AVALIAÇÃO DOS EFEITOS COLATERAIS DA IODOTERAPIA ADJUVANTE SOBRE AS GLÂNDULAS SALIVARES EM PACIENTES COM CARCINOMA BEM-DIFERENCIADO DE TIREÓIDE

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RESUMO

Almeida JP. **Avaliação dos efeitos colaterais da iodoterapia adjuvante sobre as glândulas salivares em pacientes com carcinoma bem-diferenciado de tireóide**. São Paulo; 2009. [Tese de Doutorado-Fundação Antônio Prudente].

Introdução: A saliva exerce funções fundamentais para a manutenção da função oral. Alterações qualitativas ou quantitativas na saliva interferem diretamente nas funções exercidas pela mesma na manutenção da saúde oral e funções como fala, mastigação e deglutição. As glândulas salivares têm a capacidade de concentrar iodo e a passagem do ^{131}I pelos ductos salivares durante a iodoterapia repercute em alterações salivares após o tratamento devido aos efeitos nocivos da radiação emitida por esta substância. **Objetivo:** Este estudo tem por objetivo avaliar os efeitos colaterais tardios da iodoterapia sobre as glândulas salivares e seu impacto na qualidade de vida dos pacientes submetidos a esta terapia, e investigar a eficácia da amifostina como protetor das glândulas salivares aos efeitos deletérios da iodoterapia. **Metodotologia:** Cintilografia de glândulas salivares, sialometria e aplicação do questionário de Qualidade de Vida da Universidade de Washington e algumas questões elaboradas pelos pesquisadores foram utilizadas para avaliar tanto os efeitos tardios como o efeito protetor da amifostina aos danos associados a iodoterapia. **Resultados:** Em relação aos efeitos colaterais tardios da iodoterapia verificamos que a idade é um fator importante na função das glândulas salivares, onde pacientes acima de 45 anos apresentam fluxo salivar não-estimulado e estimulado menores, mas que pacientes submetidos a iodoterapia apresentam uma dificuldade de eliminação concentrada principalmente em parótidas verificada tanto por cintilografia das glândulas salivares como por sialometria. Em relação a qualidade de vida verificou-se que doses de iodoterapia acima de 150 mCi impactam em funções associadas com a função salivar como fala, mastigação e deglutição. Na avaliação do efeito protetor da amifostina nos efeitos deletérios da iodoterapia sobre as glândulas salivares, nas condições deste estudo, não verificamos eficácia desta medicação para este propósito com efeitos adversos graves associados à

administração endovenosa da medicação. **Conclusão:** O presente estudo reforça teoria de que o principal efeito do ^{131}I sobre as glândulas salivares resulta em uma dificuldade de eliminação da saliva produzida em quantidades normais por uma constrição ductal devido a fibrose periductal induzida pela radiação. Além disso, estas alterações causam impacto na qualidade de vida e queixas acentuadas relacionadas à deglutição. O uso da amifostina náo foi eficaz na prevenção dos efeitos deletérios do ^{131}I sobre as glândulas salivares no presente estudo. A administração da amifostina, um medicamento com efeito adverso de hipotensão potencial, em pacientes em estado de hipotireoidismo deve ser realizada com cautela, visto que estes pacientes apresentam dificuldade de compensão da pressão diastólica.

SUMMARY

Almeida JP. **[Evaluation of adjuvant radioactive iodine therapy side effects on salivary glands in patients with well-differentiated thyroid carcinoma].** São Paulo; 2009. [Tese de Doutorado-Fundação Antônio Prudente].

Introduction: Saliva plays important functions in maintaining oral functions. Qualitative or quantitative saliva alterations can impact on functions as oral health maintainance, speeking, chewing and swallowing functions. The salivary glands are able to concentrate iodine and the ^{131}I passing through salivary ducts, during radioiodine therapy, results as salivar alterations after treatment due to emission of radiotion by iodine. **Objective:** This study aims to evaluate the late side effects of radioactive iodine therapy (RIT) on salivary glands and its impact on quality of life of these patients, and to investigate the efficacy of amifostine as salivary gland protector to iodine side effects. **Methods:** Salivary gland scintigraphy, sialometry and the questionnaire of University of Washington Quality of Life and some questions designed by the researches were used to evaluate the late side effects and the protector efficacy of amifostine to salivary gland damage associated to RIT. **Reults:** About late side effects of RIT, the age was an important factor in the function of salivary glands, with patients older 45 years having a descreased unstimulated and stimulated salivary flow. Patients submitted to RIT have more difficulty to eliminate saliva, mainly from parotids, verified by salivary gland scintigraphy and sialometry. In relation to quality of life, doses of iodine higher than 150 mCi have impact in salivary functions as speech, chewing and swallowing. Evaluating the protective effect of amifostine on late effects of RIT on salivary glands, it was not verified the efficacy of this drug, with serious side effects associated to endovenous via of administration. **Conclusion:** The present study reinforce the theory that the main effect of ^{131}I on salivary glands results in difficulty to eliminate the saliva produced, in normal quantities, by a ductal constriction due to periductal fibrosis induced by radiation. Besides that, these alterations have impact on quality of life and severe complaints related to swallowing. The amifostine was

not able to prevent side effects of RIT on salivary glands in the present study. The amifostine administration, a drug with known hipotensive effect, in patients withdraw thyroid hormone must be done carefully, since these patients have difficulty to compensate the diastolic blood pressure.

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LISTA DE ABREVIATURAS

$^{99m}TcO^{-}_{4}$	Pertecnetato de sódio
CBDT	Carcinoma bem diferenciado de tireóide
CGS	Cintilografia de glândulas salivares
DRI	Dose real injetada
FSE	Fluxo salivar estimulado
FSNE	Fluxo salivar não estimulado
LI	Local da injeção
PDPre	Parótida direita pré
PDPos	Parótida direita pós
PEPre	Parótida esquerda pré
PEPos	Parótida esquerda pós
QV	Qualidade de vida
ROI	Regiões de interesse
SF	Solução fisiológica
SDPre	Submandibular direita pré
SDPos	Submandibular direita pós
SEPre	Submandibular esquerda pré
SEPos	Submandibular esquerda pós
SPre	Seringa pré-injeção
SPos	Seringa pós-injeção
UW-QOL	University of Washington – Quality of Life

ÍNDICE

1 INTRODUÇÃO

1.1 CÂNCER DE TIREÓIDE

A American Cancer Society em 2007 estimou a ocorrência de 33.550 novos casos de câncer de tireóide nos Estados Unidos em 2007, um número de óbitos de 1530 casos (JAMEL et al. 2008). A maioria dos pacientes com câncer de tireóide apresenta carcinomas bem-diferenciados (papilifero ou folicular). O tratamento inicial de escolha é a tireoidectomia total, seguida por mapeamento de corpo inteiro com ^{123}I ou ^{131}I para detecção de doença residual remanescente ou metástases, e ablação com iodoterapia (^{131}I) (MAZZAFERRI 1999). A dose administrada de ^{131}I para terapia ablativa varia de 30 a 150mCi, tornando-se às vezes necessário doses maiores ou adicionais (NEWKIRK et al. 2000).

A terapia com ^{131}I é considerada como de grande valor no tratamento adjuvante de carcinomas bem-diferenciados de tireóide (CBDT). Em geral, os efeitos colaterais são moderados e autolimitados e complicações graves são raras, tornando esta modalidade terapêutica de baixo risco (BUSHNELL et al. 1992; ALEXANDER et al. 1998). Os efeitos colaterais mais comumente relatados durante o tratamento são náuseas, vômitos, epigastralgia, sialodenites e alteração do paladar. Entretanto, com altas doses de ^{131}I, seqüelas graves como leucemia, depressão severa de medula óssea seguida por hemorragias e complicações infecciosas, pneumonite por radiação e/ou fibrose pulmonar, embora raramente, têm sido relatadas (BUSHNELL et al. 1992; ALEXANDER et al. 1998).

1.2 FISIOLOGIA DO IODO NAS GLÂNDULAS SALIVARES

A saliva tem participação significativa na manutenção da função oral através da ação de proteínas como amilase, imunoglobulinas e lisozimas, bem como através da lubrificação da cavidade oral facilitando a fala, a deglutição e a sensação de paladar. A perda ou diminuição do fluxo salivar pode alterar a eficiência destas funções, resultando assim em morbidade significativa (NEWKIRK et al. 2000). A capacidade de concentração de iodo radioativo nas glândulas salivares as tornam vulneráveis durante e após o uso destas substâncias no manejo de pacientes com CBDT.

As glândulas salivares têm a capacidade de concentrar iodo seletivamente por razões ainda não bem determinadas. Alguns estudos sugerem que a captação de iodo nas glândulas salivares, e da mesma forma o pertecnetato de sódio ($^{99m}TcO^-_4$), ocorre através do sistema de co-transporte de $Na^+/K^+/Cl^-$, sendo posteriormente secretados na saliva (MARTINEZ e CASSITY 1985; HELMAN et al. 1987). Estudos mais recentes mostram por imunohistoquímica a expressão deste sistema de co-transporte também denominado "Na/I Symporter – NIS" exclusivamente nos ductos salivares (Jhiang et al. 1998; Vayre et al. 1999). A concentração salivar de iodo varia de 20 a 100 vezes mais que a encontrada no plasma (GOOLDEN et al. 1957; MASON et al. 1967; MAIER e BIHL 1987). É esta habilidade de concentração crítica responsável pelos danos glandulares quando o ^{131}I é utilizado.

O principal local de transporte do iodo para a saliva é o epitélio dos ductos intralobulares das glândulas parótidas. O iodo se difunde através dos capilares periductais e concentra-se no epitélio ductal, onde é excretado dentro do lúmen

ductal e, finalmente, transportado para a cavidade oral. Tem sido calculado que mais de 24% de todo o ^{131}I administrado para terapia de carcinomas de tireóide é perdido na saliva (MAIER e BIHL 1987; MANDEL e MANDEL 2003), no entanto, há relatos de que este iodo excretado pela saliva é reabsorvido no trato gastrointestinal, retornando ao plasma (MAIER e BIHL 1987).

No processo de concentração de iodo radioativo, as glândulas salivares são expostas aos efeitos deletérios da radiação. Embora todas as glândulas salivares sejam envolvidas no transporte de iodo radioativo para a saliva, as glândulas parótidas são as mais ativas e as células serosas parecem ser mais susceptíveis que as mucosas aos efeitos deletérios da radiação ionizante (MALPANI et al. 1996; ALEXANDER et al. 1998; CAGLAR et al. 2002; MANDEL e MANDEL 2003). Esta diferença de sensibilidade à radiação entre células serosas e mucosas não é bem esclarecida, mas tem sido sugerido que a hipofunção aguda das glândulas salivares induzida por radiação é atribuída à morte precoce das células serosas como resultado da ruptura da membrana causada por apoptose. É discutido se as alterações nucleares que ocorrem são causadas diretamente pela radiação ou indiretamente por outros mecanismos, incluindo alterações na membrana celular e/ou liberação de enzimas lizossomais (JENSEN et al. 2003).

A irradiação das glândulas salivares pelo ^{131}I causa danos endoteliais na vasculatura glandular (MAIER e BIHL 1987). Um aumento na permeabilidade capilar resulta na perda de proteínas plasmáticas e eletrólitos para o tecido intersticial. Simultaneamente, os ductos intralobulares lesados pela radiação perdem a habilidade de filtrar proteínas plasmáticas para a saliva. Como resultado destes dois mecanismos, elevação dos valores proteícos na saliva são encontradas

principalmente nas glândulas parótidas (MAIER e BIHL 1987). Elevados níveis de sódio e cloro também são encontrados na saliva de parótidas devido ao dano ductal causado pela radiação, o qual perde a capacidade de reabsorver estes eletrólitos secretados pelas células acinares terminais através do sistema ductal. Além disso, os níveis de fosfato estão diminuídos devido ao dano das paredes do epitélio ductal intralobular, o qual falha na sua função normal de transportar fosfato para a saliva (MAIER e BIHL 1987).

O efeito do ^{131}I sobre o parênquima e os ductos excretores são independentes um do outro. Captação anormal de parênquima e função excretória anormal ou ambos foram observadas com análises utilizando $^{99m}TcO^{-}_{4}$ (MALPANI et al. 1996). Inicialmente, a captação de $^{99m}TcO^{-}_{4}$ pelas glândulas salivares pode estar normal, mas devido aos danos tardios da parede ductal a excreção de $^{99m}TcO^{-}_{4}$ é atrasada e resulta numa aumentada retenção de $^{99m}TcO^{-}_{4}$ na região glandular. Mais tarde, a captação diminuída de $^{99m}TcO^{-}_{4}$ resulta da fibrose vascular causada pelo efeito destrutivo do ^{131}I. Devido ao efeito dose-dependente do efeito do ^{131}I ser tardio a secreção salivar tende a dimuinir gradualmente com o tempo devido a fibrose periductal causada pela radiação (MALPANI et al. 1996).

O primeiro caso de sialodenite associado a iodoterapia foi relatado em 1955 por RIGLER e SCANLON e posteriormente outros casos isolados foram relatados (GOOLDEN et al. 1957; WIESENFELD et al. 1983). Até meados da década de 80 sialodenites associadas a iodoterapia eram relatadas como um efeito colateral raro em pacientes submetidos a este tipo de tratamento. Em 1984, ALLWEISS et al. analisaram 87 pacientes que receberam doses terapêuticas de ^{131}I e verificaram que sialodenites crônica e/ou aguda ocorriam com mais freqüência do que vinham sendo

relatadas na literatura, acometendo cerca de 11.5% destes pacientes. Posteriormente, MAIER e BIHL (1987) demonstraram que além de xerostomia, todos os pacientes submetidos a iodoterapia apresentavam alterações na composição salivar, como o aumento da atividade de α-amilase e aumento nas concentrações de proteínas e sódio. Outro estudo com 203 pacientes demonstrou uma incidência de sialodenite maior que a de 11.5% relatada por ALLWEISS et al. (1984), ocorrendo em 33% (67/203) dos pacientes. Neste estudo, em 80.6% dos casos (54/67) a glândula parótida estava envolvida (unilateralmente: 14; bilateralmente: 40), e em 46.3% (31/67) a glândula submandibular foi afetada (unilateralmente em 8 casos e bilateralmente em 23). A freqüência de sialodenite mostrou uma associação linear e dose-dependente. Interessantemente, 27% (55/203) dos pacientes apresentaram uma perda transitória e dose-dependente de paladar e de olfato (ALEXANDER et al. 1998).

1.3 CINTILOGRAFIA DE GLÂNDULAS SALIVARES

O efeito deletério do iodo radioativo nas glândulas salivares tem sido demonstrado através de estudos por cintilografia de glândulas salivares (CGS), as quais demonstram uma incapacidade de secreção salivar no período imediato às altas doses de radiação (OLMOS et al. 1994). Cintilografias de glândulas salivares mostram que o dano glandular torna-se mais evidente num período de alguns meses após o tratamento com a diminuição da produção salivar (OLMOS et al. 1994; MALPANI et al. 1996), estando estas alterações tardias estreitamente relacionadas com a dose de iodo radioativo administrada (MALPANI et al. 1996; CAGLAR et al.

2002), e sendo mais evidentes nas glândulas parótidas (CAGLAR et al. 2002). MALPANI et al. (1996) mostraram que de 33 pacientes tratados com ^{131}I, 72.7% apresentaram concentração e excreção anormal de $^{99m}TcO^{-}_{4}$. A concentração de $^{99m}TcO^{-}_{4}$ ou resposta a sialogogo (suco de limão) foi dose-dependente, sendo mais acentuada com doses maiores de iodo radioativo, além das glândulas parótidas serem mais afetadas que as glândulas submandibulares. Mais tarde, CAGLAR et al. (2002) relataram que 69% (31/45) dos pacientes tratados com ^{131}I apresentavam disfunção de glândulas salivares avaliada por cintilografia após iodoterapia. 54% (21/39) dos pacientes relataram queixa de boca seca, geralmente 1 ano após o tratamento (75.6%), sendo que destes 21 pacientes com queixa clínica de xerostomia, 86% apresentavam disfunção à CGS.

1.4 PILOCARPINA

Com o intuito de reduzir os danos nas glândulas salivares produzidos pelo ^{131}I, o uso de sialogogos como sucos ácidos ou ácido cítrico tem sido recomendado para aumentar a salivação durante a administração de iodo radioativo. Estas medidas aumentam o fluxo salivar e diminuem o tempo de estase do ^{131}I nas glândulas salivares e a concentração de iodo radioativo na saliva. Entretanto, recentemente NAKADA et al. (2005) mostraram que o estímulo salivar com suco de limão para diminuir a estase do ^{131}I nas glândulas salivares deve-se iniciar somente 24 horas após a administração do ^{131}I, visto que no período imediato a sua administração a concentração e a atividade do iodo é muito alta gerando maiores efeitos colaterais sobre as glândulas salivares (NAKADA et al. 2005). O tempo de trânsito pela

glândula salivar do ^{131}I também poderia ser diminuído com o uso de drogas colinérgicas como a pilocarpina e o cevimeline, no entanto, ao contrário de pacientes submetidos à radioterapia externa, nos quais diversos estudos comprovaram a eficácia da pilocarpina como um estimulante salivar (LEVEQUE et al. 1993; HAMLAR et al. 1996; ZIMMERMAN et al. 1997; HORIOT et al. 2000; LEEK e ALBERTSSON 2002; HADDAD e KARIMI 2002; GORSKY et al. 2004; MOSQUEDA-TAYLOR et al. 2004), resultados sobre o uso de 5mg de pilocarpina a cada 8 horas por uma semana após a iodoterapia, publicados recentemente por SILBERSTEIN em 2008, mostram que a pilocarpina não foi capaz de reduzir a ocorrência de sialodenite nestes pacientes. ALEXANDER et al. (1998) utilizaram pilocarpina em pacientes submetidos a iodoterapia, e já não haviam observado diferença significativa do grau de disfunção salivar em relação aos pacientes que não fizeram uso da medicação. Entretanto, os autores não descrevem quantos pacientes fizeram uso do medicamento e, tampouco, apresentam gráficos de comparação entre os grupos, dificultando assim a análise e a confiabilidade dos dados. Com outro enfoque ao uso da pilocarpina, AFRAMIAN et al. (2006) avaliaram a eficácia de uma única dose de 5mg de pilocarpina no fluxo salivar não estimulado e estimulado em pacientes submetidos a ioterapia há pelo menos 3 meses que apresentavam sialodenite recorrente e xerostomia. Os resultados deste estudo mostram uma significante elevação dos fluxos salivares não estimulado e estimulado sem alterações significantes das pressões sistólica e diastólica, temperatura corporal e pulso (frequência cardiaca).

1.5 AMIFOSTINA

Outra medicação alternativa sugerida como prevenção aos danos glandulares causados pelo iodo radioativo é a amifostina. Alguns trabalhos, tanto em modelos animais como em humanos, têm demonstrado redução significativa dos danos em glândulas salivares com o uso de amifostina durante a iodoterapia, promovendo uma significante melhora na qualidade de vida destes pacientes (BOHUSLAVIZKI et al. 1998a, b, 1999; MENDOZA et al. 2004).

Estudos sobre o efeito protetor da amifostina foram iniciados no final da década de 60, extendendo-se em modelos animais até o final da década de 70 (UTLEY et al. 1976; PRATT et al. 1980; UTLEY et al. 1981; MENARD et al. 1984) e só nas décadas seguintes iniciaram-se os estudos em humanos.

