, doses measured by TLDs during treatment provide reliable estimates of the radiation dose deposited in the region of the gland. At least two measurements were obtained for each treatment field in some sessions.

TLDs were provided and analyzed by the Radiation Therapy Quality Program of the Brazilian National Cancer Institute José de Alencar Gomes da Silva (INCA), Ministério da Saúde, in Rio de Janeiro. The dosimeters were Harshaw TLD-100 (Thermo RMP) chips (lithium fluoride doped with magnesium and titanium [LiF:MgTi], dimensions: 3x3x0.9mm^3). One pair of TLDs was used for each treatment field, and the mean of two measured values calculated for analysis. The pair of TLDs was placed into a chrome-nickel steel hemispherical build-up cap (radius 15 mm) to accomplish electronic equilibrium and to ensure maximal readings.

Determination of the dose absorbed into TLDs took into account background radiation (BG), the dose linearity correction factor (k_{lin}), and the calibration coefficient (CC) of the TLDs employed, as this was a relative dosimetry system—i.e. doses were obtained by comparison between the TLD and a TLD exposed to a known radiation dose under reference conditions. Although the energy dependence of TLDs is well known, it was not taken into account, as all measurements were obtained at the same energy of dosimeter calibration. The fading effect was also not taken into account, as all dosimeters were irradiated and read together on the same day.

Under reference conditions for TLD irradiation, the absorbed dose used in the experimental array was 40 cGy. TLDs were placed between two 5 cm-thick acrylic slabs (as a phantom to simulate body mass), at center beam, with a distance of 100 cm between the radiation source and the surface, a (10x10) cm^2 field, a dose rate of 200 MU/min, and a nominal energy of 6 MV.

TLDs were calibrated by adjusting the measurements in thermoluminescent (TL) signal with the doses provided by the linear accelerator, taking into account a dose of 40 cGy (the reference dose, D_{ref}), which was the most expected for the majority of patients. To deliver this dose, the accelerator was set to 164 MU.

The linear accelerator was calibrated with a Farmer-type ionization chamber (PTW TN30004, S/N 244) and a PTW Unidos E electrometer (S/N T10010-00055), in accordance with the IAEA TRS-398 protocol.

TLD readouts were performed in a PCL3 (Fimel) reader at the Radiation Therapy Quality Program, INCA, Rio de Janeiro. Annealing was performed with an EDG1800 oven (EDG Equipamentos, Brazil) and a Fanem 315SE drying oven (Fanem, Brazil).

Dose counts are shown in the reader as a TL signal and then converted to an absorbed dose unit (cGy). This value is then multiplied by the calibration coefficient (CC) after subtracting the background dose (BG).

The calibration coefficient (CC) was calculated with Equation 1:

Equation 1

$$\boxed{CC = \frac{D_{ref}}{TL - BG}}$$

The uncorrected dose (D_{uncorr}) is the uncorrected dose at the measurement TLD, as per Equation 2:

Equation 2

$$\boxed{D_{uncorr} = CC(TL - BG)}$$

Finally, the patient, or corrected, dose was calculated by correction of D_{uncorr} by the aforementioned factors (Equation 3):

Equation 3

$$D_{corr} = D_{uncorr}.k_{lin}$$

To correct for nonlinear dose-response, a linearity correction curve was plotted for the radiation beam (Figure 1), using 15 pairs of TLDs in the same experimental array used for irradiation of the calibration TLDs.

Three pairs of TLDs were used for each of the five known doses: 10, 20, 35, 50, and 85 cGy. These doses were chosen in view of the expected doses for the type of treatment used in the study sample. The vertical axis in Figure 1 represents the correction factor for nonlinearity (k_{lin}).

The determining points (k_{lin}) of the best-fit curve for correction of nonlinearity were calculated using Equation 4 where M is the TLD readout (or TL signal), D is the absorbed dose, and parameters with an index of zero represent reference values or normalization points.

