UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE

PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA

Câncer de pele após transplante cardíaco: uma revisão sistemática.

PESQUISADORA RESPONSÁVEL: Nathalia Hoffmann Guarda Aguzzoli

ORIENTADOR: Prof. Dr. Renan Rangel Bonamigo

Porto Alegre, 2023

Nathalia Hoffmann Guarda Aguzzoli

Câncer de pele após transplante cardíaco: uma revisão sistemática.

Dissertação de Mestrado submetida ao Programa de Pós Graduação em Patologia da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para obtenção do grau de Mestre

Professor Orientador: Dr. Renan Rangel Bonamigo

Porto Alegre, 2023

Catalogação na Publicação

Hoffmann Guarda Aguzzoli, Nathalia
Câncer de pele após transplante cardíaco: uma revisão sistemática. / Nathalia Hoffmann Guarda Aguzzoli. -- 2023.
60 p. : il., tab. ; 30 cm.

Dissertação (mestrado) -- Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Patologia, 2023.

Orientador(a): Renan Rangel Bonamigo.

1. Results of search strategy. 2. Summary of all the articles of the study. 3. Summary the quality analysis. I. Título.

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

Agradecimentos

Dedico essa tese de mestrado ao meu falecido avô, Nativo Hoffmann, vítima de complicações da Covid-19 durante a pandemia, o qual sempre foi forte exemplo de dedicação aos estudos. Lembro do dia que nos encontramos no hospital, após 41 dias entubado na UTI, num despertar lento e confuso, ainda com dificuldades para falar devido a traqueostomia. Apesar disso, sua primeira pergunta inesperada e rápida para as circunstâncias - foi: "estás estudando Pretinha? Como está o mestrado?". Confirmei com a cabeça e o tranquilizei.

Recentemente, ao organizar as mensagens no celular, encontrei nossa última troca de mensagens. Em meio a explicações da razão que não poderia comparecer a minha formatura em
Dermatologia, pois iria viajar para sua última viagem, ele reiterou por mensagem sua única solicitação como avô: parabéns por mais uma formação, que não seja a última, devendo partir para especializações dentro da atividade que você escolheu. Grande abraço e espero que não me esqueça. Vô, jamais vou lhe esquecer e seus conselhos sempre irão estar presentes na minha memória e guiar minhas escolhas e meu caminho.

Agradeço imensamente ao meu marido Cristiano Schaffer Aguzzoli pelo leal companheirismo em todas as etapas do mestrado e também da vida. Agradeço principalmente pela paciência. Unidos a gente é muito melhor.

Aos meus pais, Nauceli Hoffmann Guarda e Fladimir José Guarda, por caminharem lado a lado comigo, incansáveis, me incentivarem em todas minhas escolhas e não medirem esforços para meu crescimento pessoal e profissional.

Ao meu professor orientador Dr. Renan Bonamigo, por quem a admiração cresce com a convivência, devido ao conhecimento imensurável dermatológico e de vida, além de ser exemplo de uma postura ética. Responsável por despertar em mim o interesse pelo meio acadêmico, agradeço pela confiança de estendermos os laços durante o mestrado.

Agradeço minha colega Ana Laura Bueno, pela parceria e amizade fortalecida durante esses anos, obrigada por dividir risadas, cafés e também angústias durante todo o processo, o caminho foi melhor por ter você por perto.

A todos que de alguma forma contribuíram para a conclusão desse trabalho, meus sinceros agradecimentos.