A amifostina é um composto tiofosfato orgânico, administrado na forma de uma pró-droga WR-2721 intravenosa ou subcutaneamente, que é metabolizada na sua forma ativa pela atividade da fosfatase alcalina. Nos tecidos, a amifostina sofre desfosforilação transformando-se no metabólito ativo – WR-1065 (NEWKIRK et al. 2000; BARDET et al. 2002). A conversão é mais efetiva em meio alcalino dos tecidos normais que no meio ácido do tecido tumoral. Em adição, a concentração de fosfatase alcalina é 100 vezes maior no tecido normal que no tecido tumoral. Uma vez que o metabólito ativo da amifostina torna-se disponível, age capturando radicais livres de oxigênio, os quais são responsáveis pelos danos teciduais causados pela radiação (NEWKIRK et al. 2000; BARDET et al. 2002; MANDEL e MANDEL 2003). Esta droga foi originalmente desenvolvida como um agente radioprotetor no final dos anos 50 como parte do Programa de Desenvolvimento de Drogas

Antiradiação nos Estados Unidos pelo *Walter Reed Army Institute of Research and Development*. Dentre os mais de 4000 produtos químicos investigados neste programa, o grupo aminotiol mostrou-se o mais promissor por sua habilidade de proteção tecidual contra quimio e radioterapia. A amifostina é o aminotiol mais extensivamente estudado (BONNER e SHAW 2002).

Estudos clínicos para avaliar a eficácia da amifostina como protetor de glândulas salivares em pacientes irradiados na região de cabeça e pescoço e como protetor de diversos órgãos e tecidos em pacientes recebendo quimioterapia começaram a ser publicados a partir da década de 80 (BLUMBERG et al. 1982; GLICK et al. 1982; WOOLLEY et al. 1983). O grande desafio enfrentado no uso da amifostina na prática clínica são os efeitos colaterais associados à droga. O paciente em uso de amifostina pode apresentar efeitos colaterais como hipotensão, geralmente com diminuição da pressão sistólica, náuseas, vômitos e mal estar durante as infusões, geralmente nos primeiros 20 minutos (RADES et al. 2004). A partir destas dificuldades, SHAW et al. (1999) mostram resultados favoráveis em relação à administração da amifostina na via subcutânea e KOUKOURAKIS et al. (2000) publicaram posteriormente um estudo fase II utilizando amifostina subcutânea durante radioterapia fracionada, mostrando que esta droga adiministrada por via subcutânea é bem tolerada, reduzindo efetivamente a toxicidade aguda da radioterapia. Outros estudos mais recentes avaliando a eficácia e melhor tolerabilidade da amifostina via subcutânea têm sido publicados com resultados favoráveis a esta via de administração (OZSAHIN et al. 2006; LAW et al. 2007; ANNÉ et al. 2007).

O uso da amifostina é bem estabelecido pela literatura nos tratamentos de quimio e radioterapia (BRIZEL et al. 2000; ANTONADOU et al. 2002), mas em pacientes com câncer de tireóide submetidos a iodoterapia adjuvante os primeiros dados foram apresentados por Bohuslaviszki et al. em 1998 e mais recentemente por KIM et al. em 2008. O estudo publicado por BOHUSLAVIZKI et al. (1998b) é um estudo controlado, duplo cego, com 50 pacientes incluídos, que mostrou uma redução do dano no parênquima das glândulas salivares causado pela iodoterapia com o uso da amifostina. O estudo publicado por KIM et al. (2008) é um estudo não randomizado, com 80 pacientes onde não se verificou os efeitos protetores da amifostina sobre as glândulas salivares em pacientes submetidos a ioterapia adjuvante.

1.6 QUALIDADE DE VIDA EM PACIENTES ONCOLÓGICOS

Tradicionalmente, a principal forma de avaliar a evolução de pacientes oncológicos é a sobrevida baseada no controle tumoral, mas recentemente reconhece-se cada vez mais que o diagnóstico e o tratamento do câncer pode ter um significativo impacto na qualidade de vida destes pacientes (TAN et al. 2007). O objetivo do tratamento oncológico tornou-se não só controlar a doença e aumentar a sobrevida como também preservar a qualidade de vida (HUANG et al. 2004), e quantificar as alterações na qualidade de vida (QV) destes pacientes tem sido considerado de grande importância nos dias atuais (VARTANIAN et al. 2004; TAN et al. 2007).

Qualidade de vida é definida como a percepção do indivíduo e sua posição na vida, em um contexto cultural e sistema de valores no qual este indivíduo vive e em relação aos seus objetivos, expectativas, parâmetros e preocupações (WHOQOL Group 1993). A Qualidade de Vida relacionada à Saúde se refere a um conceito multidimensional, o qual compreende a percepção de aspectos negativos e positivos de pelo menos quatro dimensões: as funções física, emocional, social e cognitiva as quais podem ser influenciadas pela doença ou o tratamento desta (CREVENNA et al. 2003).

Nos últimos 20 anos um crescente número de estudos tem avaliado a QV diária como o ponto final na avaliação do impacto da doença e seu tratamento (DAGAN et al. 2004; VARTANIAN et al. 2006). Entretanto, há relativamente poucos estudos de QV relacionada à Saúde voltados especificamente para pacientes com câncer de tireóide (CREVENNA et al. 2003; DAGAN et al. 2004; TAN et al. 2007). A falta de instrumentos específicos para aferir a Qualidade de Vida em pacientes com câncer de tireóide associada a baixas taxas de mortalidade e morbidade do tratamento podem explicar o reduzido número de estudos neste campo.

A maioria dos estudos publicados utiliza o questionário SF-36 que é um instrumento genérico para verificar QV e não possui domínios específicos para avaliar o impacto de possíveis efeitos colaterais associados ao tratamento. Vários instrumentos têm sido desenvolvidos para aferir a qualidade de vida em pacientes com câncer de cabeça e pescoço. Entre eles, o questionário de Qualidade de Vida da Universidade de Washington é um instrumento validado, de acurácia e internacionalmente aceito. O uso deste questionário permite a avaliação da QV relacionada à Saúde e leva a um melhor entendimento das expectativas do paciente

(VARTANIAN et al. 2004). Embora não comumente utilizado em pacientes com câncer de tireóide, o questionário de Qualidade de Vida da Universidade de Washington tem um valor preditivo na QV destes pacientes visto que é possível avaliar pontos que podem estar associados a efeitos colaterais do tratamento como um todo – cirurgia e iodoterapia.

2 OBJETIVOS

2.1 OBJETIVOS PRINCIPAIS

1. Avaliar os efeitos colaterais tardios da iodoterapia sobre as glândulas salivares maiores.
2. Testar a eficácia da amifostina em prevenir danos nas glândulas salivares após o tratamento.

2.2 OBJETIVOS SECUNDÁRIOS

1. Avaliar a qualidade de vida após o término do tratamento de pacientes com carcinoma bem-diferenciado de tireóide.
2. Avaliar a resposta ao uso da pilocarpina nos pacientes submetidos a iodoterapia que apresentam queixa clínica de xerostomia.
3. Avaliar a incidência de alterações salivares agudas durante o tratamento com iodo radioativo.

3 MATERIAL E MÉTODOS

Para alcançarmos todos os objetivos propostos, este trabalho foi dividido em dois estudos: ESTUDO I – um estudo transversal de carater retrospectivo com coleta prospectiva da função de glândulas salivares para alcançarmos os objetivos principal 1 e secundários 1 e 2; ESTUDO II – um ensaio clínico, randomizado e duplo cego para alcançarmos os objetivos principal 2 e secundários 1 e 3.

3.1 ESTUDO I

Todo o Estudo I foi desenvolvido no Hospital A. C. Camargo com a colaboração dos Departamentos de Cirurgia de Cabeça e Pescoço, para triagem dos pacientes, e de Imagem - Medicina Nuclear para realização dos exames de CGS.

3.1.1 Critérios de seleção

Pacientes com carcinoma papilífero ou folicular de tireóide, atendidos em consulta de seguimento no período de 1997 a 2006, submetidos a tireoidectomia total seguido ou não de iodoterapia adjuvante.

3.1.2 Critérios de exclusão

Pacientes submetidos a radioterapia externa prévia na região de cabeça e pescoço e pacientes com sintomas prévios de síndrome *sicca*.

3.1.3 Divisão dos Grupos

Grupo I - pacientes submetidos a tireoidectomia total que não foram submetidos a I^{131}.

Grupo II – pacientes submetidos a tireoidectomia total e ao I^{131} independente da dose.

3.1.4 Amostra e variáveis coletadas

Quatrocentos pacientes que preenchiam os critérios de inclusão foram convidados a participar do estudo durante suas consultas de seguimento. Destes, 184 pacientes aceitaram participar e assinaram o Termo de Consentimento Livre e Esclarecido (Anexo 1) aprovado pelo Comitê de Ética do Hospital A. C. Camargo (Anexo 2).

Dos 184 pacientes avaliados dados como idade, gênero, subtipo tumoral, TNM, estadio clínico, data da cirurgia, esvaziamento cervical, data e dose recebida na iodoterapia, comorbidades presentes avaliadas pela classificação de risco cirúrgico da American Society of Anesthesiology (ASA) e o uso de medicação xerostômica (anti-hipertensivos, antidepressivos e anti-histamínicos) foram coletados dos prontuários.

3.1.5 Avaliação de dados subjetivos

Os pacientes responderam ao questionário de Qualidade de Vida da Universidade de Washington, validado em língua portuguesa e disponibilizado para uso público (VARTANIAN et al. 2006) e a algumas questões elaboradas pelos pesquisadores visando identificar os efeitos colaterais da iodoterapia sobre as glândulas salivares sempre antes da coleta dos dados objetivos (Anexo 3).

O questionário de Qualidade de Vida da Universidade de Washington foi desenhado para que o paciente fosse capaz de respondê-lo sem qualquer ajuda. Desta forma, o questionário foi aplicado em um dia específico reservado para o estudo e os pacientes que por algum motivo não se sentiram aptos a responder sozinhos ao questionário tiveram auxílio do acompanhante para fazê-lo.

3.1.6 Avaliação de dados objetivos

Para avaliação objetiva da função das glândulas salivares os pacientes foram submetidos a cintilografia de glândulas salivares e sialometria de fluxo salivar, dos quais estão descritas abaixo as metodologias utilizadas.

- ✓ **Cintilografia de Glândulas Salivares**

As CGS neste estudo I foram realizados de acordo com o protocolo adotado pelo Departamento de Imagem – Medicina Nuclear do Hospital A. C. Camargo. Os pacientes foram instruídos a não ingerir alimentos, não fazer sua higiene oral e não fumar pelo menos 90 minutos antes do procedimento e tomar 3 copos de água para garantir uma boa hidratação 30 minutos antes da realização do exame.

Equipamentos utilizados:

1) Gama câmera de um detector (modelo GE StarCam 4000, GE Medical System, Milwaaukee, WI, EUA).

2) Colimador LEHR (low energy high resolution).

3) Energia 140KeV (janela de 15%).

4) Work Station (GE Entegra, GE Medical System, Milwaaukee, WI, EUA).

Radioisótopo e dose utilizados:

1) $^{99m}TcO^{-}_{4}$ (pertecnetato de Sódio) fornecido pelo IPEN, CNEN-SP.

2) 10mCi (370MBq) com via de administração endovenosa.

Metodologia do exame:

1) Preparação: aquisição de imagem para a contagem da dose de $^{99m}TcO^{-}_{4}$ que seria administrada em imagem estática de 1 minuto, com matriz 128 x 128 W.

2) FASE 1 – Estudo dinâmico de fluxo sanguíneo: foram realizadas 90 imagens de 1 segundo na projeção anterior, e duração total de 90 segundos, em matriz 128 x 128 W.

3) FASE 2 – Estudo estático das glândulas salivares pré-estímulo: captação de 3 imagens nas projeções anterior, lateral direita e lateral esquerda, nesta respectiva sequência, no sentido antero-posterior com duração de 3 minutos cada, aguardando-se 5 minutos após imagem de fluxo sanguíneo, em matriz de 256 x 256 W.

4) Estímulo: fornecido ao paciente por 5 minutos um comprimido de 1g de ácido ascórbico (Cewin®, Sanofi-Aventis, Brasil) para dissolução na cavidade oral com finalidade de estimular o fluxo salivar, e realizado neste intervalo o exame de sialometria de fluxo salivar.

5) FASE 3 – Estudo estático das glândulas salivares pós-estímulo: captação de 3 imagens (anterior, lateral direita e lateral esquerda) com duração de 3 minutos cada, em matriz de 256 x 256 W.

6) Ao final foi realizada a contagem da dose residual de $^{99m}TcO^{-}_{4}$ na seringa após a administração e do local da injeção, em imagem estática de 1 minuto de duração cada, com matriz 128 x 128 W.

Processamento e quantificação das imagens adquiridas:

1) Criação de regiões de interesse (ROIs) nas imagens de seringa pré-injeção (SPre), seringa pós-injeção (SPos), local da injeção (LI) e as imagens estáticas com projeção anterior pré e pós estímulo, nas topografias das glândulas salivares [glândulas parótidas direita (PD) e esquerda (PE) e submandibular/sublingual direita (SD) e esquerda (SE)].

2) Quantificação do número de contagens em cada ROI (SPre, SPos, LI, PDPre, PEPre, SDPre, SEPre, PDPos, PEPos, SDPos, SEPos).

3) Cálculo da captação e eliminação em cada glândula salivar pelas seguintes fórmulas:

Dose real injetada (DRI) = SPre – SPos – LI

% Captação (CPD) = PDPre * 100 / DRI

% Eliminação (EPD) = PDPos * 100 / CPD

✓ **Sialometria de fluxo salivar**

A metodologia de sialometria utilizada foi baseada no método descrito por KOSEKI et al. (2004) e os parâmetros de normalidade de fluxo salivar total adotados foram de 0.3 ml/min para o fluxo não estimulado e 1.5 ml/min para o fluxo

estimulado publicados por JENSEN et al. (2003). Os pacientes foram instruídos a não ingerir alimentos, não fazer sua higiene oral e não fumar pelo menos 90 minutos antes do procedimento.

Fluxo salivar total não estimulado (FSNE)

1 Coleta do fluxo salivar total não estimulado em um tubo Falcon de 15ml, no período de 5 minutos. O total de saliva coletado em ml foi dividido por 5 obtendo-se assim o fluxo salivar em ml/min.

2 Fluxo salivar total estimulado (FSE)

Um comprimido de 1g de ácido cítrico foi fornecido ao paciente para dissolução contínua em cavidade oral durante 5 minutos e o fluxo salivar total estimulado coletado em um tubo Falcon de 15ml. O total de saliva coletado em ml foi dividido por 5 obtendo-se assim o fluxo salivar em ml/min.

3.1.7 Melhora da xerostomia com o uso de pilocarpina

Aos pacientes que apresentaram queixa clinica de xerostomia, alteração de fluxo salivar à sialometria e na análise visual da CGS apresentaram glândula residual funcionante, e não apresentaram contra-indicações ao uso da pilocarpina (portadores de asma, hipertensão arterial, problemas cardíacos e glaucoma de ângulo fechado), foi entregue um frasco com 90 capsulas de 5mg de pilocarpina e instruções para uso 3 vezes ao dia, com o objetivo de avaliar uma possível eficácia terapêutica nos casos de xerostomia. Os pacientes preencheram um relatório durante a primeira semana de uso e avaliação subjetiva da eficácia da pilocarpina foi realizada (Anexo 4).

3.2 ESTUDO II

Todo o Estudo II foi desenvolvido no Departamento de Medicina Nuclear da Fundação Pio XII – Hospital do Câncer de Barretos. Todos os pacientes incluídos no estudo assinaram o Termo de Consentimento Livre e Esclarecido aprovado pelo Comitê de Ética da Instituição (Anexos 5 e 6).

3.2.1 Critérios de seleção

Pacientes com carcinoma papilífero, folicular ou células de Hurtle de tireóide, submetidos a tireoidectomia total que seriam submetidos a terapia complementar com iodo radioativo pela primeira vez.

3.2.2 Critérios de exclusão

Pacientes submetidos previamente a qualquer dose de iodo radioativo, pacientes submetidos a radioterapia externa prévia na região de cabeça e pescoço, pacientes com sintomas prévios de síndrome *sicca* e pacientes que apresentassem contra-indicações para o uso da amifostina (pacientes com hipersensibilidade ao aminotiol, hipotensos, em estado de desidratação, com insuficiência renal ou hepática, com idade superior a 70 anos, mulheres grávidas ou em período de lactação).

3.2.3 Randomização

Os pacientes foram randomizados em dois grupos através de uma tabela de números aleatórios com 60 números, onde estabeleceu-se que os números pares

corresponderiam aos pacientes que comporiam o grupo placebo e os números ímpares aos pacientes que comporiam o grupo estudo/amifostina. Toda a randomização foi duplo-cega contando com uma única pessoa responsável pela randomização, preparo da medicação e quebra do sigilo caso necessário (Anexo 7).

Ao grupo placebo foi administrado 1ml SF 0,9% estéril por via subcutânea e ao grupo amifostina foi administrado 200mg/m^2 amifostina (Ethyol®, Shering Plough do Brasil) diluída em 1ml SF 0,9% estéril por via subcutânea, 15 minutos antes da ingestão do iodo radioativo. Pressão arterial foi aferida antes e 30 minutos após a infusão em todos os pacientes, e todos os pacientes foram acompanhados por equipe especializada.

3.2.4 Avaliação de dados subjetivos

Os pacientes foram submetidos ao questionário de qualidade de vida, UW QOL – University of Washington Quality of Life validado em língua portuguesa e disponibilizado para uso público (VARTANIAN et al. 2006*)* - em dois tempos diferentes, antes de iniciarem a iodoterapia e 3 meses após o término da iodoterapia (Anexo 3).

3.2.5 Avaliação de dados objetivos

Para avaliação objetiva da função das glândulas salivares os pacientes foram submetidos a exames de cintilografia de glândulas salivares e sialometria de fluxo salivar imediatamente antes de iniciarem iodoterapia e 3 meses após o término da iodoterapia.

✓ **Cintilografia dinâmica de glândulas salivares**

As cintilografias foram realizadas de acordo com o protocolo adotado pelo departamento de Medicina Nuclear da Fundação Pio XII – Hospital do Câncer de Barretos e sob supervisão do Dr. Euclides Timóteo da Rocha.

Através da administração intravenosa de pertecnetato, obtido a partir da eluição diária de geradores de tecnécio fornecidos pelo IPEN (Instituto de Pesquisas Energéticas e Nucleares) em São Paulo, foram realizadas mensurações de fluxo sangüíneo, inicialmente, e posteriormente acúmulo e excreção. Os pacientes tinham conhecimento com antecedência de como era o procedimento, e as dúvidas residuais, quando presentes, eram esclarecidas. Para todos os pacientes foi solicitado jejum de 2 horas antes da realização do exame. Após esclarecimento de dúvidas, o paciente era conduzido à sala da gama-camara, posicionado deitado na mesa de exames com a cabeça e região cervical sob o detetor, região cervical livre de objetos atenuantes, nariz centralizado e cabeça levemente extendida, e um cateter inserido em um vaso superficial do membro superior onde foram administrados 370MBq (10mCi) de ^{99m}Tc-pertecnetato com aquisição de imagens imediatamente após a infusão.