Equation 4

$$\boxed{k_{lin} = \frac{\left[\frac{M_{D_0}}{D_0}\right]}{\left[\frac{M_D}{D}\right]}}$$

Computerized planning of 3D conformal radiation therapy

In patients who underwent computerized planning of 3D conformal radiation therapy, a radiologist singled out the thyroid gland in their planning CT scans. The estimated scattered dose to the thyroid during radiation therapy was then calculated with the Eclipse 10.0 TPS (VARIAN Medical Systems, USA). This software package uses pencil beam convolution and anisotropic analytical algorithms for dose calculation.

Scattered doses to the thyroid gland and to the skin overlying the thyroid isthmus, where TLDs were placed, were estimated in the TPS. Field and total radiation doses were calculated. Dose-volume histograms were used to determine the minimum, mean, and maximum dose to the gland, and the mean dose was used for statistical analyses.

The distance between the skin overlying the thyroid isthmus to the treatment field hot spot was also measured.

In two patients who received spinal irradiation, part of the main beam dose also contributed to the measured doses.

The procedures carried out with the patients in this study were reviewed and approved by the Research Ethics Committee of the institution where the study was conducted, in accordance with standards set by the committee and in compliance with the 1975 Helsinki Declaration and its 2000 revision. Assent from patients and informed consent from their legal guardians was obtained before the study.

Statistical analysis

This was a cross-sectional study based on a sample of children and adolescents who underwent treatment at the radiation therapy service of a large tertiary care hospital. The sample comprised 16 patients, from whom 102 scattered dose measurements were obtained by TLDs and 72 paired dose estimates were calculated by TPS. This number is within the range suggested by Altman (17) and Bland (18), who propose that 50 to 100 observations are required to measure agreement in method comparison studies.

Normally distributed quantitative data were expressed as means and standard deviations. Skewed data were expressed as medians and ranges, and categorical data, as counts and percentages.

To evaluate the difference between TPS estimates of radiation scattered to the thyroid gland (TPSthyroid) and to the point of skin overlying the thyroid isthmus (TPSskin), where the TLDs were placed, data were log-transformed to reduce asymmetry. Groups were then compared using a linear mixed effects model, which takes into account the fact that repeated observations are available for each patient.

To assess the correlation between TPSskin and TLD, Pearson correlation coefficients were calculated for the log-transformed measurements using a mixed model. Due to the known limitations of the Pearson correlation coefficient for analysis of agreement, we chose to use the Bland–Altman method to compare actual TLD-measured doses of radiation and TPSskin estimates. As TPSskin and TLD values were asymmetrically distributed, we chose to use TPSskin/TLD ratios as an alternative to logarithms (19). Furthermore, only TLD measurements rather than the mean of TPSskin and TLD measurements were plotted onto the x-axis, as recommended when one of the methods under study is considered the gold standard (19). Results were then plotted on log scale to facilitate visualization of the calculated values. Repeated measures were clustered by patient and analyzed with a mixed effects model, which estimated bias values (mean difference between ratios for each method) and 95% limits of agreement (95%LA).

To assess the impact of prescribed radiation dose and TLD–hot spot distance on TLD measurements, data were log-transformed (to reduce asymmetry), z scores were calculated (to standardize units), and a mixed model was used for analysis.

The significance level adopted was $\alpha=0.05$.

Data were processed and analyzed in the SPSS 18.0, R 2.14.1 and SigmaPlot 11.0 software environments.

Results

The sample profile is shown in Table 1.

Comparison between TPSthyroid and TPSskin values did not reach statistical significance (P=0,842). Therefore, TPSskin was considered appropriate for comparison with actual TLD-measured doses.

There was a significant correlation between the TLD-measured dose and the TPSskin-estimated dose (r=0.94, P<0.001) (Figure 2).

Analysis of Bland-Altman plots for the TPSskin/TLD ratio at different levels of radiation showed that the bias of the TPS/TLD ratio behaved differently in relation to TLD-measured doses. Below 1 cGy, the TPS overestimated the actual dose, as measured by TLDs. Between 1 and 10 cGy, the bias ranged around 1, showing agreement between the two methods. Above 10 cGy, the TPS was more likely to underestimate the scattered dose as compared with actual TLD measurements. Although the overall bias was small (bias = 1.02), the 95% limits of agreement were broad (95%LA: 0.05 to 21.09) (Figure 3A). Analysis by site of irradiation showed different TPS/TLD biases according to the proximity of the thyroid gland to the treatment field.