RESUMO DA DISSERTAÇÃO

Introdução: Um amplo espectro de doenças cutâneas afeta os pacientes receptores de transplantes de órgãos sólidos, visto que os mesmos necessitam de terapia imunossupressora de longo prazo para prevenir a rejeição do órgão transplantado. Dentre as complicações cutâneas mais prevalentes no seguimento clínico desses pacientes, encontra-se o câncer de pele. **Objetivos:** Verificar a frequência de câncer de pele em pacientes transplantados cardíacos a partir de dados da literatura. Através de uma revisão de literatura, avaliar a frequência de câncer de pele não melanoma, melanoma e sarcoma de Kaposi em pacientes transplantados cardíacos. Como objetivos secundários, avaliar possíveis fatores clínicos e medicamentosos associados ao câncer de pele em pacientes transplantados cardíacos. Avaliar a qualidade dos artigos e a metodologia utilizada nos trabalhos existentes na literatura. Organizar os dados encontrados com base na literatura a fim de oferecer estratégias e equidade em cuidados dermatológicos para essa população específica de pacientes. **Material e Métodos:** realizada revisão sistemática da literatura, a busca compreensiva da literatura foi efetuada utilizando as plataformas do PubMed, EMBASE e Scopus. **Resultados:** Um total de 2589 artigos foram inicialmente encontrados na literatura. Realizados uma primeira seleção lendo os títulos dos artigos e em seguida a segunda seleção, lendo títulos e resumos, após essas duas etapas, 2123 artigos foram excluídos. Identificamos 175 artigos repetidos. Ao final, 291 artigos foram lidos na íntegra e de acordo com os critérios de inclusão e exclusão, 43 artigos foram incluídos nessa revisão sistemática. **Conclusão:** Pacientes transplantados cardíacos apresentam alta frequência de câncer de pele e que chegamos no momento de analisar exclusivamente a população de transplantados cardíacos, especificamente focando no desfecho câncer de pele. Mais estudos são necessários para entender a complexidade da terapia imunossupressora específica desses pacientes e a interação com os fatores de risco individuais para o desenvolvimento de câncer de pele. Este estudo reforça que os dermatologistas desempenham um importante papel no seguimento a curto e

longo prazo dos pacientes transplantados cardíacos. Essa população de pacientes merece cuidados contínuos do médico dermatologista, visto que essa prática clínica multidisciplinar pode alterar a morbimortalidade e a qualidade de vida após o transplante cardíaco. Assim, a atuação conjunta entre os cardiologistas especialistas em transplante cardíaco e os dermatologistas é uma ação crucial e essencial no atendimento a essa população. **Palavras chaves:** Câncer de pele, câncer, neoplasias, transplantados; transplante cardíaco; imunossupressão, imunossupressores.

ABSTRACT

Introduction: A wide spectrum of skin diseases affect solid organ transplant recipients, as they require long-term immunosuppressive therapy to prevent transplanted organ rejection. Among the most prevalent skin complications in the clinical follow-up of these patients is skin cancer. **Aim of the study:** To verify the frequency of skin cancer in heart transplant patients from literature data. Through a literature review, to evaluate the frequency of non-melanoma skin cancer, melanoma, and Kaposi's sarcoma in heart transplant patients. As secondary objectives, to evaluate possible clinical and drug factors associated with skin cancer in heart transplant patients. Evaluate the quality of articles and the methodology used in existing works in the literature. Organize the data found based on the literature to offer strategies and equity in dermatological care for this specific patient population. **Material and Methods:** The comprehensive search strategy was performed on Pubmed, EMBASE and Scopus platforms **Results:** A total of 2589 records were initially identified through the literature search. We performed the first screening by reading the titles. From the selected titles, we screened the abstracts, and 2123 articles were excluded in this process. We identified 175 duplicated articles. In the end, a total of 291 articles were read to the full extent and after screening for eligibility and inclusion criteria, 43 studies were included in this systematic review. **Conclusion:** In conclusion, heart transplant patients have a high frequency of skin cancer and other skin conditions. This study reinforces that Dermatologists play an important key role in the short and long term follow up of heart transplant patients. This population deserves a careful and continuous evaluation and care from the Dermatologist. This clinical practice can change the morbidity, mortality, and the quality of life after the heart transplant. So, improving the communication between the transplants cardiologists and the dermatologists is a crucial and essential action in the care of heart transplant patients. **Keywords:** Skin cancer, cancer, neoplasms, transplanted; heart transplantation; immunosuppression, immunosuppressants.

LISTA DE ABREVIATURAS

ADS: Ambulatório de Dermatologia Sanitária

CBC: Carcinoma Basocelular

CEC: Carcinoma de Células Escamosas

EUA – Estados Unidos da América

HCPA: Hospital de Clínicas de Porto Alegre

ISHLT: *International Society for Heart and Lung Transplantation* (Sociedade Internacional de Transplante de Coração e Pulmão).

PMP: por milhão da população

PPG: Programa de Pós-Graduação

UFCSPA: Universidade Federal de Ciências da Saúde de Porto Alegre

UFRGS: Universidade Federal do Rio Grande do Sul

LISTA DE FIGURAS

LISTA DE TABELAS

SUMÁRIO

1. INTRODUÇÃO: REFERENCIAL TEÓRICO

Um amplo espectro de doenças cutâneas afeta os pacientes receptores de transplantes de órgãos sólidos, visto que os mesmos necessitam de terapia imunossupressora de longo prazo para prevenir a rejeição do órgão transplantado[1]. Com o aumento do número de transplantes realizados e da sobrevida desses pacientes, cada vez mais são encontradas complicações cutâneas no seguimento clínico dessa população, dentre elas o câncer de pele[1,2].