As aquisições das imagens foram realizadas em três equipamentos de dois detetores (MILLENNIUM VG e MILLENNIUM MG, General Electric Medical System; e FORTE, Philips), equipados com colimadores de alta resolução. Foi utilizado como protocolo padrão aquisição com uma imagem a cada 3 segundos no primeiro minuto, e a cada 30 segundos durante 30 minutos empregando-se uma matriz de 128x128 pixels, e magnificação de 1,5 vezes. Imagens estáticas não foram obtidas ao longo do estudo para evitar interrupção da aquisição dinâmica. Além

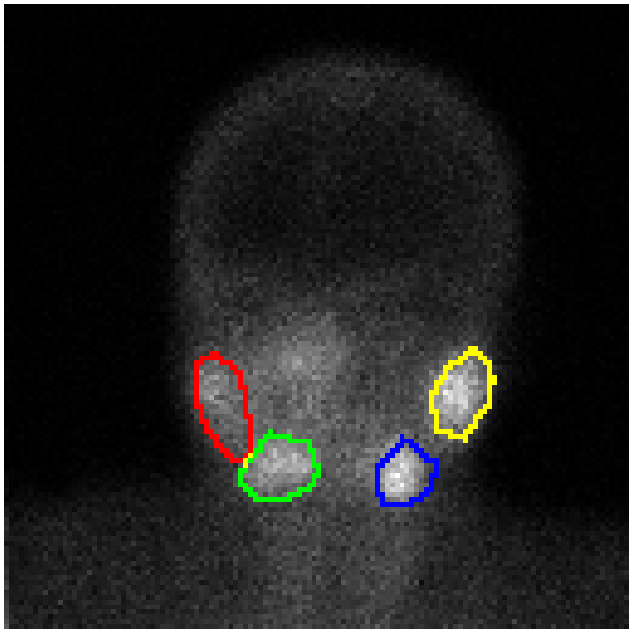
disto, deve ser acrescido que o estímulo com suco de limão foi realizado aos 20 minutos do início do estudo com a finalidade de provocar secreção salivar.

Interpretação das imagens de medicina nuclear:

Tanto aquisições estáticas quanto as dinâmicas podem ser realizadas para avaliar as glândulas salivares, no entanto, no presente estudo apenas as dinâmicas foram obtidas. Os exames foram analisados por um único médico nuclear, cego para os dados clínicos. Estes foram avaliados quanto a movimentações, contaminações ou outras alterações artefatuais que pudessem trazer prejuízo às analises visual ou semi-quantitativa. No campo visual observamos as glândulas parótidas e submandibulares, cavidade oral que captam o radiotraçador (Figura 1). Os achados cintilograficos em glândulas normais são aumento agudo e simétrico da captação, demonstrado pelas curvas de tempo/atividade, com queda abrupta, fase excreção, após estímulo com o sialagogo, e, subseqüente retorno da captação do radiotraçador pela glândula (Figura 2).

Para realizar as medidas de atividade em função do tempo, porcentagem de captação (uptake) em função do tempo, fração de excreção, atividade pré-administração do suco de limão, atividade pós-administração do suco de limão, porcentagem de captação pré-administração do suco de limão, porcentagem de captação pós-administração do suco de limão e $T_{1/2}$ após-administração do suco de limão para parótidas direita e esquerda, e submandibulares/sublinguais direita e esquerda foi desenvolvido software em ambiente de desenvolvimento MATLAB versão 7.0.0.19920-R14.

O algoritmo empregado pelo software inicia solicitando definição das Regiões de Interesse (ROI) referentes a cada glândula em estudo (Figura 1).



Legenda: À esquerda superiormente temos a delimitação da parótida direita e à esquerda inferiormente a submandibular direita, à direita superiormente temos a parótida esquerda e à direita inferiormente a submandibular esquerda.

Figura 1 - Regiões de Interesse (ROI).

Após definição das ROI é apresentado um gráfico de contagem em função do tempo para a parótida direita com objetivo de definir o instante da administração do suco de limão (Figura 2). A partir desta curva é feita a derivada primeira no software e então é determinado o momento da injeção que serve como referência para quantificação da porcentagem de captação pré-administração do suco de limão e pós-administração do suco de limão.

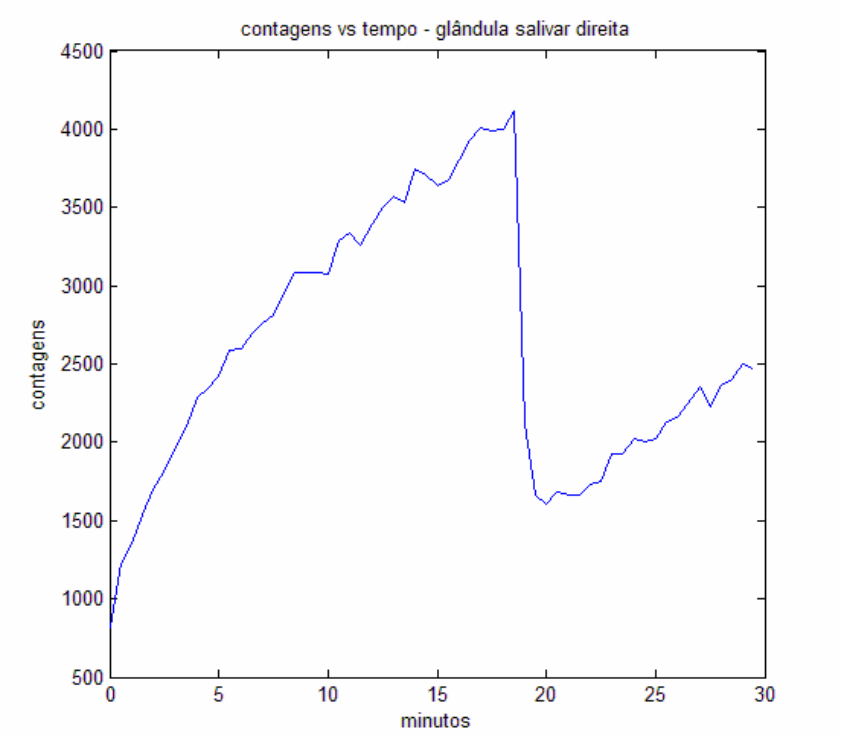


Figura 2 - Curva de tempo/atividade da concentração do radiotraçador em uma glândula salivar no período de 30 minutos de cintilografia de glândula salivar.

O programa fornece também o momento em que a derivada primeira da curva acima sofre inversão abrupta para auxiliar a definição do momento exato da administração do suco de limão.

Uma vez definido e informado ao programa este momento, o programa faz o cálculo das variáveis: atividade (em μCi), uptake (em %) e $T_{1/2}$ (em min) pós-administração do suco de limão. A primeira é feita através da equação:

$$A(\mu Ci) = contagens\ na\ ROI \cdot fator\ de\ calibração\ ,$$

onde o fator de calibração ó obtido experimentalmente para cada câmara de cintilação através de teste de sensibilidade plana do sistema [TECDOC 6.02/IAEA]. A expressão para este fator de calibração é:

$$fator\,de\,calibração = \frac{1000}{37 \cdot 30 \cdot sensibilidade},$$

onde o número 30 refere-se ao tempo por frame e a sensibilidade é expressa em contagens/MBq (contagens por megaBequerel).

A variável porcentagem de captação é calculada através da equação:

$$U[\%] = \frac{A(\mu Ci)}{atividade\ injetada(\mu Ci)} = \frac{contagens\,na\,ROI \cdot\ fator\,de\,calibração}{atividade\ injetada(\mu Ci)}.$$

A fração de excreção é obtida pela equação:

$$EF[\%] = \frac{U_{2\min\,pré}[\%] - U_{2\min\,pós}[\%]}{U_{2\min\,pré}[\%]},$$

onde $U_{2\min\,pré}[\%]$ é a média da porcentagem de captação calculada sobre os frames a partir de 3 minutos que antecedem a administração do suco de limão, durante um intervalo de tempo de 2 minutos e $U_{2\min\,pós}[\%]$ corresponde à média da porcentagem de captação calculada sobre os frames a partir de 3 minutos após a administração do suco de limão, durante um intervalo de tempo de 2 minutos.

A variável $T_{1/2}$ pós-administração do suco de limão é obtida fazendo-se o ajuste exponencial pelo método dos mínimos quadrados ao subconjunto de pontos da curva de contagens em função do tempo, obtido tomando-se o intervalo correspondente do máximo até o mínimo subseqüente (Figura 3).

A equação ajustada é:

$$C(t) = C_{máx} \cdot e^{-\lambda \cdot t},$$

onde $C_{máx}$ é a contagem máxima, λ é a constante de eliminação e t o tempo.

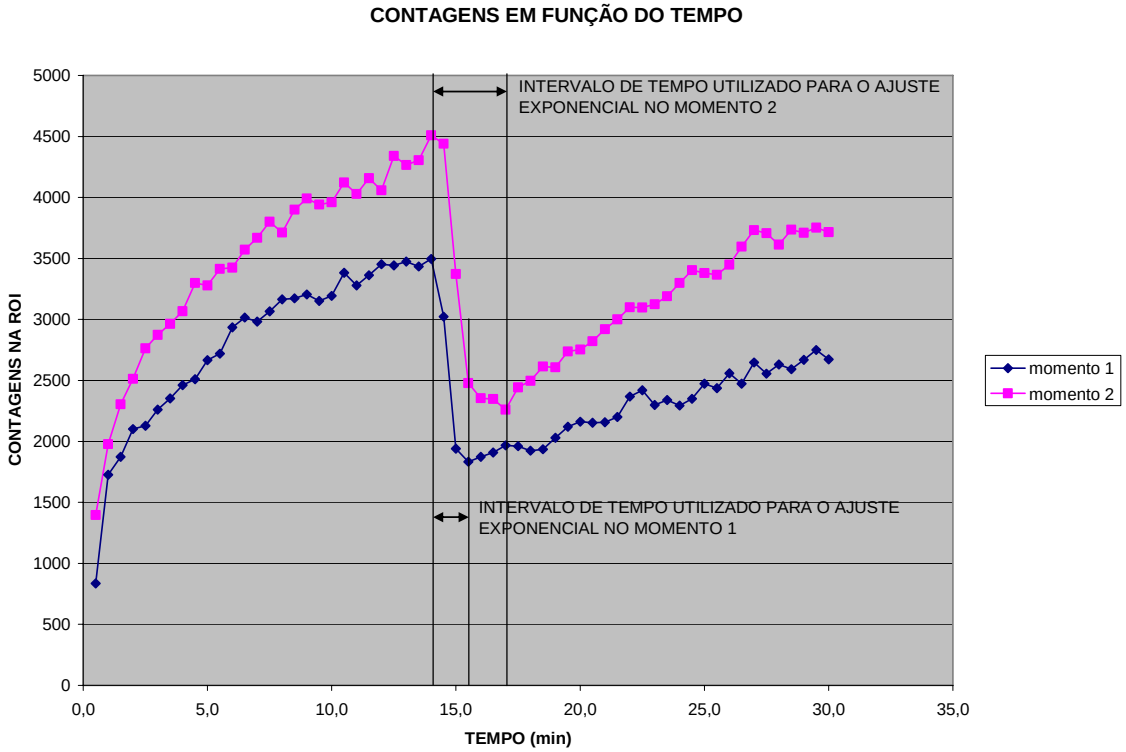


Figura 3 - Ilustração da seleção de pontos feita pelo software para realizar o ajuste exponencial pelo método dos mínimos quadrados e então calcular $T_{1/2}$ pós-administração do suco de limão.

Após ajuste exponencial $T_{1/2}$ é calculado pela equação:

$T_{1/2} = \frac{0{,}693}{\lambda}$, onde λ é a constante do expoente do ajuste exponencial.

✓ **Sialometria de fluxo salivar**

A metodologia de sialometria utilizada foi a mesma descrita no Estudo I baseada no método descrito por KOSEKI et al. (2004) com parâmetros de normalidade de fluxo salivar total adotados foram de 0.3 ml/min para o fluxo não estimulado e 1.5 ml/min para o fluxo estimulado publicados por JENSEN et al.

(2003). Os pacientes também foram instruídos a não ingerir alimentos, não fazer sua higiene oral e não fumar pelo menos 90 minutos antes do procedimento.

- ✓ **Observações**

Este estudo começou a ser desenvolvido no Departamento de Medicina Nuclear do Hospital Samaritano em São Paulo. Entretanto, dois pacientes apresentaram efeitos colaterais sérios e quebrando o duplo-cego para relatar o ocorrido ao CEP constatamos que os dois pacientes eram do grupo amifostina. No total foram incluídos quatro pacientes nesta fase do estudo, mas infelizmente após o ocorrido a pesquisadora colaboradora no Hospital Samaritano não considerou prudente continuarmos o estudo, mesmo com parecer favorável do CEP ao prosseguimento, e o estudo foi interrompido. No Hospital A. C. Camargo não foi possível a realização do estudo por dificuldades institucionais relacionadas com a recém-inaugurada unidade de iodoterapia.

4 RESULTADOS

4.1 ESTUDO I

Os resultados do estudo I estão descritos em artigos publicados e submetidos para publicação.

4.1.1 Artigo 1: *Clinical predictors of quality of life among patients with initial differentiated thyroid cancers*

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Abstract

Background: Patients with differentiated thyroid carcinomas (DTC) usually present a good prognosis with overall survival rates over 90%. Traditionally, the success of the treatment of cancer patients has been evaluated by the survival time. Recently, it has been observed that the diagnosis and treatment of cancer have also a strong impact on the quality of life (QOL) of these patients. This study aims to assess the QOL in DTC patients and its potential clinical predictors. **Methods:** One hundred

and fifty four patients submitted to thyroidectomy from 1997 to 2006 were evaluated through the Brazilian-Portuguese validated University of Washington - Quality of Life Questionnaire. **Results:** Patients under or equal 45 years had better recreation score than patients older than 45 years (p=0.036). Of the 154 patients, 38 patients were submitted to neck dissection. Patients submitted to modified radical neck dissection reported worse scores on chewing and shoulder pain than patients only submitted to selective paratracheal lymph node dissection or without neck dissection (p=0.003 and p=0.004, respectively). Patients that received more than 150mCi reported significantly worse scores to pain, swallowing, chewing, speech, taste, anxiety and composite score. Comorbidities evaluated by ASA classification showed statistical significant impact on recreation, activity, speech, saliva and composite score (p=0.015; p=0.046; p=0.020; p=0.011 and p=0.008 respectively). In a multivariate analysis radioactive iodine therapy (RIT) is the only variable associated with a worse composite score (p=0.003). **Conclusions:** These results show that although the QOL after treatment in thyroid cancer patients can be considered good for most patients, those patients submitted to RIT with doses higher than 150mCi are particularly at risk for poor quality of life and therefore may need more intensive follow up and treatment.

Keywords: thyroid cancer, radioiodine therapy, quality of life.

Introdution

Differentiated thyroid cancer (DTC) patients in general have a very good prognosis, and the overall long-term survival rate is higher than 90%, with variations

among subsets of patients.[1-2] In DTC surgery is the therapy of choice. Surgical options include lobectomy with istimectomy or total thyroidectomy with or without neck lymph node dissection. The choice of procedure is influenced by well-defined prognostic factors. Ablative surgery of the thyroid and possible neck disease, with post-operative radioactive iodine treatment (RIT) result in prolonged survival but may lead to voice alterations, dysfagia, sialodenitis, taste disturbance and xerostomia.[3-5]

Traditionally, the main outcome measure in oncologic patients has long been survival, based on tumor control, but recently it has been increasingly recognized that the diagnosis and management of cancer can have a major impact on every aspects of a patient's quality of life (QOL).[1] The aims of cancer treatment became not only to increase survival but also to preserve quality of life[2] and measuring these changes has been considered to be of paramount importance.[1,6]

Quality of life (QOL) is defined as an individual's perceptions of his or her position in life, in the context of the culture and value systems in which he or she lives and in relation to his or her goals, expectations, standards and concerns (WHOQOL Group 1993). The Health-Related Quality of Life (HR-QOL) refers to a multidimensional concept which encompasses perception of both negative and positive aspects of at least the four dimensions of physical, emotional, social and cognitive functions which could be influenced by the disease or its treatment.[7] Several instruments have been developed to assess QOL in patients with head and neck cancer. Among them, the University of Washington Quality of Life (UW-QOL) questionnaire is a validated, accurate, and internationally accepted survey instrument.

The use of such questionnaire allows evaluation of HR-QOL and leads to better understanding of patient's expectations.[6]

In the last 20 years, an increasing number of studies have measured QOL as an endpoint in the evaluation of the impact of the disease and its treatment on the patient's daily life.[6,8] However, there have been relatively few HR-QOL studies looking specifically into thyroid cancer patients.[1,7,8] The aims of this study are to assess the QOL in DTC patients and evaluate if different modalities of treatment can interfere in the QOL of these patients.

Patients and methods

Design

A cross-sectional analysis of adults patients with initial DTC treated with total thyroidectomy and submitted or not to adjuvant radioiodine therapy (RIT) from 1997 to 2006 at a single Tertiary Cancer Institution was performed. Patients submitted to prior head and neck radiation or with Sicca Syndrome' symptoms were excluded. The study was approved by the institutional ethics committee and all patients signed an informed consent form.

The patients were invited to participate of this study in their follow-up medical consultation. All of them had normal thyroid hormone levels, and patients from 4 months to 10 years since the end of treatment were included, with a median time of 2 years post-treatment. The independent variables were age, gender, time since treatment, RIT dose, neck dissection, and comorbidities. The dependent variables were 13 QOL scales from the UW-QOL questionnaire.

Sample

Four hundred patients that completed the inclusion criteria were invited to participate of this study. Of those, 184 patients agreed to participate and 154 completed the questionnaire and had clinical stages I and II tumors. A total of 137 (89%) were female and 17 (11%) were male and the mean age was 46.9 and the median age 46 years (21y – 87y). All patients were submitted to a total thyroidectomy, and 38 patients were also submitted to a neck dissection of levels II-IV (2 patients), II-VI (9 patients) and level VI (27 patients). One hundred fifty one patients had papillary carcinoma and 3 patients had follicular carcinoma. The clinical stages were 85% of tumors in stage I and 15% in stage II. Ninety three (60%) patients were submitted to RIT and the median doses was 130mCi (30 – 700mCi). Seventy three patients received doses up to 150 mCi and 20 patients received doses higher than 150mCi. According comorbities the ASA classification was used and it was possible to collect data from 137 patients. Thirty eight patients were classified as ASA I, 97 patients as ASA II and 2 patients as ASA III. The data are summarized in the Table 1.1.

Measures

Demographic measures included age in years (≤ or > 45 years) and gender. The age of 45 years was used as a reference due to its important prognostic value in DTC patients.

The classification to neck dissection was paratracheal (level VI), radical (level II-IV) and extend radical (level II-VI). At the analysis these patients were grouped as none (no neck dissection), paratracheal (neck dissection of level VI) and radical (neck dissection of level II-IV and level II-VI).

Many studies have discussed that radioactive iodine effects are dose-dependent and a recent study of our group showed that doses higher than 150mCi have more side effects on salivary glands. In this way, we categorized the variable RIT in patients that were not submitted to RIT, patients that received up to 150mCi and those that received more than 150mCi.

Time since treatment was measured in months and categorized into 12 months or less and more than 12 months.

The American Society of Anesthesiologist's physical status classification (ASA), which is graded in: I – healthy patients, no medical problems, II – mild systemic disease, III – severe systemic disease but not incapacitating, IV – severe systemic disease that is constant threat to life, and V – moribund, not expected to live 24 hours irrespective of operation, was used to grade the comorbidities of the patients and to associate them with the quality of life of these patients. See details on Table 1.1.

Quality of life assessment

A Brazilian-Portuguese version of the University of Washington Quality of Life (UW-QOL) questionnaire validated by Vartanian *et al*[9] was used. The UW-QOL questionnaire was designed as a self-reported scale and for this reason the patients answered it by themselves. Patients that did not feel able to answer the UW-QOL questionnaire alone had help of their companion. The UW-QOL questionnaire was applied during the year of 2006 in days reserved only to this study.

The questionnaire consists of 12 questions that evaluate the following domains: pain, appearance, activity, recreation, chewing, swallowing, speech, shoulder, taste, saliva, humor and anxiety and the score vary from 0 to 100, with the

score 100 indicating the best function. The composite score is the mean of the scores of all 12 domains. There is a general agreement that a composite score between 75-100 has a little impact on the QOL, a score between 50-74 has a relative impact on the QOL, and a composite score under 50 has an important impact on the QOL. Three general questions evaluate the global QOL and the HR-QOL. We scored the individual domains according to the UW-QOL guidelines. Composite score was calculated as the mean of the domains scores.