Figures 3 and 4 show dose behavior by site of irradiation. The dose scattered to the thyroid was <0.1 cGy when the pelvis or abdomen were irradiated. The TPS overestimated the scattered dose, and there was little agreement between TPS and TLD measurements—bias of 15.01 (95%LA 9.16 to 24.61) and 5.12 (95%LA 3.04 to 8.63) respectively (Figures 3B and 3C).

The TPS and TLDs provided similar measurements of radiation scattered to the thyroid when the site of irradiation was the orbit, head, or spine, with biases of 1.52 (95%LA 0.48 to 4.79), 0.44 (95%LA 0.11 to 1.82), and 0.83 (95%LA 0.39 to 1.76) respectively (Figures 3D, 3E and 3H).

When the lungs or mediastinum were irradiated, TPS estimates and TLD measurements behaved in a similar fashion, with broad limits of agreement and a bias of 1.13 (95%LA 0.03 to 40.90) and 0.39 (95%LA 0.02 to 7.14) respectively (Figures 3F and 3G). At doses >10 cGy, the TPS underestimated the scattered dose up to tenfold as compared to TLD-measured values.

The TLD detected irradiation of the thyroid region even in patients in whom no TPS had been used and whose treatment site was remote from the thyroid.

The distance between the skin overlying the thyroid isthmus to the treatment field hot spot of radiation therapy had a greater impact on TLD measurements ($b = -2.26$; $P<0.001$) than prescribed dose ($b = 1.26$; $P<0.001$), although the two impacts were independent.

Discussion

Most dosimetry studies on scattered dose to the thyroid gland are performed in-phantom, and are thus retrospective simulations of radiation therapy (8,20). A previous study conducted *in vivo* dosimetry of the scattered dose to the thyroid, using TLDs, in adult patients undergoing radiation therapy for breast cancer (21). In the present study, measurements were obtained in children who were receiving radiation for cancers at a variety of sites, with different doses and several distances from the hot spot. There was significant scatter of radiation to the thyroid gland, even when treatment was targeted at different organs, in different locations, that did not include the thyroid in the treatment field.

TPSs are commonly used to estimate the dose scattered to non-target organs, such as the thyroid gland, which can in fact be measured with TLDs, as we did not find any difference between dose measurement on the skin and TPS-based estimation of doses within the gland. At sites where there was good agreement between both measurements, such as the orbit, head, and spine, TPS estimates are quite reasonable. However, at more remote locations, such as the abdomen and pelvis, the TPS overestimated the scattered dose as compared with actual doses measured by TLDs. The algorithms used for TPS dose estimation are developed for calculation of radiation doses within the treatment field—in fact, only a few centimeters from the field edges—, which also may have influenced bias findings.

Agreement was low and the limits of agreement broad for the lung and mediastinum because the thyroid was too close to the dosimetric penumbra zone, that is, the edges of the treatment field, where the irradiated dose is 20% to 80% of the prescribed dose at the central axis.

In children, the distance between body segments and the irradiation field is smaller, which causes concern with respect to the percent dose scattered to the thyroid gland. Our study showed that the distance from the thyroid to the treatment field hot spot has a greater impact than prescribed dose on TLD measurements, although the two impacts were independent. Even when the thyroid was farther from the irradiation field TLDs measured doses that although small were enough to cause injuring (6).

Conclusion

Any exposure of the thyroid gland to radiation is cause for concern, particularly in children. *In vivo* dosimetry plays an important role in the characterization of real hazards with respect to dose escalation. As TPSs are constructed with algorithms that have treatment as their objective, correction of mathematical coefficients for the estimated dose that reaches major structures outside the main treatment field may be enhanced with the knowledge obtained from *in vivo* dosimetry. TLDs and TPS exhibit excellent agreement with radiation doses at the central-axis position, but further studies are required to determine their behavior for different energy peaks outside the central axis.