1.1 Transplante Cardíaco

No ano de 2017, o Brasil foi o segundo país em número absoluto de transplantes renais[3]. Sabemos que grande parte da literatura em pacientes transplantados provém de estudos realizados na população de receptores renais e renais-pancreáticos[1],

O transplante cardíaco é uma medida que salva vidas e é considerado o tratamento padrão ouro para pacientes com insuficiência cardíaca refratária, apesar da grande melhora na expectativa de vida com tratamento clínico[4].

No Brasil, de acordo com o Registro Brasileiro de Transplantes de órgãos, nos últimos 6 anos (2012 a 2018) a taxa de realização de transplantes cardíacos aumentou 21,4%[4]. No mesmo ano, a região Sul obteve uma taxa de 35,9 pmp (por milhão da população), superior duas vezes à taxa do Brasil (17,0 pmp) e da região Sudeste (18,3 pmp)[3].

Dados do primeiro trimestre de 2019 da Associação Brasileira de Transplante evidenciam que o transplante cardíaco apresentou crescimento de 17,6%, atingindo 2 transplantes pmp, próximo à meta estabelecida para 2019 (2,1 pmp).[5]

O ano de 2017 foi um marco, pois comemorou-se o 50º aniversário do primeiro transplante cardíaco realizado no ano de 1967, a partir de então,

principalmente após a introdução da ciclosporina na decáda de 70, esse procedimento apresentou uma evolução crescente em todo o mundo.[6]

No contexto mundial, de acordo com dados da Sociedade Internacional de Transplante de Coração e Pulmão (International Society for Heart and Lung transplantation – ISHLT), após um declínio no número de transplantes cardíacos no período entre 1993 e 2004, ele tem apresentado um crescente aumento, especialmente nos últimos três anos, sendo registrado um número total de 5074 transplantes cardíacos (adultos e pediátricos) no ano de 2015, em 285 centros.[6]

Apesar deste crescimento mundial e brasileiro na área, ao nosso conhecimento, não há estudos realizados no nosso país sobre dermatoses em receptores cardíacos. Ademais, os estudos internacionais não são muito numerosos e podem não refletir com exatidão os fenômenos brasileiros.[7–11]

1.1.1 Imussupressão em Transplante Cardíaco

Terapia imunossupressora eficaz é a base do tratamento no seguimento dos pacientes transplantados, essencial na determinação da longevidade do enxerto[12]. Sabe-se que a imunossupressão após transplante cardíaco é mais intensa do que a utilizada em transplantes renais, com o intuito de prevenir e tratar possível rejeição do enxerto e suas graves consequências.[12,13]

As drogas utilizadas após transplante cardíaco apresentam um amplo espectro de toxicidades e efeitos adversos e o aumento no risco de cânceres após o procedimento representa a maior causa de morbidade e mortalidade nesses pacientes. Em pacientes transplantados, a incidência global de malignidades é de 5 a 6%, o que é 100 vezes maior do que a população geral.[13]

Transplantados cardíacos parecem ter maior tendência do que outros receptores de órgãos sólidos a desenvolver neoplasias potencialmente

ameaçadoras à vida, particularmente linfomas e malignidades cutâneas.[13]Estudo multicêntrico realizado com mais de 50.000 pacientes transplantados renais e cardíacos de centros da Europa e América do Norte evidenciou que a incidência de linfoma não Hodgkin foi significativamente maior entre os pacientes transplantados cardíacos (0,2% dos receptores renais e 1,2% dos receptores cardíacos), achado consistente com a maior dose de imunossupressão recebida por esses pacientes.[10]

Os regimes de imunossupressão geralmente se classificam em: terapia de indução, de manutenção e anti-rejeição.[14] O esquema tríplice constituído por corticosteroide, inibidor da calcineurina e agente antiproliferativo, continua sendo utilizado de forma rotineira pela maioria dos serviços .[8,13–15] Abaixo, discorreremos brevemente sobre as principais drogas imunossupressoras utilizadas nos transplantados cardíacos.