Statistical Analyses

Statistical analysis was performed using version 15.0 of the SPSS statistical program (SPSS Inc, Chicago, III) for Windows. A descriptive analysis of the results was performed. Bivariate analyses were conducted comparing each of the independent variables of age, gender, neck dissection, RIT, time since treatment and comorbidities to each of the 13 QOL scales on the UW-QOL questionnaire using non-parametric Mann-Whitney or Kruskal-Wallis tests. To determine significant predictors of QOL controlling for one another, multivariate analysis was conducted using multiple linear regression.

Results

In answering the UW-QOL global questions on overall health, 94.4% of patients reported that their health was the same or better than it was prior to treatment, 83.9% of patients reported good HR-QOL, and 83.3% of patients reported good general QOL. There were no significant differences in these global questions regarding age, gender, RIT, neck dissection or comorbidities. The median composite score was 93.05 (53.5 – 100) which is associated with a good quality of life.

Bivariate Analyses

Evaluating demographic variables, age had impact on the recreation domain, with patients older than 45 years showing worse score than younger patients (p=0.043). To the other domains age did not have significant association. In the same way, the gender did not have impact on any domain (Table 1.2).

RIT had impact on many domains and doses higher than 150 mCi had a strong association with worse scores in several domains, as pain (p=0.045), swallowing (p=0.028), chewing ($p < 0.001$), speech (p=0.004), shoulder (p=0.037), taste (p=0.006), anxiety (p=0.004) and composite score (p=0.012). The patients submitted to neck dissection from level II-VI had significant worse scores to chewing (p=0.003) and shoulder (p=0.004) domains. The time since treatment was not associated with worse scores in any domain.

Patients classified as ASA II and III had worse scores in activity (p=0.046), recreation (p=0.015), speech (p=0.020), saliva (p=0.011) domains and in the composite score (p=0.008). All these data are summarized in the Table 1.2.

Multivariate Analyses

To conserve power and because gender and time since treatment were not significant in the bivariate analyses, they were omitted from the multivariate analyses. Variables with p value up to 0.250 were considered in multiple linear regression to determine the greatest predictor of QOL in thyroid cancer patients controlling for one another.

RIT was the strongest predictor factor affecting many domains as chewing, speech, taste, saliva and anxiety. It was the only variable that influenced the composite score. Comorbidities measured by ASA classification was the second

predictor to worse QOL affecting several domains as recreation, speech and saliva. Neck dissection affected chewing and shoulder, and age affected recreation. The data are summarized in Table 1.3 with the value of unstandardized coefficient B and each p value.

Discussion

At this study, in univariate as well as in multivariate analysis the greatest predictor of quality of life in thyroid cancer patients was RIT doses with higher dosages showing decreased QOL through the composite score. The composite score shows the impact of all domains evaluated and worse scores in specific domains will reflect at the final score. Functions as taste, speech, chewing and swallowing are strongly associated to RIT salivary gland effects as it is seen through the association between RIT and these domains in the UW-QOL questionnaire. Until now, in our literature review, none of published studies showed the impact of RIT or doses of radioactive iodine in the thyroid cancer patients' quality of life. This is an important finding, since that the indication of RIT should also consider the late effects of the treatment.

The side effects of RIT are well recognized, and in general are mild and self-limited and severe complications are rare enough that the benefit of therapy typically outweighs its risk.[14,15] The common acute side effects reported are nausea, vomiting, epigastralgia, taste disturbance and sialodenitis[15], and the late side effects normally restrict to the salivary glands as sialodenitis and xerostomia.[3] Recent findings of our group reinforce the hypothesis of Maier and Bihl (1987)[16] that patients submitted to RIT have an impairment to drain the saliva and it reflects as clinical dysphagia.

Considering that many of patients with differentiated thyroid cancer are submitted to RIT, the impact of those specific side effects and those resulting from the surgical procedure on the quality of life of such patients were not previously extensively described. There have been relatively few and recent HR-QOL studies looking specifically into thyroid cancer patients.[1-2,7-8,17-20] The paucity of specific instruments to assess the QOL of thyroid cancer patients associated to low mortality and morbidity rates of the treatment can explain so few studies in this field.

The majority of the published studies uses the SF-36 that is a generic QOL instrument and do not have specific domains to evaluate the impact of possible side effects of the treatment. The UW-QOL questionnaire, while not commonly used among thyroid cancer patients, has value in predicting QOL among these patients since it makes possible to evaluate points that can be related to side effects of the surgery and RIT.

The main post-operative complications of thyroidectomy are vocal cord palsy due to dysfunction of the recurrent laryngeal nerve and hypocalcemia. Neck dissection and paratracheal lymph node dissection when associated with total thyroidectomy were significantly associated with transitory and permanent hypocalcemia.[12-13] Besides that, swallowing changes, and occasional dysphagia are sequelae reported after thyroid resection, even long time after the surgical procedure.[5]

Interesting, the neck dissection was associated to chewing function instead of swallowing function, what is commonly reported at the literature due to the injury of recurrent nerve. As expected neck dissection affected the shoulder domain of QOL instrument.

Pre-existent comorbidities are associated to a decreased recreation, what was expected, and domains as speech and saliva. Worse scores of these last domains associated to the presence of comorbidities probably can be explained by the intake of some medications that can interfere with the salivary flow.

To our knowledge there is only one study that evaluated the impact of the resulting side effects of surgical and radioactive iodine on such patients. This study used an UW-QOL questionnaire adapted and not validated.[8] The authors evaluated 20 thyroid cancer patients and reported that patients older than 45 years had worse scores to general health, appearance and chewing, but did not show association of RIT or neck dissection with any domain.

Different from data of Dagan *et al* (2004)[8] our patients reported good general QOL, with a light impact of the treatment on their health QOL. However, in our study patients older than 45 years had worse recreation score, and pre-existent comorbidities had impact on activity, recreation, speech, saliva. The great impact on the QOL with specific domains was the doses of RIT. Patients submitted to doses higher than 150mCi had many domains affected as pain, swallowing, chewing, speech, taste, anxiety and composite score. Morbidities of the surgery are detected in chewing and shoulder functions. The time since treatment and gender were not associated with alterations on the QOL.

These results reveal that in spite of thyroid cancer patients have a good general QOL there is a subset of patients that live with some comorbidities of the cancer treatment. The doses of RIT can impact on specific activities in daily life of these patients. The impacts of RIT on specific functions had not been assessed and reported at the literature until this moment, and more studies are needed to confirm

these findings. Certainly this study has some limitations, since it is a cross-sectional study and there is neither a baseline QOL before the treatment nor a follow up over the time. Evaluation of QOL in different points of time since treatment could be another limitation, but at the analysis it seems not influence the results. Prospective studies associating videofluoroscopy to evaluate the different phases of swallowing and salivary gland function studies with patients receiving more than 150mCi can contribute to clarify these findings.

Table 1.1 - Description of demographic and treatment variables.

	Total	N	Percent
Age	154		
≤ 45y		73	47%
> 45y		81	53%
Gender	154		
Male		17	11%
Female		137	89%
RIT	154		
None		61	40%
≤ 150 mCi		73	47%
>150 mCi		20	13%
Neck dissection	154		
None		116	75%
Paratracheal		27	17%
Radical		11	8%
Clinical Stage	154		
I		131	85%
II		23	15%
ASA	137		
I		38	28%
II		97	71%
III		2	1%

Table 1.2 - Bivariate associations between demographic and treatment variables and each function domain and composite score of UW-QOL questionnaire*.

	Pain	Appearance	Activity	Recreation	Swallowing	Chewing	Speech	Shoulder	Taste	Saliva	Humor	Anxiety	Composite Score
Age													
≤ 45y				94,52									
> 45y				90,12									
p Value	0,736	0,257	0,291	**0,043**	0,192	0,566	0,894	0,898	0,148	0,226	0,327	0,256	0,056
Gender													
Male													
Female													
p Value	0,058	0,091	0,449	0,825	0,113	0,893	0,831	0,108	0,312	0,423	0,549	0,773	0,051
RIT													
None	86,48				95,92	98,36	98,38	89,62	96,72			88,03	91,56
≤ 150 mCi	88,01				96,84	99,32	98,64	85,89	94,55			89,58	91,82
> 150 mCi	76,25				90,10	87,5	91,75	71,70	85,05			76,85	84,03
p Value	**0,045**	0,562	0,121	0,519	**0,028**	**< 0,001**	**0,004**	**0,037**	**0,006**	0,196	0,647	**0,004**	**0,012**
Neck dissection													
None						98,28		86,80					
Paratracheal						98,15		90,15					
Radical						94,00		60,73					
p Value	0,860	0,154	0,765	0,553	0,321	**0,003**	0,329	**0,004**	0,829	0,941	0,193	0,094	0,563
Time since Tx													
≤ 12 m													
> 12 m													
p Value	0,877	0,610	0,742	0,195	0,721	0,639	0,495	0,569	0,576	0,202	0,136	0,712	0,555
ASA													
I			91,45	94,08			97,39			95,66			93,20
II			85,57	92,27			98,64			90,11			90,02
III			75,00	62,50			83,50			67,00			83,37
p Value	0,241	0,153	**0,046**	**0,015**	0,126	0,777	**0,020**	0,335	0,345	**0,011**	0,468	0,329	**0,008**

*UW-QOL – Universitiy of Washington Quality of Life.

** Mean values for statistical significant variables are shown above p values.

Table 1.3 - Multiple linear regressions with the significant variables on the bivariate analyses.

	Pain	Appearance	Activity	Recreation	Swallowing	Chewing	Speech	Shoulder	Taste	Saliva	Humor	Anxiety	Composite Score
Age	-	-	-		-	-	-	-	-	-	-	-	-
≤ 45y				0.028									
> 45y				(-5.899)									
RIT	-	-	-	-	-			-			-		
None/≤ 150 mCi						0.001	0.016		0.004	0.010		0.049	0.003
> 150 mCi						(-9.358)	(-4.705)		(-10.889)	(-10.925)		(-10.960)	(-7.182)
Neck dissection	-	-	-	-	-		-		-	-	-	-	-
None/Paratracheal						0.027		0.006					
Radical						(-7.700)		(-22.205)					
ASA	-	-	-		-	-		-	-		-	-	-
I/II				0.013			0.004			0.041			
III				(-27.560)			(-15.384)			(-23.786)			

The values are the p Value and the B value to the confidence interval of 95%.

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4.1.2 Artigo 2: *Late side effects of radioactive iodine therapy on salivary gland function in patients with thyroid cancer*

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Summary

One hundred eighty two patients were evaluated in a retrospective cohort study to describe late side effects of Radioiodine Therapy (RIT) on salivary gland function in patients with well-differentiated thyroid cancer. One hundred six patients were submitted to total thyroidectomy and adjuvant RIT and 76 underwent only total thyroidectomy. Assessment of salivary function was performed with salivary gland scintigraphy (SGS), sialometry and subjective questions to assess the common side effects of RIT on salivary glands function. Five patients reported recurrent swellings of the salivary glands after RIT with or without pain, and 28 patients reported taste disturbance. At univariate analyses RIT had a strong association with decreased elimination counts at SGS. Age was the only variable associated with unstimulated salivary flow (USSF) and to stimulated salivary flow (SSF) age and use of

xerostomic drugs were strongly associated with decreased mean values of salivary flow ($p<.001$ and $p=.001$, respectively). Dysphagia complaint was strongly associated with RIT ($p=.002$). At multiple logistic regression age was an important factor associated to salivary gland dysfunction and RIT is strongly associated with impairment of saliva excretion. These results show that age is an important factor to salivary gland function, but also show that patients submitted to RIT have more difficulty in draining saliva, mainly from the parotid glands. This finding suggests that the mechanism of sialodenitis associated with RIT is more influenced by a ductal system constriction than significant acinar damage.

Key words: thyroid cancer, radioactive iodine, salivary gland dysfunction, head and neck cancer.

Introduction

Saliva has several significant roles in maintaining oral function, through the action of proteins such as amylase, immunoglobulins and lysozymes. It also lubricates the oral mucosa, allowing proper speaking, swallowing and tasting. Loss or decrease of salivary production or flow can impair the ability to perform these functions and is remarkably associated with post-radiation or radioiodine treatment morbidities (1). In the unstimulated state, about two-thirds of the normal volume of saliva is produced by submandibular glands. However, depending on the type of stimuli, the parotid glands can account for about 50% of the volume of saliva (2).

According to Helman *et al.* (3), salivary glands concentrate iodine, substituting the Cl^- as a substrate for the $Na^+/K^+/Cl^-$ co-transport system. This ability

to concentrate iodine and radioactive iodine makes the salivary glands potential targets during and after the diagnostic or therapeutic use of these substances (1, 4). As a consequence, sialadenitis, taste disturbances, xerostomia and an increase in the number of dental cavities are recognized as short- and long-term effects of radioiodine therapy (RIT) on salivary glands (1).

The aim of this study is to describe the late side effects of RIT associated with salivary gland function in patients treated for differentiated thyroid carcinoma submitted to total thyroidectomy followed or not by adjuvant therapeutic doses of radioactive iodine.

Patients and Methods

Design

A cross-sectional study of patients with differentiated thyroid cancer (DTC), who underwent total thyroidectomy associated or not to adjuvant radioiodine therapy (RIT) from 1997 to 2006 was performed. Patients submitted to prior head and neck radiation or with symptoms of sicca syndrome were excluded. The study was approved by the institutional ethics committee and all patients signed an informed consent form.

The patients were invited to participate in this study on their follow-up medical consultations. All the patients were under suppressive doses of levothyroxine and had normal thyroid hormone levels. Only patients from 2 months to 10 years from treatment end were included, with a median post-treatment time of 24.0 months. The independent variables were age, gender, RIT dose, use of xerostomic drugs, xerostomia and dysphagia complaints. The dependent variables

were the uptake and elimination percentage of salivary gland scintigraphy and the unstimulated and stimulated salivary flow of sialometry.

Data about xerostomic drug use were obtained by asking the patient if they used any antidepressant, antihistaminic or hypotensive drugs.

Sample

Four hundred patients that fulfilled the inclusion criteria were invited to participate in this study. Of those, 182 patients agreed to participate, 168 patients completing salivary gland scintigraphy and 179 patients performing sialometry. A total of 159 (87.5%) were female and 23 (12.6%) were male with the mean age of 49.7 years and the median age of 49 years (range, 23-89 years). One hundred seventy-seven patients had papillary carcinoma and 5 patients had follicular carcinoma and all patients were submitted to a total thyroidectomy. One hundred six (58.2%) patients were submitted to RIT and the median dose was 135mCi (from 30 to 450mCi). Eighty-two patients received doses up to 150 mCi and 26 patients received doses higher than 150mCi. Seventy-nine (43.4%) patients reported to occasionally or continuously use xerostomic drugs and 17 (9.5%) patients reported to feel dry mouth and/or dysphagia. Data are summarized in Table 2.1.

Measures

Patients were categorized in age ≤ or > 45 years, since the age of 45 years is used as an important prognostic value reference in DTC patients (5).

Many studies have discussed that radioactive iodine effects are dose-dependent and a recent study of our group showed that doses higher than 150mCi have more side effects on salivary glands (6, 7). Therefore, we subcategorized the

RIT variable into patients that received up to 150mCi and those that received more than 150mCi.

Some subjective questions were answered by all patients: (a) “Do you feel your mouth is dry?”; (b) “For what periods of the day?”; (c) “Do you have difficulty eating?”; (d) “What kinds of foods?”; (e) “Do you have any difficulty speaking?”; (f) “Do you have any taste disturbances?”; (g) “What flavors?”; (h) “Do you have any swelling in the salivary gland regions?”; and (i) “When does it occur?”. These questions were created to identify the most common complaints related to salivary gland dysfunction.

Salivary Gland Scintigraphy

Salivary gland scintigraphy (SGS) was performed with a gamma camera (GE StarCam 4000, GE Medical System, Milwaukee, WI, USA), fitted with a low-energy high-resolution (LEHR) collimator, energy peak set at 140KeV and 15% window. Each patient received 10 mCi (370MBq) of $^{99m}TcO^{4-}$, intravenously administrated. Dynamic images were obtained in 90 seconds (one second/image) with a 128 X 128 matrix in anterior projection. Static images of anterior and lateral projections, with a 256 X 256 matrix, were obtained during 180 seconds per image, before and after salivary gland stimulation with 500mg ascorbic acid (Cewin®, Sanofi-Synthelabo, Brazil) orally administrated for five minutes. At the workstation computer, regions of interest (ROIs) were created on the salivary gland regions and the regional counts were verified. The uptake rate was calculated to each major salivary gland, bilateral parotid and bilateral submandibular, as the count percentage of the real dose retained in each pair of glands. The real dose was 10mCi in counts subtracting the dose in counts retained in the local of injection and the dose in counts remained in the

syringe. The elimination fraction was calculated as the difference between the count in each pair of glands pre-stimulus and post-stimulus. This difference was converted as a percentage of the total uptake. SGS was intended to evaluate the salivary gland function through the percentage of $^{99m}TcO^{4-}$ uptake and elimination.

Sialometry

Sialometry was performed as described by Koseki *et al.* (8), and whole saliva was collected in a tube of 15 ml for five minutes and 500mg ascorbic acid (Cewin®, Sanofi-Synthelabo, Brazil) orally administrated was used to obtain the stimulated salivary flow. The salivary flow was expressed in ml/min. The normal parameters were based on data published by Jensen *et al.* (2), who described cutoffs of unstimulated salivary flow (USSF) at 0.3 ml/min and stimulated salivary flow (SSF) at 1.5 ml/min.

Statistical Analysis

For statistical analysis, t-test was employed for univariate analysis, with multivariate analysis by multiple linear regressions employed to determine the real independent variables that affected the sialometry and scintigraphy values. For comparisons, a p-value < 0.05 was considered significant.

Results

Five patients (2.8%) reported at the time of the study recurrent swelling of the salivary glands after RIT with or without pain. From these five patients, three had swelling of the salivary glands only while eating and two spontaneously. Most patients that reported recurrent sialadenitis were unable to give precise information on the temporal relationship with RIT. Sialadenitis was diagnosed by a swelling in

the region of major salivary glands with or without pain with spontaneous resolution and without clinical signs of bacterial or viral infection. The diagnosis of sialadenitis was clinical on the basis of patients' complaints and physical findings. Twenty-eight (15.6%) patients reported some kind of persisting taste disturbance and 19 (67.8%) of those patients had been submitted to RIT.

Univariate Analysis

Only gender showed an association with uptake phase of SGS. Men had a decreased uptake in all major salivary glands (parotid glands p=.05; submandibular glands p=.02; all salivary glands p=.03) when compared to women. Other variables did not show any association. In relation to elimination phase of SGS, as expected, RIT had a strong association with decreased excretion ability in parotid glands, and this impairment reflects when elimination was calculated to all glands together (parotid glands p<.001; all salivary glands p=.002). When doses of radioiodine were analyzed, there was no influence of doses up to 150mCi or higher than 150mCi in the uptake or elimination ability. The data are summarized in Table 2.2.

For sialometry, age was the only variable associated with USSF. Patients 45 years of age or younger had a mean value of USS higher than patients older than 45 years of age (p=.02). Other variables did not show association. For SSF, age and the use of xerostomic drugs were strongly associated with decreased mean values of salivary flow (p<.001 and p=.001, respectively). Different from salivary gland scintigraphy, RIT was not associated with altered SSF. Data are summarized in Table 2.3.

The association of RIT with xerostomia complaint was not statistically significant (p=.63), with 11 patients who reported this complaint had previously been

submitted to RIT and 6 patients had not. For dysphagia complaint, this association was strongly significant (p=.002). Of those 17 patients with a complaint of dysphagia, 16 had been submitted to RIT.

Multivariate Analysis

Age was the strongest predictor to parotid gland dysfunction, affecting uptake and elimination phases of the parotid glands at SGS, USSF and SSF at sialometry. Gender remains affecting uptake phase of SGS and RIT interferes with the excretion ability of salivary glands, mainly in parotid glands, verified by elimination phases and SSF in SGS and sialometry, respectively. The use of xerostomic drugs affected the SSF at sialometry (Table 2.4).