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Table 1. Sample profile

Variable	n=16
Age, years (range)	5.7 (1.3–17.7)
Sex, n (%)	
Male	11 (68.8)
Female	5 (31.3)
Cancer type, n (%)	
Adrenal neuroblastoma	3 (18.8)
Acute lymphoblastic leukemia	2 (12.5)
Retinoblastoma	2 (12.5)
Wilms' tumor	2 (12.5)
Acute myeloid leukemia	1 (6.3)
Hodgkin's lymphoma	1 (6.3)
Non-Hodgkin lymphoma	1 (6.3)
Medulloblastoma	1 (6.3)
Mediastinal neuroblastoma	1 (6.3)
Rhabdomyosarcoma	1 (6.3)
CNS tumor	1 (6.3)
Irradiated region, n (%)	
Abdomen	3 (18.8)
Mediastinum	3 (18.8)
Head	2 (12.5)
Head and spine	2 (12.5)
Orbit	2 (12.5)
Lower extremity	1 (6.3)
Pelvis	1 (6.3)
Lung	1 (6.3)
Testicle	1 (6.3)
Thyroid–hot spot distance, cm	14 (4–27)
Total prescribed dose, cGy	3600 (1350–14400)
Scattered dose to the thyroid (TPS), cGy	
Min	92 (9–3780)

Mean	186 (12–4111)
Max	542 (17–4370)
Scattered dose to the thyroid (TLD), cGy	283 (1–6754)

Data are expressed as n (%) or median (range).