1.1.1.1 Terapia de indução

O período imediato ao transplante caracteriza-se por uma imunossupressão mais intensiva com o objetivo de reduzir o risco de rejeição aguda e também de facilitar a introdução das medicações utilizadas na imunossupressão de manutenção.[12,16] As drogas mais utilizadas incluem a timoglobulina (anticorpos anti-linfócitos) e o basiliximabe (antagonistas da interleucina 2) .[15]

Sua utilização ainda é controversa na literatura e vem sendo amplamente estudada, segundo dados da Sociedade Internacional de Transplante de Coração e Pulmão (International Society for Heart and Lung Transplantation – ISHLT), aproximadamente 50% dos programas de transplantes cardíacos empregam essa estratégia de imunossupressão aumentada, sendo mais frequente na América do norte do que na Europa.[6]

Ainda de acordo com a ISHLT, de uma forma geral a terapia de indução não foi associada a diferenças na sobrevida, porém um relato recente a instituição sugere melhores desfechos associados com o uso da indução com globulina anti timócito comparada com basiliximabe.[6]

1.1.1.2 Corticosteroides

Possuem efeito potente de imunossupressor e anti-inflamatório. Nas fases iniciais pós transplante e também nos episódios de rejeição aguda, são utilizados em doses altas .[12] Devidos seus inúmeros efeitos colaterais relacionados ao uso a longo prazo, deve ocorrer redução gradual e sua retirada tem sido preconizada a partir dos 6 meses após transplante, principalmente em pacientes com histórico favorável a rejeições.[12,14,15]

O último registro da Sociedade Internacional de Transplante de Coração e Pulmão (ISHLT), relata que o uso da prednisona apresenta decréscimo e é utilizada em um pouco mais de 80% dos pacientes no primeiro ano após transplante .[6]

1.1.1.3 Inibidores da calcineurina

Os dois inibidores da calcineurina disponíveis são a ciclosporina e o tacrolimus. Ambos são agentes altamente eficazes, porém alguns estudos recentes demonstraram menor incidência de rejeição com o uso do tacrolimus.[13] Nas situações de rejeição (resistentes a corticoides) preconiza-se a substituição da ciclosporina pelo tacrolimus.[12,15] Segundo o último registro da ISHLT, o tacrolimus tem sido o inibidor da calcineurina prefererido.[6]

1.1.1.4 Agentes anti-proliferativos

Representados pela azatioprina e micofenolato mofetil. Estudos comparando ambos em transplante cardíaco revelaram superioridade do micofenolato em relação à rejeição e à sobrevida.[12,15] Em relação a sintomas colaterais gastrointestinais, infecções virais por herpes zoster, herpes simples e por citomegalovírus os estudos favorecem mais o uso da azatioprina.[12,15]

Pacientes em uso de azatioprina que desenvolvem rejeição grave ou persistente, a orientação é realizar a troca para micofenolato. Em pacientes com Doença de Chagas, estudos evidenciaram elevada incidência de reativação da doença com o uso de micofenolato, levantando o questionamento sobre a utilização da azatioprina nestes pacientes

específicos.[12,15] De acordo com o último registro da ISHLT, o micofenolato de mofetila é o agente antiproliferativo mais utilizado.[6]

1.2.1.5 Inibidores do Sinal da Proliferação

Nova classe de medicamentos conhecida como inibidoras do sinal de proliferação tem sido utilizada em pacientes selecionados e é representada pelo everolimus e sirolimus . Essa classe de medicamentos inibe a atividade de enzima *mamalian target rapamycin* (mTOR), interferindo nos mecanismos celulares de proliferação e crescimento, tanto no sistema imune como também em outros tecidos.[12,15]

Estudos evidenciaram melhora ou preservação da função renal nos esquemas de retirada/redução da ciclosporina, diminuição da progressão da doença vascular do enxerto e redução de infecções virais e neoplasias.[12,15] Porém, sabe-se que a utilização precoce esteve associada a aumento na incidência de infecções bacterianas, complicações na cicatrização da ferida operatória e quando utilizados em esquemas com associação à ciclosporina esteve relacionada à piora da função renal.[1] Entretanto outros estudos não confirmaram tais achados.[16]