Discussion

In this study, incidences of sialadenitis and taste disturbance are small as compared to those published by Alexander *et al.* (6). Our sialadenitis rate was 2.8% and taste disturbance was 15.6%, while Alexander *et al.* (6) published an incidence of 33% and 27%, respectively. These differences can probably be explained based on the design of the studies. The data published by Alexander *et al.* (6) were collected in a prospective cohort-type study, which has more sensitivity power when subjective data are collected. In our study, which is retrospective cohort-type, we depend on the memory of patients and how important those side effects are to them.

As discussed in many studies (9, 10, 11), age is an important factor that affects salivary gland function. This study reinforced the role of age on salivary gland function, with patients older than 45 years of age showing lower uptake and elimination counts at SGS, and lower values to USSF and SSF at sialometry.

Different from all studies published about the influence of gender on salivary gland function (10, 12), which always report that females had lower salivary gland function, our study showed lower uptake counts at SGS in men, but no other alteration in elimination counts or USSF/SSF associated to gender.

As previously reported by other studies (4, 6, 13), salivary glands can present dysfunction when exposed to radioiodine. Their ability to eliminate $^{99m}TcO^{4-}$ after RIT diminishes significantly. The crossing of radioiodine through the $Na^{+}/K^{+}/Cl^{-}$ co-transport system depends on its correct functioning, and it is known that this system is affected by radiation during the RIT (3, 14). This excretion impairment can be associated with ductal system constriction, acute periductal inflammation and chronic sclerosis induced by radioiodine, since this transport system is mostly prevalent in the ductal cells (15). Confirming this theory, the results of univariate and multivariate analysis showed impairment of the elimination phase mainly in parotid glands and of SSF at sialometry. Possibly because salivary gland damage related to radioactive iodine is more concentrated in the ductal system, there were no effects on uptake phase at SGS which can show the $^{99m}TcO^{4-}$ in the periductal region. Furthermore, periductal constriction makes saliva excretion more difficult when the production of saliva is higher, reflecting in a diminished SSF rate.

It is important to understand that SGS and sialometry are different ways to verify salivary gland function and both focus in different phases of saliva production. SGS is able to detect the path some important ions are delivered into the duct system to compose the whole saliva with water, proteins and other ions. Sialometry is only able to quantify the volume of whole saliva that can be composed for all components in normal quantities or not.

Xerostomic drugs were associated with a lower SSF, probably because they alter the quantity of liquid that will compose the saliva (16). Xerostomia and dysphagia complaints were not associated with any method to verify salivary gland function, but dysphagia complaint was strongly associated to RIT. Dysphagia is a very well recognized side effect of thyroid cancer treatment (17, 18) and recently our group published new data about patients submitted to doses higher than 150mCi that had worse scores for swallowing and many other functional domains of the University of Washington Quality of Life Questionnaire with a significant impact on the quality of life (7).

Conclusion

This study has some limitations since it is a retrospective cohort-type study. However, these results reinforce the influence of age on salivary gland function and the side effects of RIT on saliva excretion suggesting that the mechanism of sialadenitis associated with RIT is more influenced by an effect on the ductal system than by significant acinar damage. This saliva excretion impairment can be reflected clinically as dysphagia, which has an important impact on the quality of life of these patients. Prospective studies using videofluoroscopy exams to verify different phases of swallowing will be important to clarify the impact of surgery and doses of RIT on the swallowing function.

Table 2.1 - Descriptive analyses of dependent variables.

	Total	N	Percent
Age	182		
≤ 45y		72	39.6
>45y		110	60.4
Gender	182		
Male		23	12.6
Female		159	87.4
RIT	182		
Yes		106	58.2
No		76	41.8
Xerostomic	182		
Drugs		79	43.4
Yes		103	56.6
No			
Xerostomia	179		
Yes		162	90.5
No		17	9.5
Dysphagia	179		
Yes		162	90.5
No		17	9.5

RIT – Radioiodine Therapy

Table 2.2 - Univariate analyses associating salivary gland scintigraphy results with dependent variables.

	% parotid uptake*	% submandibular uptake*	% total uptake*	% parotid elimination*	% submandibular elimination*	% total elimination*
Age						
≤ 45y	1.48	1.67	3.14	29.37	27.74	28.91
>45y	1.32	1.59	2.90	28.43	29.37	29.52
P Value	.18	.51	.30	.63	.23	.66
Gender						
Male	1.08	1.25	2.33	28.76	27.20	28.27
Female	1.42	1.67	3.09	28.80	28.93	29.42
P Value	**.05**	**.02**	**.03**	.99	.40	.58
RIT						
Yes	1.36	1.66	3.02	24.76	27.97	27.37
No	1.40	1.56	2.96	33.52	29.66	31.76
P Value	.76	.44	.81	<.001	.22	**.002**
RIT						
≤150mCi	1.41	1.70	3.11	26.14	28.75	28.24
>150mCi	1.20	1.51	2.71	22.44	25.46	24.65
P Value	.36	.42	.38	.28	.12	.11
Xerostomic Drugs						
Yes	1.36	1.63	2.99	27.61	28.61	28.75
No	1.39	1.61	3.00	29.77	28.83	29.72
P Value	.76	.91	.92	.27	.87	.48
Xerostomia						
Yes	1.47	1.70	3.17	29.88	28.70	29.63
No	1.36	1.61	2.97	28.56	28.75	29.20
P Value	.59	.65	.61	.69	.98	.85
Dysphagia						
Yes	1.25	1.55	2.80	24.00	28.58	27.10
No	1.38	1.62	3.00	29.18	28.76	29.47
P Value	.49	.71	.59	.12	.93	.30

*Mean values; RIT – Radioiodine Therapy

Table 2.3 - Univariate analyses associating sialometry results with independent variables.

	USSF*	SSF*
Age		
≤ 45y	.54	2.72
>45y	.40	2.08
P Value	**.02**	**<.0001**
Gender		
Male	.55	2.51
Female	.44	2.31
P Value	.20	.36
RIT		
Yes	.42	2.23
No	.50	2.47
P Value	.17	.10
RIT		
≤150mCi	.42	2.29
>150mCi	.41	2.01
P Value	.87	.25
Xerostomic Drugs		
Yes	.40	2.07
No	.49	2.53
P Value	.12	**.001**
Xerostomia		
Yes	.33	2.36
No	.46	2.32
P Value	.17	.84
Dysphagia		
Yes	.32	2.00
No	.47	2.35
P Value	.15	.16

*Mean values; USS – Unstimulated Salivary Flow; SSF – Stimulated Salivary Flow; RIT – Radioiodine Therapy

Table 2.4 - Multiple linear regression with independent variables.

	% parotid uptake*	% submandibular uptake*	% total uptake*	% parotid elimination*	% submandibular elimination*	% total elimination*	USSF*	SSF*
Age								
≤ 45y	**.045**	.135	.056	**.039**	.837	.322	**.010**	**<.001**
>45y								
Gender								
Male	**.026**	**.016**	**.024**	.825	.461	.717	.249	.528
Female								
RIT								
Yes	.817	.357	.719	**<.001**	.269	**.002**	.093	**.036**
No								
Xerostomic Drugs	.911	.764	.832	.575	.799	.650	.444	**.028**
Yes								
No								

*P Values; USS – Unstimulated Salivary Flow; SSF – Stimulated Salivary Flow; RIT – Radioiodine Therapy.

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4.1.3 Artigo 3: *The use of pilocarpine to treat xerostomia in patients submitted to radioactive iodine therapy: a pilot study.*

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Abstract

Objectives: Report the experience with use of pilocarpine on the treatment of xerostomia in thyroid cancer patients submitted to adjuvant radioactive iodine therapy (RIT). Subjects and methods: Five patients meeting the inclusion criteria received 5mg of pilocarpine, 3 times per day, for one week. Side effects of the drug and subjective response to xerostomia complaints after treatment were evaluated. Results: Sudoresis was the most frequent side effect of pilocarpine use, followed by fatigue and headache. Two patients reported relief of xerostomia using pilocarpine, but only one patient was able to tolerate the side effects. Conclusions: Pilocarpine seems to relieve xerostomia complaints in thyroid cancer patients since it is able to stimulate salivary flow, but the observed side effects made the patients refuse long-term therapy continuation.

Keywords: xerostomia; pilocarpine; thyroid cancer; radioactive iodine therapy

Introduction

The saliva plays an integral part in maintaining oral functions and the loss or decrease of salivary flow or production can impair the ability to perform its functions and is associated with increased morbidity, thus impacting the patient's quality of

life. The ability to concentrate iodine on the salivary glands makes them potential targets during and after radioiodine therapy (RIT) (Newkirk et al. 2000).

Serious acute complications with RIT are extremely rare. However, intermediate and long-term side effects are well described in the literature as sialodenitis, transient loss of taste, xerostomia and cavities (Bushnell et al. 1992, Alexander 1998, Newkirk et al. 2000).

Xerostomia is the sensation of dry mouth reported by the patient (Jensen et al. 2003). Xerostomia can be caused by many factors as local and systemic diseases, medications, radiation, and chemotherapy. Alexander et al. (1998) and Caglar et al. (2002) reported rates of xerostomia associated to RIT as high as 42.9% and 54%, respectively, normally 1 year after the therapy. Our studies have shown that 11.2% of the patients submitted to RIT have persistent xerostomia complaints (during the entire day) (Almeida et al. 2009).

Treatment of xerostomia is difficult and involves symptomatic relief by the administration of sour-tasting sugarless candies, sips of water, saliva substitutes and drug treatment with the use of sialogogues. Pilocarpine is a parasympathomimetic agent with mild β-adrenergic properties that stimulate cholinergic receptors on the surfaces of the exocrine glands, causing a reduction of the symptoms of xerostomia. Reported serious adverse events are rare with pilocarpine, but side effects as sweating, flushing and urinary frequency are common, with typically mild or moderate intensity for a relatively short duration (Fox et al. 2004).

The aim of this pilot study is to describe the feasibility and efficacy of pilocarpine as a treatment of xerostomia in patients submitted to RIT.

Patients and methods

This report is part of a large study that invited 400 patients treated for well-differentiated thyroid cancer, submitted or not to RIT from 1997 to 2006. Of those, 184 patients accepted to participate in the study and signed a consent form. One hundred eighty patients had papillary carcinoma and only four had follicular carcinoma. The mean age of the patients was 49.9 years and the median age was 49 years (25 - 89y). One hundred eight (58.7%) patients were submitted to RIT and 76 (41.3%) were not. Seventy-eight (42.4%) patients used some kind of xerostomic drug. All patients were submitted to sialometry and salivary gland scintigraphy.

The criteria to enter the pilocarpina protocol was: patients submitted to RIT presenting at the same time with xerostomia complaints, abnormal values at sialometry (unstimulated $\leq$ 0.3 ml/min; stimulated $\leq$ 1.5 ml/min) (Jensen 2002) and visual dysfunction at the salivary gland scintigraphy, and without clinical contra-indications to pilocarpine such as asthma, hypertension, cardiac diseases and close-angle glaucoma. Blood pressure was verified before the beginning of pilocarpine treatment and the treatment consisted of 5 mg of pilocarpine 3 times per day as recommended by the literature (Fox 2004), mainly before meals and at night, during 1 week. The patients filled out a control questionnaire about side effects and reported all symptoms during seven days.

Results

Of 108 patients submitted to adjuvant RIT, 65.4% (70 patients) reported xerostomia at least one period of the day and 11.2% (12 patients) all the time. Of these 70 patients, only nine patients met the criteria for pilocarpine treatment. The mean age of the patients was 52.1 years and the median age was 56 years (36–65y).

The mean dose received of radioactive iodine was 183.3 mCi and the median dose was 150 mCi (100–450 mCi). Of these nine patients, four patients were not included in the study. One patient did not accepted to participate in the study, and three patients had arterial hypertension. The data of treated patients are summarized in table 3.1.

Table 3.1 - Data of five patients who completed one week of treatment with pilocarpine

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Age	38	56	57	58	36
RIT (mCi)	200	100	150	250	450
USSF (ml/min)	0.02	0.24	0.30	0.24	0.30
SSF (ml/min)	0.42	1.38	1.10	1.16	1.50
Blood pressure (mmHg)	140 x 80	120 x 80	140 x 90	120 x 80	110 x 60
Sudoresis	✓	✓	✓		✓
Urinary frequency	✓		✓		
Lacrimation	✓		✓		
Shivering			✓	✓	
Fatigue		✓	✓	✓	
Dizziness				✓	✓
Nausea				✓	✓
Headache		✓		✓	✓
High blood pressure	✓				
Taquicardia	✓				
End result	NT	T	NT	T	NT

NT – No Tolerance to treatment due to side effects of pilocarpine; T – Tolerance to treatment and the patient was able to use pilocarpine for one week and had relief of xerostomia symptoms.

The most frequent side effect reported by the patients was sudoresis, affecting 4 out of 5 patients. Fatigue and headache were reported by 3 out of the 5 patients. Increase of urinary frequency, lacrimation, shivering, dizziness and nausea had the frequency of 2 in 5 patients. Alterations of blood pressure and taquicardia were reported by the same single patient. Evaluating the relief of xerostomia after pilocarpine use, two patients reported improvement of dry mouth sensation, but one with many side effects considered the use unacceptable.

Discussion

As opposite to external radiation, Iodine-131 therapy does not completely destroy salivary gland ability to secrete saliva, adequately preserving functional parenchyma to respond upon stimulus. Xerostomia is reported by 11 to 54% of patients submitted to RIT (Alexander et al. 1998, Caglar et al. 2002, Almeida et al. 2009). As differentiated thyroid cancer has good prognosis, reduction of RIT long-term oral side effects is essential in maintaining the patient's quality of life.

Contrary to external radiation therapy, which has many studies showing the efficacy of pilocarpine on salivary gland stimulus (LeVeque et al. 1993, Hamlar et al. 1996, Zimmerman et al. 1997, Horiot et al. 2000, Leek e Albertsson 2002, Haddad e Karimi 2002, Gorsky et al. 2004, Mosqueda-Taylor et al. 2004), the literature lacks studies analyzing the efficacy of pilocarpine to relieve xerostomia symptoms associated to RIT. Silberstein (2008) published results of the use of pilocarpine in a single-blind controlled study with 60 patients for one week after RIT trying to prevent sialadenitis associated to Iodine-131. This study showed that pilocarpine also did not reduce the occurrence of radiation sialadenitis. These results confirm data

published by Alexander et al. ten years before, that did not observe significant difference between the patients who received pilocarpine during RIT and those who did not.

Aiming to show another use of pilocarpine, Aframian et al. (2006) published a study showing the efficacy of a single-dose of pilocarpine on the entire unstimulated and stimulated salivary flow in five patients suffering from thyroid cancer treated with adjuvant RIT at least 3 months prior to study. The results showed significant elevation of unstimulated and stimulated saliva flow rate in four patients without significant alteration of systolic and diastolic blood pressure, pulse rate and body temperature.

Until the moment, no study in the literature uses pilocarpine for long-term treatment of xerostomia associated to RIT and evaluates the tolerability of the drug. The present study shows results that are not favorable to the use of pilocarpine as a routine treatment. The side effects with 3 doses per day for one week were not well tolerated by thyroid cancer patients and the use of this drug could not be further recommended since the benefits did not offset the side effects.

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4.2 ESTUDO II

Os resultados do estudo II estão descritos no artigo.

4.2.1 Artigo 4: *Amifostine protection of radioiodine side effects on salivary glands: a prospective, randomized and double-blind study*

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Abstract

Purpose: Radioactive iodine therapy (RIT) has many salivary glands effects and amifostine has been suggested to protect salivary glands during this therapy. This randomized, double-blind study aims to describe the protection effects of amifostine on salivary glands in patients submitted to RIT as adjuvant treatment to well-differentiated thyroid carcinomas. Patients and methods: thirty patients were randomized to receive 200 mg/m^2 of subcutaneous amifostine or saline solution as placebo before to receive therapeutic dose of radioactive iodine. Patients were evaluated with salivary gland scintigraphy, sialometry and subjective questions before and 3 months after RIT to investigate the efficacy of amifostine to protect salivary glands. Results: There were no differences between groups in all variables before treatment. During RIT, amifostine neither decreased the incidence of sialodenitis related to ^{131}I, nor the pain related to sialodenitis or the taste disturbance related to ^{131}I, but it was able to decrease the mean time of sialodenitis related to ^{131}I from 6.27 days in placebo to 3.5 days in amifostine group (P = .02). Three months after RIT there were no differences of parotid/submandibular uptake pre-stimulus between groups (amifostine P = .86; placebo P = .86). Values of parotid constant of excretion of -1.69%/min *versus* -5.03%/min in amifostine and placebo groups, respectively, show a diminished excretion function of parotid in both groups 3 months after RIT, higher in placebo but with no significant difference (P = .86). The values of submandibular constant of excretion of 1.51 %/min *versus* 1.99 %/min (P = .91) in amifostine and placebo groups, respectively, show that submandibular glands maintain the excretion function better than parotid glands after RIT. Conclusion: 200 mg/m^2 of subcutaneous amifostine was not able to protect salivary glands of acute side effects of RIT. More studies are needed to determine the safe and effective dose of amisfotine in thyroid cancer patients.

Key words: radioactive iodine, sialodenitis, side effects, amifostine, slivary glands

Introduction

Salivary glands concentrate iodine, substituting the Cl^- as a substrate for the $Na^+/K^+/Cl^-$ co-transport system.[1] This ability to concentrate iodine and radioactive iodine makes the salivary glands potential targets during and after the diagnostic or therapeutic use of these substances.[2-3] As a consequence, sialadenitis, taste disturbances, xerostomia and an increase in the number of dental caries are recognized as short- and long-term side effects of radioiodine therapy (RIT) on salivary glands.[2-4]

Amifostine is a thiophosphate that has been suggested to play a salivary gland protection against radiation and chemotherapy.[5] It has been used in head and neck radiation with controversial results in the literature,[6-7] but with thyroid cancer patients submitted to radioiodine therapy (RIT) the first data were presented by Bohuslavizki et al[8] in 1998 and subsequently by Kim et al[9] in 2008. The study published by Bohuslavizki et al[8] is a double-blind and placebo-controlled study, with 50 patients included, that showed reduction of parenchymal damage in salivary glands caused by RIT with the use of amifostine. The study published by Kim et al[9] is a non-randomized study, with 80 patients that did not show cytoprotective effects of amifostine for differentiated thyroid cancer patients treated with ^{131}I. The side effects of RIT as sialodenitis, xerostomia and taste disturbance are well discussed in the literature,[2-4] and the impact of these side effects on quality of life of these patients has been showed recently.[10] Effective ways to protect the patients to the side effects of RIT must be investigated to improve the long-term quality of life of these patients.

The aim of this study is to describe the protection effects of amifostine on salivary glands in patients submitted to RIT as adjuvant treatment to well-differentiated thyroid carcinomas.

Patients and methods

Design

This is a prospective, randomized and double-blind study of 30 patients, who underwent total thyroidectomy and were submitted to adjuvant radioiodine therapy (RIT). Patients submitted to prior RIT, head and neck external radiation, with symptoms of *Sicca* Syndrome or any contraindication to amifostine use (hypersensibility to aminothyol, low blood pressure, dehydratation, kidney or liver insufficiency, age over 70 years, pregnancy or lactation period) were excluded. The study was approved by the institutional ethics committee and all patients signed an informed consent form. This study was also registrated at Brazilian National Information System on Research Ethics under the number 1342.0.022.000-06.