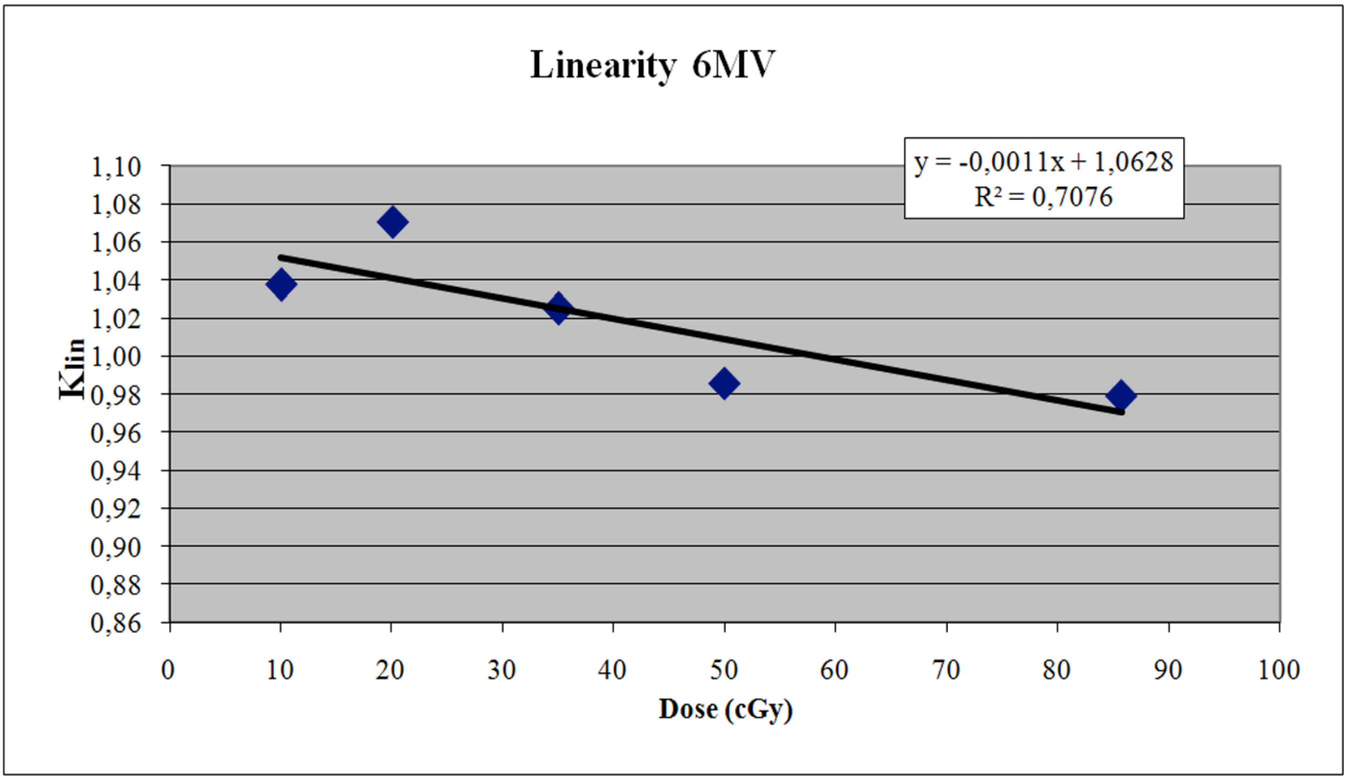

Figure 1. Plot and trendline of the linearity coefficient of TLD values as a function of absorbed dose in the acrylic phantom.

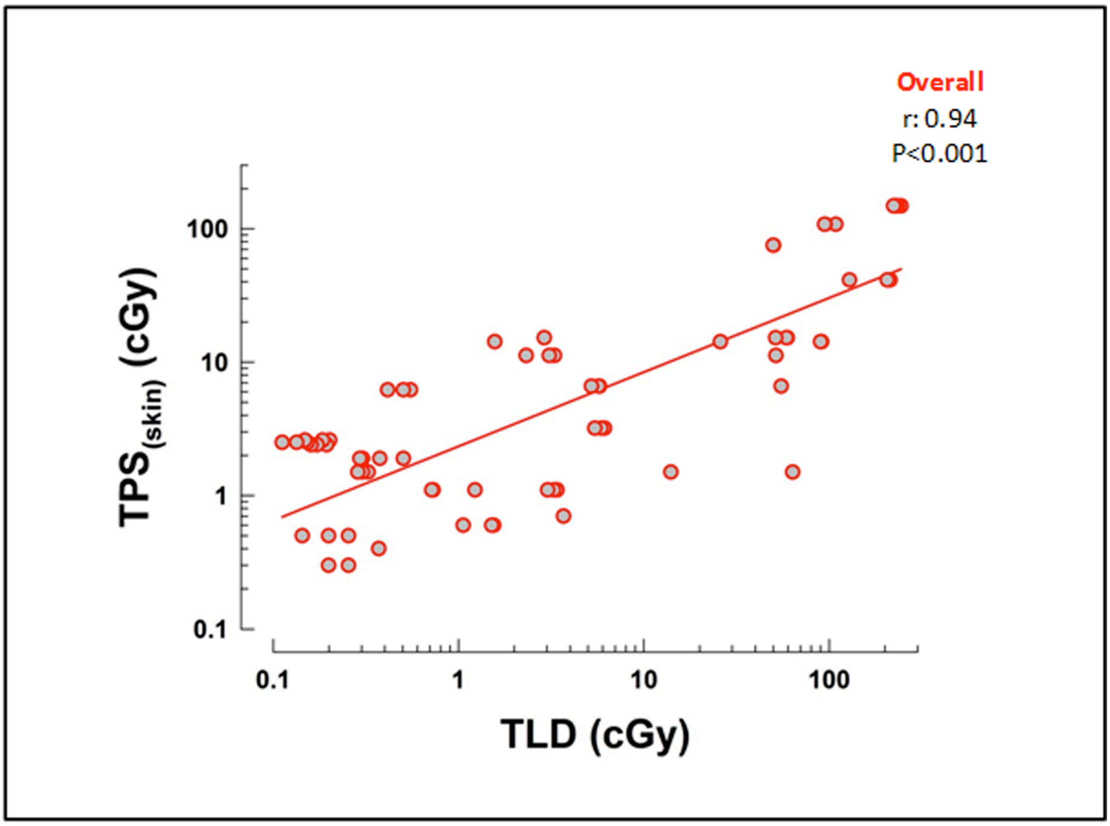

Figure 2. Scatterplot representing the relationship between TPS_{skin} and TLD values. r: Pearson correlation coefficient; p: statistical significance.