Publicações recentes em transplantados renais demonstraram uma redução no risco de câncer de pele nos pacientes tratados com sirolimus como terapia de primeira linha.[16] Outro estudo de coorte recente, realizado em Massachusetts (EUA), demonstrou que pacientes transplantados gerais que utilizaram sirolimus após o desenvolvimento de câncer no pós transplante (qualquer tipo), apresentaram menor risco de desenvolver câncer de pele subsequente, alertando os médicos a estarem atentos aos fatores de risco para câncer de pele (particularmente pacientes com história prévia de neoplasias cutâneas) e a considerarem diminuição da imunossupressão ou conversão para regime utilizando inibidores mTOR.[16] Por ser uma classe recente de imunossupressores, estudos continuados são necessários para estabelecer seu papel em transplante cardíaco.[12]

Devido às diferenças no tratamento imunossupressor recebido por cada paciente e as potenciais diferenças na prevalência e no tipo de doenças cutâneas encontradas que podem ser diretamente influenciadas pelos fármacos utilizados, é reiterada a necessidade de estudar as características dos receptores de transplantes cardíacos, especificamente.

1.2 Manifestações dermatológicas em pacientes transplantados

De forma geral, as complicações dos transplantes podem ser divididas em precoces e tardias, sendo as primeiras geralmente cirúrgicas e as últimas clínicas.[1]

A pele é frequentemente afetada em receptores de transplantes de órgãos sólidos. Afecções cutâneas são reportadas em 45% a 100% dos pacientes e representam uma importante causa de morbimortalidade e grande impacto na qualidade de vida desta população.[1,17]

Com o desenvolvimento de programas de transplante de órgãos durante as últimas três décadas, a dermatologia se tornou uma das especialidades mais frequentemente consultadas. Este fato deve-se ao aumento do número de complicações cutâneas principalmente causadas pelo uso prolongado de imunossupressores e corticosteroides.[17]

As lesões cutâneas mais comuns nos pacientes transplantados são infecções virais, fúngicas e bacterianas e lesões pré-malignas e tumores de pele.[18]

As doenças infecciosas cutâneas nesses pacientes possuem diferentes tipos de apresentações, muitas vezes atípicas, e por isso uma extensa lista de diagnósticos diferenciais.[1,19] O tipo de drogas imunossupressoras utilizadas e sua dosagem variável após o transplante provavelmente influenciam o tipo e a aparência das infecções da pele.[1] Sua frequência varia entre 27% e 66% de acordo com diferentes estudos, sendo os principais agentes causais os vírus e os fungos.[1]

O espectro de infecções cutâneas difere de acordo com o período pós-transplante. Durante o primeiro mês pós-procedimento, as infecções resultam principalmente de intervenções cirúrgicas. Após o primeiro mês pós-transplante, a natureza das doenças infecciosas da pele é mais frequentemente resultado de imunossupressão severa, manifestando-se como infecções por vírus (vírus herpes simplex, vírus varicela zoster, citomegalovírus, vírus Epstein-Barr), leveduras (Candida) e bactérias.[18]

Após 6 meses, como a imunossupressão é reduzida, o espectro de organismos causadores se aproxima do população geral, com micoses e infecções por papilomavírus humano (HPV) predominando.[1]

Outras frequentes complicações tardias são as neoplasias de pele, provavelmente subnotificadas, cujo risco nesse grupo de pacientes é aumentado em três a cinco vezes, em comparação com a população em geral.[1] Os tipos de câncer de pele mais prevalentes são os carcinomas de células escamosas (CECs), seguidos dos carcinomas basocelulares (CBCs).[18] As drogas imunossupressoras, além do efeito direto, podem potencializar os efeitos de outros carcinógenos, como a radiação ultravioleta.[19]

A seguir serão apresentadas as afecções cutâneas mais importantes que podem acometer esta população de pacientes.

1.2.1 Dermatoses Malignas

Dentre as condições malignas em pacientes transplantados, os cânceres de pele são as mais comuns e contribuem significativamente para morbidade e mortalidade de tais pacientes.[2] Os cânceres de pele não melanoma, predominantemente os carcinomas de células escamosas (CEC) e os carcinomas basocelulares (CBC) correspondem cerca de 90% de todas as neoplasias cutâneas em pacientes transplantados.[2,20]

1.2.1.1 Fatores de risco e etiopatogênese

A radiação ultravioleta parece ser o fator de risco mais importante para o desenvolvimento de câncer de pele nessa população. As maiores incidências se encontram em países com alta exposição solar, como por exemplo a Austrália, além disso, as neoplasias cutâneas - principalmente os CEC`s- tem seu surgimento relacionado a áreas do corpo expostas com fotodano intenso e pacientes com maior acúmulo de radiação antes do transplante também implica em maior risco, o que apoia o papel da radiação UV na etiopatogenia dos tumores cutâneos.[1,2]