Initially, the patients randomized to amifostine group (AG) received 500 mg/m^2 (Ethyol®, Shering Plough Brazil) intravenously and those patients randomized to placebo group (PG) received 1 ml of physiologic saline solution. After inclusion of 4 patients, due to reasons related bellow, dose of amifostine has been changed to 200 mg/m^2 administrated subcutaneously. Blood pressure was verified before and 15 minutes after administration of solutions and just after radioiodine was administrated. In this initial protocol were included 4 patients, but the last 2 included patients presented serious side effects after infusion. One patient had blood pressure 30 x 60 mmHg and it was very difficult to recovery the blood pressure, and the last patient had vomiting for 3 consecutive hours with no response to antiemetic

medications. After these events we broke the double-blind to report to ethics committee and confirmed that the first two patients had been randomized to placebo group and the last two patients had been randomized to amifostine group. After these serious side effects we changed the protocol to go on the study and the dose of amifostine was reduced to 200 mg/m^2 administrated subcutaneously.

The independent variables were age, gender, RIT dose, use of xerostomic drugs, xerostomia, taste disturbance and dysphagia complaints. The dependent variables were the uptake and constant of elimination of salivary glands scintigraphy and the unstimulated and stimulated salivary flow sialometry. Data about use of xerostomic drugs were obtained asking to the patient if she/he used some antidepressant, antihistaminic or hypotensive drugs.

Sample

The first four patients initially included in the study were 3 women and 1 man, with a mean age of 45.5 years, but these patients were not included in the final analysis, since these patients did not complete the protocol.

With the second protocol, the study was concluded with 30 patients, but one patient did not complete the evaluation of 3 months after RIT. From 29 patients that completed the study, 11 were randomized to amifostine group (AG) and 18 were randomized to placebo group (PG). The mean age was 36.2 years in AG (median 36 years, ranging from 18 to 61 years of age) and in PG the mean age was 38.2 years (median 38.5 years, ranging from 20 to 59 years of age). There was no difference between the groups in relation to age (P = .54).

A total of 23 patients were female (10 patients in AG and 13 in PG) and 6 patients were male (1 patient in AG and 5 in PG). Nine patients of AG had papillary carcinoma, one patient had follicular carcinoma and one patient had Hurtle cell carcinoma. In PG, 16 patients had papillary carcinoma, one follicular carcinoma and one Hurtle cell carcinoma. The majority of patients had tumors in clinical stage I (11 in AG and 15 in PG). Only 2 patients of PG had tumors in clinical stage III (Table 4.1).

RIT was performed with patients receiving orientations to use lemon during the hospital admission and dimenidrinate 100 mg 6/6 hours (Dramin®, Nycomed Pharma, Brazil) if necessary. The mean dose received at RIT in AG was 6.05 GBq and in PG was 6.68 GBq. The median dose in AG was 5.55 GBq (3.70 - 7.40 GBq) and in PG was 6.47 GBq (3.70 - 14.80 GBq), with no significant difference between the groups (P = .52).

Measures

Subjective Questionnaire

Some subjective questions were answered by all patients before and 3 months after RIT: 1- Do you feel your mouth to be dry? 2- For what periods of the day? 3- Do you have difficulty eating? 4- What kinds of foods? 5- Do you have any difficulty speaking? 6- Do you have taste disturbances? 7- What flavors? 8- Do you have any swelling in salivary gland regions? 9- When does it occur? These questions were created to identify the most common complaints related to salivary gland dysfunction.

Salivary Gland Scintigraphy

The protocols used for acquisition and processing were similar for all of the subjects. After venous puncture in a superficial vein of the arm, dynamic salivary gland scintigraphy (SGS) was obtained immediately after intravenous administration of 370MBq of ^{99m}Tc-pertechnetate, in a dual time point protocol before and 3 months after RIT. Blood flow was measured and after that the uptake and excretion were verified. The acquisition of images was performed in a dual head gamma camera equipped with low-energey and high resolution collimators (Millennium VG, General Eletric Medical System). It was used a standard protocol with image acquisition every 3 seconds in the first minute, and every 30 seconds for 29 minutes, with a matrix of 128x128 pixels and magnification of 1.5 times. Furthermore, the stimulation with lemon juice was carried out at 20 minutes into the study with the purpose to cause salivary secretion.

At the workstation computer, regions of interest (ROIs) were drawn by hand on the salivary glands (parotid and submandibular salivary glands). As a measure of salivary gland function, the uptake of ^{99m}Tc-pertechnetate was calculated as a percent of the activity injected. Other variable was determined, the Constant of Excretion. It is the excretion fraction in relation to an unit of time and it is measured using Method of Least Square with exponential adjust (the constant is the coefficient of exponent) to points between the maximum (immediately before stimulation) and minimum (the minimum activity immediately after the stimulation) in the ROI and was expressed as the elimination percentage per minute (%/min). This variable provides information about the speed of the excretion.

Sialometry

Sialometry was performed as described by Koseki et al,[11] and whole saliva was collected in a tube of 15 ml along five minutes after oral administration of 500mg of ascorbic acid (Cewin®, Sanofi-Synthelabo, Brazil) in order to obtain the salivary flow stimulation. The salivary flow was expressed in ml/min. The normal parameters were based on data published by Jensen et al,[12] who described cutoffs of unstimulated salivary flow (USSF) at 0.3 ml/min and stimulated salivary flow (SSF) at 1.5 ml/min.

Statistical Analyses

For statistical analysis Fisher's Test was used to categorical variables and Mann-Whitney test was used to continuous variables, since the distribution of same variables was not normal. For comparisons, a $P < .05$ was considered statistically significant.

Results

The clinical characteristics, salivary flow by sialometry and clinical complaints pre-treatment were the same to both groups. The table 4.1 shows the distribution of gender, clinical stage, use of xerostomic drugs, stimulated and unstimulated sialometry and clinical complaints associated to salivary glands function.

The salivary glands function pre-treatment, verified by salivary glands scintigraphy, was the same to both groups (Table 4.2). The mean percentage of parotid/submandibular uptake pre-stimulus of injected dose was 0.71/0.42 and

0.68/0.39 to AG and PG, respectively, and there was no difference between these uptakes (P = .47; P = .44). To better visualize the salivary glands function, the constant of excretion was calculated and gives how much percent the glands are able to eliminate in a period of time as %/min. The parotid/submandibular constant of excretion pre-treatment were 30.35/6.85 and 26.09/7.58 in AG and PG, respectively, with no differences between these values (P = .65 to both pair of glands). See detailed date at table 4.2.

About the acute side effects of ^{131}I on salivary glands during RIT, amifostine neither decreased the incidence of sialodenitis related to ^{131}I, nor the pain related to sialodenitis or the taste disturbance related to ^{131}I (Table 4.3). However, the amifostine was able to decrease the mean time of sialodenitis related to ^{131}I from 6.27 days in PG to 3.5 days in AG (P = .02). To obtain these results an outlier patient in AG that persisted with sialodenitis over 90 days after RIT was excluded of the analysis (Table 4.4).

Although we had some serious problems, as very low blood pressure and vomiting for 3 hours with amifostine administrated intravenously, with the subcutaneous via we did not have any side effect associated with the drug administration. The blood pressure was stable to all patients. Pre-infusion, the median systolic pressure was 120 mmHg (90-140 mmHg) and 110 mmHg (100-140 mmHg), and diastolic pressure was 80mmHg (70-100 mmHg) and 70 mmHg (60-100 mmHg) in AG and PG, respectively. After infusion, the median systolic pressure was 110 mmHg (100-150 mmHg) and 110 mmHg (90-140 mmHg) and the diastolic pressure was 80 mmHg (60-100 mmHg) and 70 mmHg (60-80 mmHg) in AG and PG, respectively. There was no difference between the groups. See data in Table 4.5.

To evaluate the amifostine protection of salivary glands against the deleterious effects of ^{131}I were calculated the differences between uptake pre- and post-stimulus post- and pre-treatment and the differences between constant of excretion post- and pre-treatment. The differences of parotid/submandibular uptake pre-stimulus were -0.05/-0.04 and -0.10/-0.03 to AG and PG (P = .86; P = .86, respectively) and the differences of parotid/submandibular uptake post-stimulus were -0.05/-0.03 and -0.05/-0.02 to AG and PG (P = .82; P = .56, respectively) showing a reduced capacity to uptake and eliminate but with no statistical difference between groups. When we compared the constants of excretion, the results are the same with no differences between the groups. Values of parotid constant of excretion of -1.69%/min *versus* -5.03%/min in AG and PG, respectively, show a diminished excretion function of parotid in both groups 3 months after RIT, higher in PG but with no significant difference (P = .86). The values of submandibular constant of excretion of 1.51 %/min *versus* 1.99 %/min (P = .91) in AG and PG, respectively, show that submandibular glands maintain the excretion function better than parotid glands after RIT (Table 4.5).

Discussion

Although a series of studies of Bohuslavizki et al[8,13-14] have shown the feasibility of amifostine to protect salivary glands in patients submitted to RIT, Kim et al[9] could not confirm this find. As Kim et al[9] in our study, with the methodology used, we were unable to show the efficacy of amifostine to prevent in a short time the side effects of RIT on salivary glands.

The first point that must be discussed is the difficulty that we had to use amifostine intravenously in patients withdraw thyroid hormone. It is reported in the literature many side effects associated to intravenous administration of amifostine,[15] but all references report non-thyroid cancer patients. It is important because these patients normally are withdrawing thyroid hormones to be submitted to RIT and the reaction of these patients to amifostine had not been fully discussed in the literature until this moment. Although the two published studies using amifostine with thyroid cancer patients did not report serious side effects, we had the misfortune of two first patients included in the intravenous protocol presented serious side effects to amifostine, what made impracticable going on with that protocol.

The thyroid hormones play an important activity to control some essential functions as control of metabolic rate, cardiovascular system and blood pressure regulation.[16-17] Triiodothyronine (T3) affects transcription of many cardiac genes, including α- and β-myosin heavy chain, which comprise the thick filament of the contractile unit, the β1-adrenergic receptor, sarcoplasmic reticulum calcium ATPase (SERCA2), and its regulator, phospholamban, which regulates calcium reuptake into the sarcoplasmic reticulum and thyroid receptors α1 (TRα1). Alterations in the relative amounts of these calcium-cycling proteins and the state of phosporylation of the inhibitor phospholamban might account for changes in diastolic function.[16] Although patients with hypothyroidism are under higher risk to develop systemic hypertension due to a peripheral vasoconstriction, when these patients have an abrupt decrease in the blood pressure, the heart is not able to compensate this change, since T3 regulates the expression of many cardiac genes responsible for the cardiac functions, mainly phospholamban which is responsible for the relax phase of cardiac

cells.[17] In this context, these patients can also be in a greater risk to develop lung edema with the infusion of a high quantity of physiologic saline solution to recovery the blood pressure.

Previous studies of our group[10,18] showed that the deleterious effects of RIT on salivary glands are concentrated in an impairment of salivary glands, mainly parotid glands, to eliminate saliva and not to produce it, and it impacts in a mean time of two years after RIT in the quality of life of these patients by interfering with swallowing function. In this study, we were unable to show the efficacy of amifostine to reduce side effects of RIT on salivary glands function. Bohuslavizki et al,[8] in a prospective, randomized and double-blind study with 50 patients included, showed the efficacy of amifostine to reduce parenchymal damage in salivary glands caused by RIT, maintaining a better uptake function. The point is that salivary glands damage induced by RIT, in middle and long-term, is more serious in excretion phase, probably due to a periductal constriction by inflammatory process induced by ^{131}I. Kim et al.[9] in a non-randomized study, but analyzing 42 patients treated with amifostine and 38 patients treated with placebo were unable to show the cytoprotective effects of amifostine on salivary glands to RIT.

The only favorable find in our study was the capacity of amifostine to reduce the number of days that patients had symptomatic sialodenitis, but amifostine was not able to reduce the pain associated to it. In our view this minor benefit does not justify the risks and the cost using this drug.

Before to conclude that amifostine is not effective to protect salivary glands of RIT effects more studies are needed to find a safe via of administration, considering the status withdraw thyroid hormone of these patients, and the more

effective dose. Moreover, it is important to take into consideration, before final conclusions, the possibility of middle and long-term protective effects related to the use of amifostine. As the impact of RIT is detected normally up to two years after the therapy, it is important to follow these patients and evaluate the capacity of amifostine to prevent late side effects of RIT on salivary glands function.

Table 4.1 - Description of clinical variables of both groups pre-treatment.

Variable	Category	Amifostine n (%)	Placebo n (%)	P value
Gender	Female	10 (90.9)	13 (72.2)	.36
	Male	1 (9.1)	5 (27.8)	
Clinical stage	I	11 (100)	15 (88.2)*	.50
	III	0 (0)	2 (11.8)	
Xerostomic drugs	No	9 (81.8)	14 (77.8)	1.00
	Yes	2 (18.2)	4 (22.2)	
USSF	≤ 0.3 ml/min	2 (18.2)	3 (16.7)	1.00
	>0.3 ml/min	9 (81.8)	15 (83.3)	
SSF	≤ 1.5 ml/min	11 (100)	18 (100)	1.00
	>1.5 ml/min	0 (0)	0 (0)	
Xerostomia	No	8 (88.9)*	16 (100)*	.36
	Yes	1 (11.1)	0 (0)	
Dysphagia	No	9 (100)*	15 (93.8)*	1.00
	Yes	0 (0)	1 (6.3)	
Taste disturbance	No	8 (88.9)*	14 (87.5)*	1.00
	Yes	1 (11.1)	2 (12.5)	
Total		11 (100)	18 (100)	

*It was not possible to get information of some patients.

USSF – Unstimulated Salivary Flow; SSF – Stimulated Salivary Flow

Table 4.2 - Description of scintigraphy of salivary glands data in both groups pre-treatment.

Variable	Amifostine mean (sd)	Placebo mean (sd)	P value
Parotid uptake pre stimulus *	0.71 (0.24)	0.68 (0.30)	.47
Submandibular uptake pre stimulus*	0.42 (0.16)	0.39 (0.18)	.44
Parotid uptake post stimulus*	0.50 (0.20)	0.45 (0.18)	.56
Submandibular uptake post stimulus*	0.33 (0.11)	0.29 (0.11)	.16
Parotid ejection flow**	30.35 (18.31)	26.09 (14.66)	.65
Submandibular ejection flow**	1.52 (11.51)	1.99 (13.49)	.65

*Data of uptake in percent of the activity injected.

**Ejection flow in % of elimination per minute (%/min).

Table 4.3 - Acute side effects associated to I^{131} during RIT.

Variable	Category	Amifostine n (%)	Placebo n (%)	P value
Sialodenitis	No	1 (9.1)	7 (38.9)	.11
	Yes	10 (90.9)	11 (61.1)	
Pain	No	7 (63.6)	10 (55.6)	.72
	Yes	4 (36.4)	8 (44.4)	
Taste disturbance	No	5 (45.5)	11 (61.1)	.41
	Yes	6 (54.4)	7 (38.9)	
Total		11 (100)	18 (100)	

Table 4.4 - Amifostine and sialodenitis during RIT.

	Number of days with sialodenitis during RIT	P value
	Amifostine*	
N	8	
Mean (sd)	3.5 (2.20)	
Median (min-max)	2.5 (2-7)	**.02**
	Placebo	
N	11	
Mean (sd)	6.27 (2.15)	
Median (min-max)	7 (2-10)	

* Two patients of amifostine group were excluded of this analysis.

One outlier patient who persisted with sialodenitis over 90 days after RIT and one patient that had missing data about number of days with sialodenitis.

Table 4.5 - Differences between post- and pre-treatment values.

Variable	Amifostine mean (sd)	Placebo mean (sd)	P value
Pre-stimulus parotid difference *	-0.05 (0.27)	-0.10 (0.30)	.86
Pre-stimulus submandibular difference *	-0.04 (0.20)	-0.03 (0.17)	.86
Post-stimulus parotid differece*	-0.05 (0.26)	-0.05 (0.18)	.82
Post-stimulus submandibular differece *	-0.03 (0.18)	-0.02 (0.12)	.56
Parotid ejection flow difference**	-1.69 (19.86)	-5.03 (24.19)	.86
Submandibular ejection flow difference **	1.52 (11.51)	1.99 (13.49)	.91
Systolic pressure pre-infusion***	115.0 (17.73)	113.3 (13.45)	.64
Diastolic pressure pre-infusion***	81.2 (12.46)	74.0 (9.10)	.13
Systolic pressure post-infusion***	113.7 (15.98)	110.0 (13.09)	.69
Diastolic pressure post-infusion***	76.2 (13.02)	74.0 (6.32)	.65

*Data in percent of the activity injected; ** Data in %/min; ***Data in mmHg.

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5 CONSIDERAÇÕES FINAIS

Em relação a qualidade de vida dos pacientes antes e após a iodoterapia no estudo II, seguem abaixo detalhados nas tabelas os resultados dos questionários aplicados. Como não observamos o efeito protetor da amifostina aos efeitos colaterais da iodoterapia sobre as glândulas salivares os dois grupos passaram a não apresentar diferenças também nos domínios avaliados pelo questionário UW-QOL.

Tabela 5.1 - "Scores" médios dos 12 domínios e "score" final dos grupos amifostina e placebo pré-tratamento.

	Amifostina	**Placebo**	**p value**
	Média (dp)		
Dor	84.1 (20.2)	91.7 (14.8)	.28
Aparência	86.4 (17.2)	79.2 (19.6)	.33
Atividade	75 (25)	81.9 (18.8)	.50
Recreação	81.8 (25.2)	79.2 (24.6)	.75
Deglutição	97 (9.9)	94.5 (12.6)	.57
Mastigação	95.4 (15.1)	100 (0)	.20
Fala	93.9 (20.2)	85.2 (28.5)	.27
Ombro	78.7 (30.9)	75.9 (35.8)	.88
Paladar	87.8 (27.1)	94.4 (17.2)	.55
Saliva	87.9 (22.5)	96.3 (15.8)	.12
Humor	81.8 (31.9)	81.9 (31.2)	.89
Ansiedade	69.8 (31.5)	76.1 (27.5)	.59
"Score" final	84.9 (16.3)	86.4 (10.9)	.96

Tabela 5.2 - "Scores" médios dos 12 domínios e "score" final dos grupos amifostina e placebo pós-tratamento.

	Amifostina	Placebo	p value
	Média (dp)		
Dor	88.6 (20.5)	94.4 (13.7)	.44
Aparência	90.9 (16.8)	90.3 (19.4)	.88
Atividade	81.8 (19.6)	83.3 (17.1)	.88
Recreação	93.2 (11.7)	93.1 (16.7)	.63
Deglutição	97 (9.9)	96.3 (10.7)	.86
Mastigação	100 (0)	97.2 (11.8)	.43
Fala	100 (0)	90.8 (25)	.16
Ombro	78.7 (30.9)	81.5 (34.7)	.70
Paladar	100 (0)	98.2 (7.8)	.43
Saliva	90.9 (21.6)	98.2 (7.8)	.27
Humor	84.1 (23.1)	93.1 (16.7)	.14
Ansiedade	81.9 (22.9)	89 (16)	.43
"Score" final	90.6 (9.2)	92.1 (9.8)	.73

A diferença em pontos entre os domínios antes e após no Questionário UW-QOL é considerada clinicamente significativa se for maior ou igual a 7 (VARTANIAN et al. 2004). Como vemos na tabela abaixo, no grupo amifostina em todos os domínios associados aos efeitos colaterais da iodoterapia houve manutenção ou melhora no "score" após o tratamento. No grupo placebo observamos melhora em todos os domínios, com excessão ao domínio mastigação em que o "score" médio foi negativo indicando piora neste domínio após a iodoterapia. Porém nenhuma destas diferenças entre os grupos foram significativas.

Tabela 5.3 - Diferença entre os valores pós e pré-tratamento dos domínios que refletem os efeitos colaterais associados a iodoterapia e "score" final dos grupos amifostina e placebo.