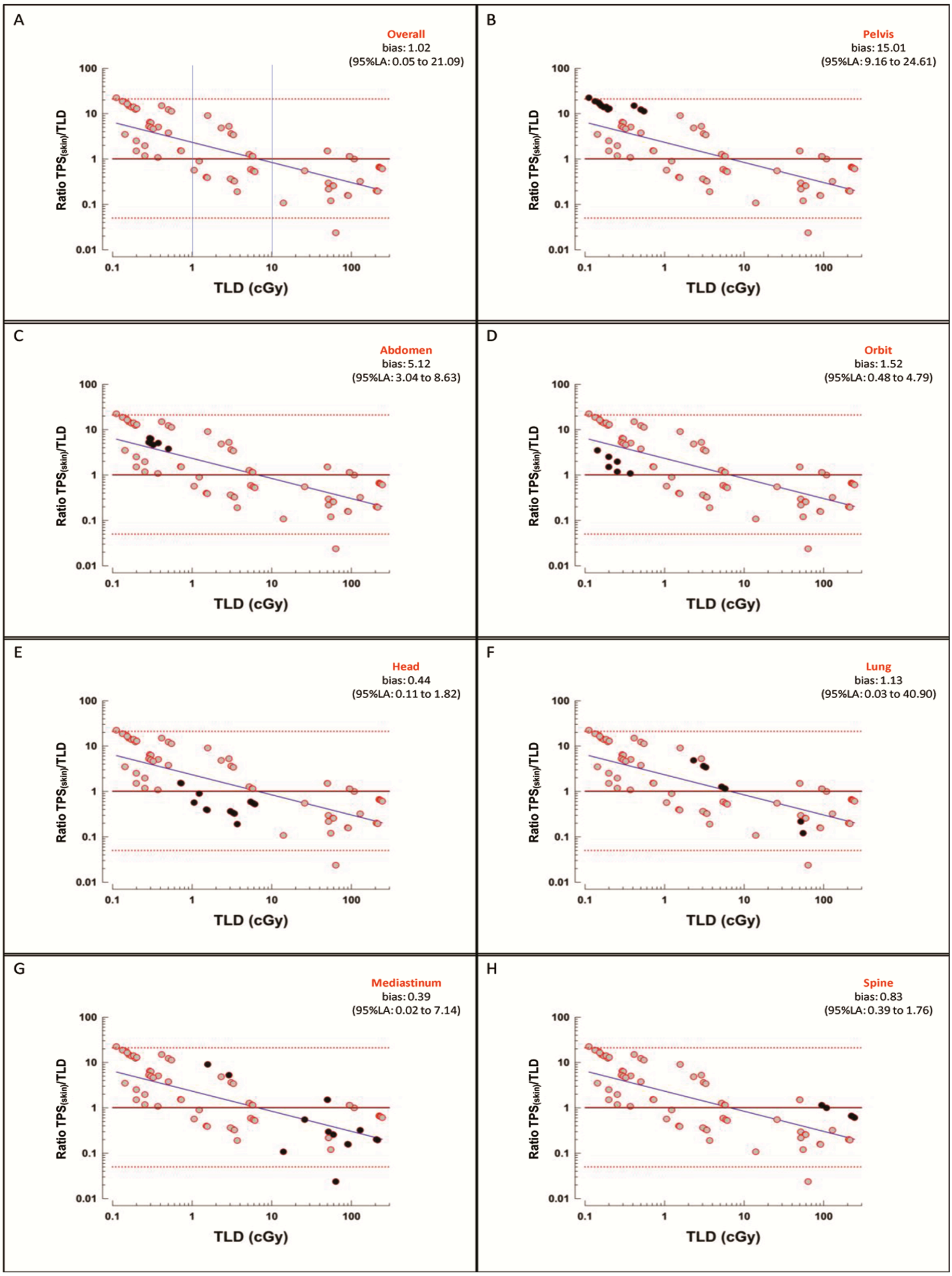

Figure 3. Bland–Altman plots representing the overall agreement of measurements between TPS_{skin} and TLD values, stratified by anatomical site, with their respective observations (black dots) and 95% limits of agreement.