	Amifostina	Placebo	p value
	Média (dp)		
Deglutição	0 (0)	1.8 (7.8)	.43
Mastigação	4.5 (15.1)	-2.8 (11.8)	.15
Paladar	12.2 (27.1)	3.7 (19.4)	.39
Saliva	3 (27.8)	1.9 (18)	.95
"Score" final	5.6 (11)	5.7 (11.3)	.75

Na Tabela 5.4 descrevemos o "status" pós-tratamento em relação aos domínios associados aos efeitos colaterais da iodoterapia nos pacientes dos grupos amifostina e placebo comparados ao "status" pré-tratamento.

Tabela 5.4 - Status pós-tratamento em relação aos domínios associados aos efeitos colaterais da iodoterapia e "score" final nos grupos amifostina e placebo.

Deglutição			
	Amifostina	**Placebo**	**Total**
	N (%)		**N (%)**
Manteve	11 (100)	17 (94.4)	28 (96.6)
Melhora	0 (0)	1 (5.6)	1 (3.4)
Piora	-	-	-
Mastigação			
Manteve	10 (90.9)	17 (94.4)	27 (93.1)
Melhora	1 (9.1)	0 (0)	1 (3.4)
Piora	0 (0)	1 (5.6)	1 (3.4)
Paladar			
Manteve	9 (81.8)	15 (83.3)	24 (82.8)
Melhora	2 (18.2)	2 (11.1)	4 (13.8)
Piora	0 (0)	1 (5.6)	1 (3.4)
Saliva			
Manteve	7 (63.6)	16 (88.9)	23 (79.3)
Melhora	2 (18.2)	1 (5.6)	3 (10.3)
Piora	2 (18.2)	1 (5.6)	3 (10.3)
"Score" final			
Manteve	2 (18.2)	1 (5.6)	3 (10.3)
Melhora	6 (54.5)	13 (72.2)	19 (65.5)
Piora	3 (27.3)	4 (22.2)	7 (24.1)

Com estes resultados podemos afirmar que os efeitos colaterais da iodoterapia sobre as glândulas salivares não apresentam impacto na qualidade de vida destes pacientes no período de 3 meses. Como vimos no estudo I, o impacto na qualidade de vida dos efeitos colaterais da iodoterapia são tardios, geralmente 2 anos após o término do tratamento, afetando principalmente o domínio de deglutição. Para verificar se a amifostina apresenta algum efeito protetor sobre as glândulas salivares em pacientes submetidos a iodoterapia a médio e longo prazo será necessário

acompanhar estes pacientes, e com isto poder-se-á avaliar também se a amifostina diminui o impacto destes efeitos colaterais sobre a qualidade de vida destes pacientes.

6 CONCLUSÕES

Com os resultados apresentados acima, podemos concluir que:

1. Os efeitos do ^{131}I sobre as glândulas salivares possivelmente ocorrem sobre os ductos salivares resultando em constrição ductal, devido à fibrose periductal induzida pela radiação, dificultando assim a eliminação da saliva produzida e resultando em quadros de xerostomia e sialodenite.
2. Esta constrição ductal com resultante retenção salivar é um dos mecanismos responsáveis pela ocorrência de sialodenite crônica tardia em alguns pacientes.
3. O uso de pilocarpina para o tratamento de xerostomia em pacientes submetidos a iodoterapia não se mostrou viável, devido aos efeitos colaterais associados ao medicamento.
4. Alterações nas funções de mastigação, deglutição e fala verificadas pelo questionário de qualidade de vida aplicado, em pacientes que receberam doses acima de 150 mCi ^{131}I, impactam na qualidade de vida dos pacientes submetidos a iodoterapia pode ser verificado normalmente dois anos após o tratamento, sugerindo que a falta de saliva pode impactar na fase oral da deglutição.
5. A incidência de efeitos colaterais agudos do ^{131}I sobre as glândulas salivares na nossa população é muito semelhante à descrita na literatura.

6. Nas condições e população estudadas, em relação a dose e via de administração, a amifostina não se mostrou eficaz na prevenção de efeitos colaterais do ^{131}I sobre as glândulas salivares a curto prazo.
7. Este estudo ressalta as particularidades e alto risco da adimistração endovenosa da amifostina em paciente hipotireoideanos.
8. A iodoterapia não apresenta impacto a curto prazo sobre a qualidade de vida dos pacientes incluídos no protocolo do estudo II/amifostina.

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Anexo 1 – TCLE estudo I

TERMO DE CONSENTIMENTO PÓS-INFORMADO
ESTUDO I

Eu, _____,

portador do RG _____, e cadastrado no Hospital do Câncer A. C. Camargo sob o RGH _____, estou ciente de que faço parte de um estudo clínico, o qual tem como objetivo investigar os efeitos coleterais da iodoterapia sobre a função das glândulas salivares. Estou ciente de que a investigação consta na realização de uma cintilografia de glândulas salivares, o qual é um exame onde será administrado uma solução de iodo por via endovenosa e que tem uma previsão de 15 minutos de duração, um exame de sialometria (medição da quantidade de saliva produzida) e aplicação de um questionário, e que estes procedimentos não irão interferir de nenhuma forma na evolução clínica da minha doença. Fui orientado de que este estudo poderá beneficiar outros pacientes no futuro, já que não se sabe a porcentagem dos pacientes que apresentam alterações salivares após iodoterapia e que este estudo poderá possibilitar a realização de outros estudos futuramente. Além disso, fui orientado caso eu apresente disfunção das glândulas salivares e apresentar os critérios para indicação do uso de pilocarpina, este medicamento será fornecido pelos pesquisadores por 01 mês na tentativa de melhorar minha qualidade de vida.

Após ter lido e esclarecido todas as dúvidas sobre minha participação no estudo, sabendo que posso solicitar minha exclusão em qualquer fase do estudo, através de contato com a Dra. Juliana Pereira Almeida no Departamento de Cabeça e Pescoço, concordo em participar como voluntário deste trabalho.

"Se a Dra. Juliana Pereira Almeida não fornecer as informações/esclarecimentos suficientes, por favor, entre em contato com o Coordenador do Comitê de Ética do Hospital do Câncer – SP, pelo telefone 2189-5000, ramais 1113 ou 1117".

São Paulo, _____ de _____ de _____.

_____

EDUARDO ANTONIO PRUDENTE
Hospital do Câncer A. C. Camargo
Comitê de Ética em Pesquisa

Anexo 2 – Aprovação CEP Fundação Antônio Prudente

HOSPITAL DO CÂNCER

Comitê de Ética em Pesquisa
CEP

São Paulo, 29 de março de 2006.

À
Dra. Juliana Pereira de Almeida

Ref.: Projeto de Pesquisa nº. 762/06
"Avaliação da função das glândulas salivares em pacientes submetidos a iodoterapia para tratamento de carcinomas bem-diferenciados de tireóide".

Os membros do Comitê de Ética em Pesquisa (CEP) da Fundação Antonio Prudente - Hospital do Câncer – A.C. Camargo, em sua última reunião de 28/03/2006, tomaram conhecimento das respostas aos esclarecimentos solicitados em reunião do dia 31/01/2006 e por unanimidade, **aprovaram** a realização deste estudo.
Salientamos que nenhum membro do Comitê de Ética em Pesquisa que possa ser o pesquisador ou orientador deste projeto, participou da votação.

Informações a respeito do andamento do referido projeto deverão ser encaminhadas à Assistente do CEP dentro de 12 meses.

Atenciosamente,

Dra. Vilma Regina Martins
Vice - Coordenador do Comitê de Ética em Pesquisa

C.C
Orientador: Prof. Dr. Luiz Paulo Kowalski

Rua Prof. Antônio Prudente, 211 – Liberdade – São Paulo – SP CEP 01509-900 - CNPJ 60.961.968/0001-06
PABX(0XX11)2189-5000 ramal 1080 Tel/Fax (0XX11)2189.5017 – cep_hcancer@hcancer.org.br
Conveniado ao Sistema Único de Saúde (SUS) conforme processo n.º2003-0.165.661-0

Anexo 3 – Questionário

Avaliação da função das glândulas salivares em pacientes submetidos a iodoterapia adjuvante para tratamento de carcinomas bem-diferenciados de tireóide.

NOME:_____

INSTITUIÇÃO DE ORIGEM:_____

RGH:_____

ENDEREÇO:_____

TELEFONE:_____

DOENÇA DE BASE:_____

DATA DE INICIO NO PROJETO:_____

DOSE I^{131}:_____

DATA I^{131}:_____

TRATAMENTO: ( )CIRURGIA ( )I^{131} ( )AMIFOSTINA ( )PLACEBO

1- AVALIAÇÃO SUBJETIVA:

Questionário de qualidade de vida da Universidade de Washington – validado em língua portuguesa e disponibilizado para uso público.

Este questionário pergunta sobre sua saúde e qualidade de vida **durante os últimos sete dias**. Por favor responda a todas as questões marcando uma alternativa para cada questão.

1. Dor (marque uma alternativa [ ])

100 [ ] Eu não tenho dor

75 [ ] Há dor leve não necessitando de medicação

50 [ ] Eu tenho dor moderada, requerendo uso de medicação regularmente

25 [ ] Eu tenho dor severa controlada somente com medicamentos controlados

0 [ ] Eu tenho dor severa, não controlada por medicação

2. Aparência (marque uma alternativa [ ])

100 [ ] Não há mudança na minha aparência

75 [ ] A mudança na minha aparência é mínima

50 [ ] Minha aparência me incomoda, mas eu permaneço ativo

25 [ ] Eu me sinto desfigurado significativamente e limito minhas atividades devido a minha aparência

0 [ ] Eu não posso estar com outras pessoas devido a minha aparência

3. Atividade (marque uma alternativa [ ])

100 [ ] Eu estou tão ativo quanto sempre estive

75 [ ] Existem vezes em que não posso manter meu ritmo antigo, mas não frequentemente

50 [ ] Eu estou frequentemente cansado e tenho diminuído minhas atividades embora eu ainda saia de casa

25 [ ] Eu não saio de casa porque eu não tenho força

0 [ ] Eu geralmente fico na cama ou na cadeira e não saio de casa

4. Recreação (marque uma alternativa [ ])

100 [ ] Não há limitações para recreação em casa ou fora de casa

75 [ ] Há poucas coisas que eu não posso fazer, mas eu ainda saio de casa para me divertir

50 [ ] Há muitas vezes que eu gostaria de sair mais de casa, mas eu não estou bem para isso

25 [ ] Há limitação severa para o que eu posso fazer, geralmente eu fico em casa e assisto TV

0 [ ] Eu não posso fazer nada agradável

5.Deglutição (marque uma alternativa [ ])

100 [ ] Eu posso engolir tão bem como sempre

67 [ ] Eu não posso engolir algumas comidas sólidas

33 [ ] Eu posso engolir somente comidas líquidas

0 [ ] Eu não posso engolir porque desce errado e me sufoca

6.Mastigação (marque uma alternativa [ ])

100 [ ] Eu posso mastigar tão bem como sempre

50 [ ] Eu posso comer alimentos sólidos leves mas não consigo mastigar algumas comidas

0 [ ] Eu não posso mastigar nem mesmo alimentos leves

7.Fala (marque uma alternativa [ ])

100 [ ] Minha fala é a mesma de sempre

67 [ ] Eu tenho dificuldade para dizer algumas palavras mas eu posso ser entendido mesmo ao telefone

33 [ ] Somente minha família e amigos podem me entender

0 [ ] Eu não sou entendido pelos outros

8. Ombro (marque uma alternativa [ ])

100 [ ] Eu não tenho problemas com meu ombro

67 [ ] Meu ombro é endurecido mas isto não afeta minha atividade ou força

33 [ ] Dor ou fraqueza em meu ombro me fizeram mudar meu trabalho

0 [ ] Eu não posso trabalhar devido problemas com meu ombro

9. Paladar (marque uma alternativa [ ])

100 [ ] Eu sinto sabor da comida normalmente

67 [ ] Eu sinto o sabor da maioria das comidas normalmente

33 [ ] Eu posso sentir o sabor de algumas comidas

0 [ ] Eu não sinto o sabor de nenhuma comida

10. Saliva (marque uma alternativa [ ])

100 [ ] Minha saliva é de consistência normal

67 [ ] Eu tenho menos saliva que o normal, mas ainda é o suficiente

33 [ ] Eu tenho muito pouca saliva

0 [ ] Eu não tenho saliva

11. Humor (marque uma alternativa [ ])

100 [ ] Meu humor é excelente e não foi afetado por causa do meu câncer

75 [ ] Meu humor é geralmente bom e é somente afetado por causa do meu câncer ocasionalmente

50 [ ] Eu não estou nem com bom humor nem deprimido por causa do meu câncer

25 [ ] Eu estou um pouco deprimido por causda do meu câncer

0 [ ] Eu estou extremamente deprimido por causa do meu câncer

12. Ansiedade (marque uma alternativa [ ])

100 [ ] Eu não estou ansioso por causa do meu câncer

67 [ ] Eu estou um pouco ansioso por causa do meu câncer

33 [ ] Eu estou ansioso por causa do meu câncer

0 [ ] Eu estou muito ansioso por causa do meu câncer

Quais problemas tem sido os mais importantes para você durante os últimos 7 dias?

Marque [] em até 3 alternativas

[] Dor [] Deglutição [] Paladar

[] Aparência [] Mastigação [] Saliva

[] Atividade [] Fala [] Humor

[] Recreação [] Ombro [] Ansiedade

Questões gerais

Comparado com o mês antes de você desenvolver o câncer, como você classificaria sua qualidade de vida relacionada à saúde (marque uma alternativa: [ ])

[ ] Muito melhor

[ ] Um pouco melhor

[ ] Mais ou menos o mesmo

[ ] Um pouco pior

[ ] Muito pior

Em geral, você poderia dizer que sua qualidade de vida relacionada à saúde nos últimos 7 dias tem sido: (marque uma alternativa [ ])

[ ] Excelente

[ ] Muito boa

[ ] Boa

[ ] Média

[ ] Ruim

[ ] Muito ruim

De um modo geral a qualidade de vida inclui não somente saúde física e mental, mas também muitos outros fatores, tais como família, amigos, espiritualidade, atividades de lazer pessoal que são importantes para sua satisfação com a vida. Considerando tudo em sua vida que contribui para seu bem-estar pessoal, classifique a sua qualidade de vida em geral durante os últimos 7 dias. (marque uma alternativa: [ ])

[ ] Excelente

[ ] Muito boa

[ ] Boa

[ ] Média

[ ] Ruim

[ ] Muito ruim

Por favor descreva quaisquer outros problemas (médicos ou não médicos) que são importantes para sua qualidade de vida e que não tenham sido adequadamente mencionados pelas nossas perguntas (você pode anexar folhas adicionais se necessário).

Questões adicionais:

1- Sente boca seca?

( )Sim ( )Não ( )Às vezes

2- Em que periodos do dia?

( )Manhã ( )Tarde ( )Noite ( )Todo o tempo

3- Sente dificuldades para se alimentar?

( )Sim ( )sólidos ( )secos ( )todos os tipos

( )Não ( )Às vezes

4- Sente dificuldade para falar?

( )Sim ( )Não ( )Às vezes

5- Apresenta alteração de paladar?

( )Sim ( )Não ( )Às vezes

6- Que tipo de alteração?

( )Doce ( )Salgado ( )Azedo ( )Amargo

7- Percebe algum inchaço na face?

( )Sim ( )Não ( )Às vezes

8- Quando?

( )Qdo me alimento ( )Qdo falo ( )Espontâneo

9- Apresentou inchaço na região das glândulas salivares durante a iodoterapia?

( )Sim ( )Não Região:_____

10- Havia dor?

( )Sim ( )Não

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11- Quantos dias demorou para se resolver este inchaço?

_____

12- Apresentou alteração de paladar durante a iodoterapia?

( )Sim ( )Não Tipo:_____

2- AVALIAÇÃO OBJETIVA:

Sialometria

Fluxo salivar não estimulado:_____ml/min

Excreção de ^{99m}Tc:_____

Fluxo salivar estimulado:_____ml/min

Excreção de ^{99m}Tc:_____

Anexo 4 – Ficha avaliação do tratamento com pilocarpina

AVALIAÇÃO DO TRATAMENTO COM PILOCARPINA

NOME:_____

RGH:_____

DATA INÍCIO TTO:_____

DOSE 5mg 3X AO DIA

Marque com um X o sintoma no dia respectivo:

Sintomas apresentados	D1	D2	D3	D4	D5	D6	D7
Suor excessivo							
Aumento da freqüência urinária							
Lacrimejamento							
Calafrios							
Fraqueza							
Tontura							
Náusea							
Dor de cabeça							
Hipertensão arterial							
Taquicardia							

Descreva aqui qualquer outro sintoma apresentado não relacionado na tabela acima:

Anexo 5 – TCLE estudo II

TERMO DE CONSENTIMENTO PÓS-INFORMADO
ESTUDO II

Eu, _____,

portador do RG _____, e cadastrado no Hospital do Câncer A. C. Camargo sob o RGH _____, estou ciente de que faço parte de um estudo clínico, o qual tem como objetivo investigar os efeitos coleterais da iodoterapia sobre a função das glândulas salivares. Estou ciente de que a investigação consta na realização de uma cintilografia de glândulas salivares, sialometria e aplicação de um questionário antes e após a iodoterapia, e que estes procedimentos não irão interferir de nenhuma forma na evolução clínica da minha doença. Estou ciente de que posso fazer parte de um grupo que fará uso do medicamento Amifostina (Ethyol®) ou um grupo placebo que fará uso de apenas SF 0,9%, mas que não saberei a qual grupo fui incluído por ser um estudo duplo-cego. Fui orientado quanto aos possíveis efeitos colaterais que possam surgir com o uso da Amifostina, como hipotensão, náusea, vômito e mal estar durante a infusão a qual irá ocorrer na forma subcutânea 15 minutos antes de tomar o iodo radioativo, e que se apresentar qualquer um destes efeitos colaterais serei amparado por equipe especializada. Além disso, não apresento contra-indicações para o uso da amifostina (hipersensibilidade ao aminotiol, hipotensão, desidratação,

insuficiência renal ou hepática, idade superior a 70 anos, grávidez ou estou em período de lactação). Fui informado de que se a droga utilizada apresentar eficácia, tanto eu como outras pessoas na mesma condição poderão se beneficiar com o tratamento proposto. Fui orientado de que este estudo poderá beneficiar outros pacientes no futuro, já que não se sabe a porcentagem dos pacientes que apresentam alterações salivares após iodoterapia e que este estudo poderá possibilitar a realização de outros estudos futuramente.

Após ter lido e esclarecido todas as dúvidas sobre minha participação no estudo, sabendo que posso solicitar minha exclusão em qualquer fase do estudo, através de contato com a Dra. Juliana Pereira Almeida no Departamento de Cabeça e Pescoço, concordo em participar como voluntário deste trabalho.

"Se o Dra. Juliana Pereira Almeida não fornecer as informações/esclarecimentos suficientes, por favor, entre em contato com o Coordenador do Comitê de Ética do Hospital do Câncer – SP, pelo telefone 2189-5000, ramais 1113 ou 1117".

São Paulo, _____ de _____ de _____ .

_____

FUNDAÇÃO ANTONIO PRUDENTE
Hospital do Câncer A. C. Camargo
Comitê de Ética em Pesquisa

Anexo 6 – Aprovação CEP Fundação Pio XII

HOSPITAL DE CÂNCER DE BARRETOS
Fundação Pio XII

Comitê de Ética em Pesquisa
CEP

Barretos, 18 de abril de 2008.

Prezado (a) Sr. (a). Investigador (a)
Euclides Timóteo da Rocha

Ref. : Projeto de Pesquisa nº. 140/2008
"Avaliação da função das glândulas salivares em pacientes submetidos a iodoterapia adjuvante para tratamento de carcinomas bem-diferenciados de tireóide".

O Comitê de Ética em Pesquisa da Fundação Pio XII – Hospital de Câncer de Barretos, analisou as pendências do protocolo citado acima e decidiu pela **aprovação** do mesmo.

Ressaltamos que as informações a respeito do andamento do referido projeto deverão ser encaminhadas à assistente do CEP dentro de 03 meses.