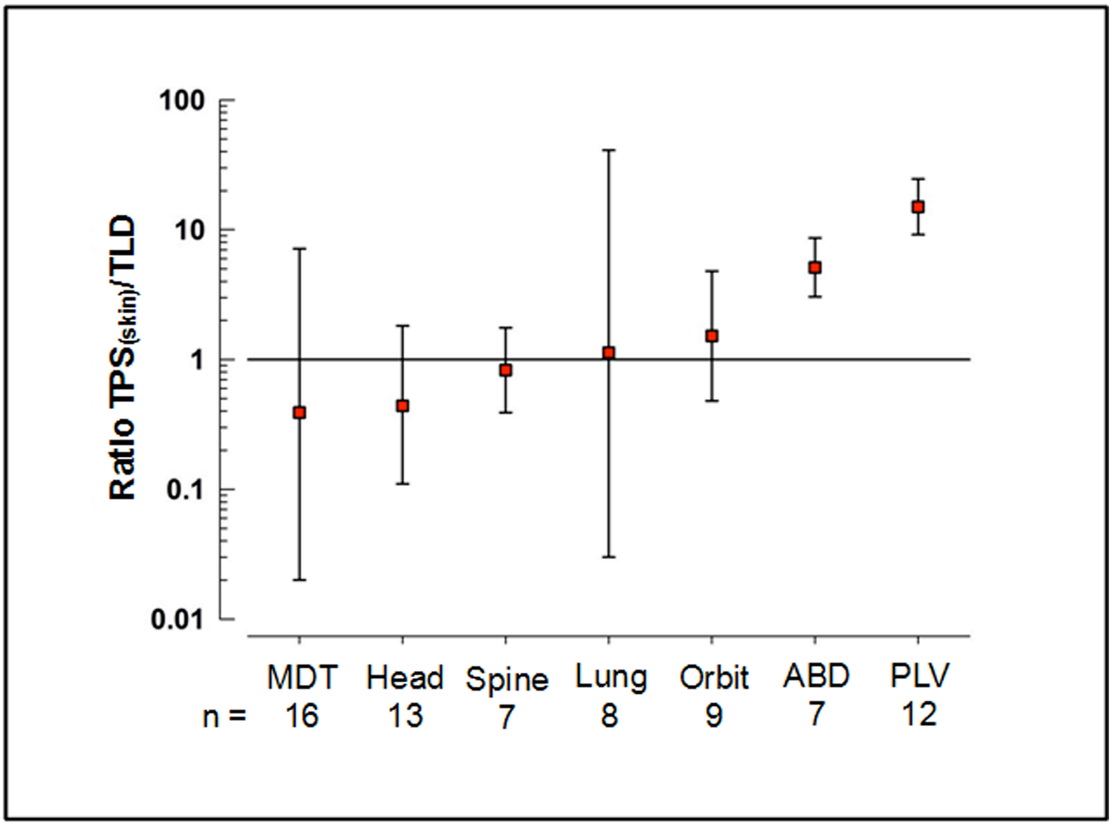

Figure 4. 95% limits of agreement for TPS(skin)/TLD ratios, by anatomical site. MDT = Mediastinum, ABD = Abdomen and PLV = Pelvis.

Considerações Finais

Mudanças no *status* hormonal tireoidiano podem ser mais significativas em crianças do que em adultos, uma vez que esse hormônio é necessário para o desenvolvimento cerebral e para o crescimento. Muitas vezes, os sintomas da disfunção tireoidiana são confundidos ou interpretados de forma errônea, sendo atribuídos à doença de base desses pacientes ou aos medicamentos utilizados no tratamento da neoplasia, resultando em diagnóstico tardio da lesão glandular.

Os resultados desta tese demonstraram que pode haver espalhamento de dose de radiação significativa para a tireoide, quando crianças e adolescentes são submetidos à radioterapia, mesmo nos casos em que essa glândula se encontra distante do campo de tratamento. Não foram observadas, com os métodos utilizados, alterações agudas da função ou do volume tireoidiano. Contudo, serão necessários estudos prospectivos precoces com amostras maiores para que se confirmem as análises apresentadas acima. O seguimento desses pacientes a longo prazo também fornecerá informações importantes sobre a relação da dose com as alterações tireoidianas.