Atenciosamente,

Dr. Renato José Affonso Junior
Coordenador do Comitê de Ética em Pesquisa

22/04/08

Rua Antenor Duarte Villela, 1331 – B. Dr. Paulo Prata – Barretos – SP CEP 14784-400 – CNPJ 49.150.352/0001-12
Tel. 17 33216600 R. 6894 – cep@hcancerbarretos.com.br

Anexo 7 – Tabela de randomização

111	119	130	134	142	143
144	157	177	198	215	217
229	237	264	267	284	296
319	339	340	358	363	380
385	393	398	399	406	426
448	455	461	463	507	563
576	586	599	643	684	692
707	729	739	752	792	800
826	839	842	847	868	880
888	905	921	962	977	979

Tabela para 60 pacientes

NÚMEROS PARES – grupo amifostina

NÚMEROS ÍMPARES – grupo placebo

SEQUÊNCIA DE LEITURA – linhas

Tabela gerada pelo programa Epi Info versão 6.04 Janeiro 2001 Center of Disease Control and Prevention (CDC) - USA

ORIGINAL ARTICLE

Clinical Predictors of Quality of Life in Patients With Initial Differentiated Thyroid Cancers

Juliana Almeida, DDS, MSc; José Guilherme Vartanian, MD, PhD; Luiz Paulo Kowalski, MD, PhD

Background: Patients with differentiated thyroid cancer (DTC) usually have a good prognosis. Traditionally, treatment success in patients with cancer has been evaluated by survival time. Recently, it has been observed that the diagnosis and treatment of cancer also have a strong effect on the quality of life (QOL) of these patients.

Objective: To assess the QOL of patients with DTC and its potential clinical predictors.

Design: Cross-sectional analysis.

Setting: A tertiary cancer institution.

Patients: One hundred fifty-four patients submitted to thyroidectomy (1997-2006) were evaluated using the University of Washington Quality of Life questionnaire.

Main Outcome Measures: Descriptive analysis of the results was done, as bivariate and multivariate analyses to compare each independent variable with each of 13 QOL domains.

Results: Patients 45 years or younger had better recreation scores than did patients older than 45 years ($P=.04$). Thirty-eight patients were submitted to neck dissection. Patients submitted to modified radical neck dissection reported worse chewing and shoulder scores than did patients submitted to selective paratracheal lymph node dissection only and those without neck dissection ($P=.003$ and $P=.004$, respectively). Patients who received more than 150 mCi of radioactive iodine therapy (RIT) reported significantly worse pain, swallowing, chewing, speech, taste, anxiety, and composite scores. Comorbidities showed significant effect on recreation, activity, speech, saliva, and composite scores ($P=.02$, $P=.046$, $P=.02$, $P=.01$, and $P=.008$, respectively). In multivariate analysis, RIT is the only variable associated with a worse composite score ($P=.003$).

Conclusion: Although QOL after treatment of thyroid cancer can be considered good for most patients, those submitted to RIT at doses higher than 150 mCi are at risk for poor QOL and, therefore, may need more intensive follow-up and treatment.

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PATIENTS WITH DIFFERENTIATED thyroid cancer (DTC), in general, have a very good prognosis, and overall long-term survival is higher than 90%, with variations in subsets of patients.[1,2] In DTC, surgery is the therapy of choice. Surgical options include lobectomy with isthimectomy or total thyroidectomy with or without neck lymph node dissection. The choice of procedure is affected by well-defined prognostic factors.[3,4] Ablative surgery of the thyroid and possible neck disease and postoperative radioactive iodine therapy (RIT) result in prolonged survival but may lead to voice alterations, dysphagia, sialadenitis, taste disturbance, and xerostomia.[5-7]

Traditionally, the main outcome measure in oncology patients has been survival, based on tumor control, but recently it has been increasingly recognized that the diagnosis and management of cancer can have a major effect on every aspect of the quality of life (QOL) of a patient.[1] The aims of cancer treatment became not only to increase survival but also to preserve QOL,[2] and measuring these changes has been considered to be of paramount importance.[1,8]

The QOL is defined as the perceptions of an individual regarding his or her position in life in the context of the culture and value systems in which he or she lives and in relation to his or her goals, expectations, standards, and concerns (WHOQOL, 1993).[9] Health-related QOL (HRQOL) refers to a multidimensional concept that encompasses perception of negative and positive aspects of physical, emotional, social, and cognitive functions, which could be affected by the disease or its treatment.[10] Several instruments have been developed to assess QOL in patients

with head and neck cancer. Among them, the University of Washington Quality of Life (UW-QOL) questionnaire is a validated, accurate, and internationally accepted survey instrument. The use of such a questionnaire allows the evaluation of HR-QOL and leads to a better understanding of the patient's expectations.[8,11]

In the past 20 years, an increasing number of studies have measured QOL as an end point in the evaluation of the effect of the disease and its treatment on the daily life of the patient.[6,8] However, there have been relatively few HR-QOL studies looking specifically at patients with thyroid cancer.[1,10,11] The aims of this study are to assess QOL in patients with DTC and to evaluate whether different modalities of treatment can interfere in the QOL of these patients.

METHODS

DESIGN

A cross-sectional analysis was performed of adults with initial DTC treated with total thyroidectomy, some of whom had undergone adjuvant RIT, between January 1, 1997, and December 31, 2006, at a single tertiary cancer institution. Patients who had received previous head and neck radiation therapy or had sicca syndrome symptoms were excluded. The study was approved by the ethics committee of Hospital A. C. Camargo, and all participants signed an informed consent form.

The patients were invited to participate in this study at their follow-up medical consultation. All of them had normal thyroid hormone levels, and patients who had ended treatment 4 months to 10 years before (median, 2 years) were included. The independent variables were age, sex, time since treatment, RIT dose, neck dissection, and comorbidities. The dependent variables were the 13 QOL scales from the UW-QOL questionnaire.

SAMPLE

Four hundred patients who met the inclusion criteria were invited to participate in this study. Of those, 184 patients agreed to participate and 154 completed the questionnaire and had clinical stage I or II tumors. A total of 137 patients (89.0%) were women, and 17 (11.0%) were men; the mean patient age was 46.9 years (median age, 46 years; age range, 21-87 years). All the patients underwent a total thyroidectomy, and 38 patients were also submitted to a neck dissection of levels II through IV (2 patients), II through VI (9 patients), and VI (27 patients). One hundred fifty-one patients had papillary carcinoma and 3 had follicular carcinoma. Regarding clinical stage, 85.1% of tumors were in stage I and 14.9% were in stage II. Ninety-three patients (60.4%) underwent RIT, and the median dose was 130 mCi (range, 30-700 mCi). Seventy-three patients received doses up to 150 mCi, and 20 patients received doses higher than 150 mCi. Comorbidities were evaluated using the American Society of Anesthesiologists (ASA) classification in 137 patients. Thirty-eight patients were classified as ASA I, 97 as ASA II, and 2 as ASA III. These data are summarized in **Table 1**.

Table 1. Demographic and Treatment Variables

Variable	Patients, No. (%) (N=154)
Age, y	
≤45	73 (47.4)
>45	81 (52.6)
Sex	
Male	17 (11.0)
Female	137 (89.0)
RIT	
None	61 (39.6)
≤150 mCi	73 (47.4)
>150 mCi	20 (13.0)
Neck dissection	
None	116 (75.3)
Paratracheal	27 (17.5)
Radical	11 (7.1)
Clinical stage	
I	131 (85.1)
II	23 (14.9)
ASA classification[a]	
I	38 (27.7)
II	97 (70.8)
III	2 (1.5)

Abbreviations: ASA, American Society of Anesthesiologists; RIT, radioactive iodine therapy.
[a] Only 137 patients provided this information.

MEASURES

Demographic measures included age (≤45 or >45 years) and sex. Age 45 years was used as a reference owing to its important prognostic value in patients with DTC. The classification of neck dissection was paratracheal (level VI), radical (levels II-IV), and extended radical (levels II-VI). At the analysis, these patients were grouped as none (no neck dissection), paratracheal (neck dissection of level VI), and radical (neck dissection of levels II-IV and II-VI).

Many studies[5,12-14] have discussed that radioactive iodine effects are dose dependent, and a recent study by us showed that doses higher than 150 mCi are associated with more adverse effects on the salivary glands. In this way, we categorized the variable RIT as patients who were not submitted to RIT, patients who received up to 150 mCi, and those who received more than 150 mCi. Time since treatment was measured in months and was categorized into 12 months or less and more than 12 months.

The physical status classification of the ASA[15] (I, healthy patients, no medical problems; II, mild systemic disease; III, severe systemic disease but not incapacitating; IV, severe systemic disease that is a constant threat to life; and V, moribund, not expected to survive without the operation) was used to grade the comorbidities of the patients and to associate them with the QOL of these patients. See Table 1 for details.

QOL ASSESSMENT

A Brazilian-Portuguese version of the UW-QOL questionnaire validated by Vartanian et al[16] was used. The UW-QOL questionnaire was designed as a self-reported scale and, for this reason, the patients completed it by themselves. Patients who did not feel able to complete the UW-QOL questionnaire independently were helped by their companion. The UW-QOL questionnaire was applied during 2006 in days reserved for only this study.

The questionnaire consists of 12 questions that evaluate the following domains: pain, appearance, activity, recreation, chewing, swallowing, speech, shoulder, taste, saliva, humor, and anxiety. Scores can range from 0 to 100, with 100 indicating the best level of overall function. The composite score is the mean of the scores of all 12 domains. There is general agreement that a composite score of 75 to 100 has little effect on QOL, a score of 50 to 74 has a relative effect on QOL, and a score less than 50 has an important effect on QOL. Three general questions

Table 2. Bivariate Associations Between Demographic and Treatment Variables and Each Function Domain and the Composite Score of the UW-QOL Questionnaire

	Domain Score, Mean[a]												
Variable	Pain	Appearance	Activity	Recreation	Swallowing	Chewing	Speech	Shoulder	Taste	Saliva	Humor	Anxiety	Composite Score
Age, y													
≤45				94.5									
>45				90.1									
P value	.74	.26	.29	.04	.19	.57	.89	.90	.15	.23	.33	.26	.06
Sex													
Male													
Female													
P value	.06	.09	.45	.83	.11	.89	.83	.11	.31	.42	.55	.77	.05
RIT													
None	86.5				95.9	98.4	98.4	89.6	96.7			88.0	91.6
≤150 mCi	88.0				96.8	99.3	98.6	85.9	94.6			89.6	91.8
>150 mCi	76.3				90.1	87.5	91.8	71.7	85.1			76.9	84.0
P value	.05	.56	.12	.52	.03	<.001	.004	.04	.006	.20	.65	.004	.01
Neck dissection													
None						98.3		86.8					
Paratracheal						98.2		90.2					
Radical						94.0		60.7					
P value	.86	.15	.77	.55	.32	.003	.33	.004	.83	.94	.19	.09	.56
Time since treatment, mo													
≤12													
>12													
P value	.88	.61	.74	.20	.72	.64	.50	.57	.58	.20	.14	.71	.56
ASA classification													
I			91.5	94.1			97.4			95.7			93.2
II			85.6	92.3			98.6			90.1			90.0
III			75.0	62.5			83.5			67.0			83.4
P value	.24	.15	.05	.02	.13	.78	.02	.34	.35	.01	.47	.33	.008

Abbreviations: ASA, American Society of Anesthesiologists; RIT, radioactive iodine therapy; UW-QOL, University of Washington Quality of Life.
[a] Mean values are shown for statistically significant variables only.

evaluate overall QOL and HR-QOL. We scored the individual domains according to the UW-QOL questionnaire guidelines.

STATISTICAL ANALYSES

Statistical analysis was performed using a software program (SPSS for Windows version 15.0; SPSS Inc, Chicago, Illinois). A descriptive analysis of the results was performed. Bivariate analyses were conducted by comparing each of the independent variables of age, sex, neck dissection, RIT, time since treatment, and comorbidities with each of the 13 QOL scales on the UW-QOL questionnaire using nonparametric Mann-Whitney or Kruskal-Wallis tests. To determine significant predictors of QOL controlling for one another, multivariate analysis was conducted using multiple linear regression.

RESULTS

In answering the UW-QOL questionnaire on overall health, 94.4% of patients reported that their health was the same or better than it was before treatment, 83.9% of patients reported good HR-QOL, and 83.3% of patients reported good general QOL. There were no significant differences in these questions regarding age, sex, RIT, neck dissection, or comorbidities. The median composite score was 93.05 (range, 53.5-100), which is associated with good QOL.

BIVARIATE ANALYSES

In the evaluation of demographic variables, age had an effect on the recreation domain, with patients older than 45 years showing worse scores than younger patients ($P=.04$). In regard to the other domains, age did not have a significant association. In the same way, sex did not have an effect on any domain (**Table 2**).

The RIT had an effect on many domains, and doses higher than 150 mCi had a strong association with worse scores in several domains, such as pain ($P=.045$), swallowing ($P=.03$), chewing ($P<.001$), speech ($P=.004$), shoulder ($P=.04$), taste ($P=.006$), anxiety ($P=.004$), and composite score ($P=.01$). Patients submitted to neck dissection from level II through VI had significantly worse chewing scores ($P=.003$) and shoulder scores ($P=.004$). Time since treatment was not associated with worse scores in any domain. Patients classified as ASA II and III had worse scores in the activity ($P=.05$), recreation ($P=.02$), speech ($P=.02$), and saliva ($P=.01$) domains and in the composite score ($P=.008$). All these data are summarized in Table 2.

MULTIVARIATE ANALYSES

To conserve power and because sex and time since treatment were not significant in the bivariate analyses, these variables were omitted from the multivariate analyses. Variables with $P\leq.25$ were considered in multiple linear regression to determine the greatest predictor of QOL in patients with thyroid cancer controlling for one another.

The RIT was the strongest predictor factor, affecting domains such as chewing, speech, taste, saliva, and anxiety. It was the only variable that affected the composite

Table 3. Multiple Linear Regression With the Significant Variables From the Bivariate Analyses[a]

Variable	Pain	Appearance	Activity	Recreation	Swallowing	Chewing	Speech	Shoulder	Taste	Saliva	Humor	Anxiety	Composite Score
Age, y													
≤4				.03									
>4				(−5.899)									
RIT													
None/≤150 mCi						.001	.02		.004	.01		.05	.003
>150 mCi						(−9.358)	(−4.705)		(−10.889)	(−10.925)		(−10.960)	(−7.182)
Neck dissection													
None/paratracheal						.03		.006					
Radical						(−7.700)		(−22.205)					
ASA classification													
I/II				.01			.004			.04			
III				(−27.560)			(−15.384)			(−23.786)			

Abbreviations: ASA, American Society of Anesthesiologists; RIT, radioactive iodine therapy.
[a]The values are the *P* value (B value) to the 95% confidence interval.

score. The presense of comorbidities, as measured by ASA classification, was the second predictor of worse QOL; it affected domains such as recreation, speech, and saliva. Neck dissection affected chewing and shoulder scores, and age affected recreation scores. The data are summarized in **Table 3** with the value of unstandardized coefficient B and each *P* value.

COMMENT

In this study, in univariate and multivariate analyses, the greatest predictor of QOL in patients with thyroid cancer was RIT dose, with higher doses showing decreased QOL through the composite score. The composite score shows the effect of all the domains evaluated, and worse scores in specific domains will reflect on the final score. Functions such as taste, speech, chewing, and swallowing are strongly associated with RIT salivary gland effects, as is seen through the association between RIT and these domains in the UW-QOL questionnaire. Until now, in the literature review, none of the published studies showed the effect of RIT or doses of radioactive iodine on QOL in the patient with thyroid cancer. This is an important finding because the indication of RIT should also consider the late effects of the treatment.

The adverse effects of RIT are well recognized and, in general, are mild and self-limiting; severe complications are rare enough that the benefit of therapy typically outweighs its risk.[17,18] The common acute adverse effects reported are nausea, vomiting, epigastralgia, taste disturbance, and sialadenitis,[18] and the late adverse effects normally restrict themselves to the salivary glands as sialadenitis and xerostomia.[5] Recent findings from our group reinforce the hypothesis of Maier and Bihl[19] that patients submitted to RIT have an impairment in the ability to drain the saliva, and it reflects as clinical dysphagia.

Considering that many patients with DTC are submitted to RIT, the effect of those specific adverse effects and those resulting from the surgical procedure on the QOL of such patients were not previously extensively described. There have been relatively few and recent HR-QOL studies looking specifically into patients with thyroid cancer.[1,2,10,11,20-23] The paucity of specific instruments to assess the QOL of patients with thyroid cancer associated with low mortality and morbidity rates of the treatment can explain why there are so few studies in this field.

Most published studies use the 36-Item Short Form Health Survey, that is, a generic QOL instrument, and do not have specific domains to evaluate the effect of possible adverse effects of treatment. The UW-QOL questionnaire, although not commonly used in patients with thyroid cancer, has value in predicting QOL in these patients because it makes it possible to evaluate points that can be related to adverse effects of surgery and RIT.

The main postoperative complications of thyroidectomy are vocal cord palsy owing to dysfunction of the recurrent laryngeal nerve and hypocalcemia. Neck dissection and paratracheal lymph node dissection, when associated with total thyroidectomy, were significantly associated with transitory and permanent hypocalcemia.[17] Besides those results, swallowing changes and occasional dysphagia are sequelae reported after thyroid resection, even long after the surgical procedure.[7]

Neck dissection was associated with chewing function instead of swallowing function, as is commonly reported in the literature, owing to injury of the recurrent nerve. As expected, neck dissection affected the shoulder domain of the QOL instrument. Preexistent comorbidities are associated with a decreased recreation score, as was expected, and with the domains of speech and saliva. Worse scores on these last domains associated with the presence of comorbidities probably can be explained by the intake of medications that can interfere with salivary flow.

To our knowledge, only 1 study[11] has evaluated the results of the adverse effects of surgery and RIT on such patients. This study[11] used a UW-QOL questionnaire that was adapted but not validated. The authors evaluated 20 patients with thyroid cancer and reported that those older than 45 years had worse general health, appearance, and chewing scores but did not show an association of RIT or neck dissection with any domain.

Different from the data of Dagan et al,[11] the present patients reported a good general QOL, with a slight effect of treatment on their HR-QOL. However, our patients who were older than 45 years had worse recreation scores, and preexistent comorbidities had an effect on the activity,

recreation, speech, and saliva domains. The greatest effect on QOL with specific domains was the dose of RIT. Patients submitted to doses higher than 150 mCi had many domains affected, such as pain, swallowing, chewing, speech, taste, anxiety, and composite score. Morbidities of the surgery are detected in chewing and shoulder functions. Time since treatment and sex were not associated with alterations in QOL.

These results reveal that despite patients with thyroid cancer having a good general QOL, there is a subset of patients who live with some comorbidities of the cancer treatment. The dose of RIT can affect specific activities in the daily lives of these patients. The effects of RIT on specific functions had not been assessed and reported in the literature until now, and more studies are needed to confirm these findings. Certainly, this study has some limitations because it is a cross-sectional study, and there is neither a baseline QOL score before treatment nor follow-up across time. Evaluation of QOL at different points in time after treatment could be another limitation, but at the time of the analysis it seems not to have affected the results. Prospective studies using videofluoroscopy to evaluate the different phases of swallowing and salivary gland function in patients receiving more than 150 mCi of RIT can contribute to the clarification of these findings.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Almeida, Vartanian, and Kowalski. *Acquisition of data:* Almeida. *Analysis and interpretation of data:* Almeida and Vartanian. *Drafting of the manuscript:* Almeida. *Critical revision of the manuscript for important intellectual content:* Vartanian and Kowalski. *Statistical analysis:* Vartanian. *Obtained funding:* Almeida and Kowalski. *Administrative, technical, and material support:* Kowalski. *Study supervision:* Vartanian and Kowalski.
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