Outros fatores de risco relacionados incluem a duração e a intensidade da imunossupressão utilizada, idade no momento do transplante, infecção por papilomavirus humano, sexo masculino, pele clara com olhos azuis, falta de conscientização do risco de câncer de pele e história prévia de câncer de pele não melanoma.[21]

O nível de imunossupressão recebida pelo paciente é proporcional à incidência de cânceres de pele.[2]

Transplantados cardíacos são particularmente propensos ao desenvolvimento de neoplasias cutâneas por causa da intensa imunossupressão a qual são submetidos para a prevenção de rejeição do órgão transplantado, além disso, em média também costumam apresentar idade mais avançada no momento do procedimento.[2]

Pacientes que desenvolvem câncer de pele também parecem ter aumento no risco de outras malignidades, como melanoma, linfoma não Hodgkin, fibrohistiocitoma maligno, cânceres anogenitais e fibroxantoma atípico.[22]

A etiopatogênese dos carcinomas cutâneos é multifatorial, razões para incidências aumentadas entre pacientes imunossuprimidos incluem diminuição da imunovigilância de neoplasias causada pelo uso da terapia de

imunossupressão unida a exposição a radiação ultravioleta .[2,20] Mutações no gene supressor de tumor p53 são provocadas pela radiação UV, a qual também causa uma imunodeficiência local devido diminuição da densidade das células de Langerhans epidérmicas.[2] Sabe-se também que em pacientes transplantados com diagnóstico de carcinoma cutâneo a contagem de CD4 é menor do que naqueles que não possuem.[2,22]

1.3.1.2 Câncer de Pele Não Melanoma – Carcinoma de Células Escamosas e Carcinoma Basocelular

Durante a terapia imunossupressora, a incidência de CEC`s e CBC`s aumenta conforme a duração da mesma, afetando 50% ou mais dos pacientes transplantados brancos.[2]

Entre os pacientes transplantados, o CEC é o mais comum, estima-se que ele ocorra numa frequência de 65 a 250 vezes maior do que na população geral.[2,22] Além disso, ele apresenta-se de forma mais agressiva nessa população, com risco de metástase 10 vezes maior do que na população geral.[1,22] As complicações não são raras, e podem corresponder à recorrência tumoral local e às metástases.[22]

Estudo que comparou a incidência de CEC entre transplantados renais e cardíacos evidenciou que o risco foi significativamente mais alto nos pacientes transplantados cardíacos do que nos transplantados renais e na população geral, mas a literatura é pouco extensa quanto a detalhes da oncogenicidade cutânea na população de transplantados cardíacos.[9,23]

Ao contrário do que ocorre na população imunocompetente, onde a incidência de CBC é maior do que a de CEC, essa relação se inverte em pacientes transplantados.[1,24] Porém o risco de desenvolver CBC também aumenta nos receptores de transplantes de órgãos sólidos; é esperado um aumento de 10 a 16 vezes quando comparado com a população geral.[1] Em um

estudo realizado no sul do Brasil, foi descrita uma provável relação entre o desenvolvimento de CBC e a presença do alelo HLA DR1.[25]

Diferentemente do CEC, o CBC que se desenvolve sob imunossupressão geralmente não é mais agressivo do que em imunocompetentes e deve ser tratado cirurgicamente se possível.[1,24] Aproximadamente entre 30 a 50% dos pacientes com diagnóstico de CEC também desenvolverão CBC`s.[2]

1.3.1.3 Melanoma Maligno

Os receptores de transplante sólidos apresentam menor risco de desenvolver melanoma do que carcinomas cutâneos; ainda assim, tem sido reportado um aumento do risco de até 4 vezes comparativamente à população geral.[2] Alguns autores não encontraram o aumento deste risco.[1,22,26]

Melanomas ocorrem principalmente em pacientes com pele clara, cabelos e olhos claros e tendência a efélides.[2,22] O intervalo médio entre o transplante e o desenvolvimento de melanoma é de 5 anos.[1,2,22] Pacientes transplantados com melanoma apresentam outros cânceres de pele em 27% dos casos.[2,27]

Estudo recente evidenciou que pacientes transplantados possuem um risco de morte pelo melanoma 3 vezes maior do que pacientes não transplantados.[28]

O melanoma pode ser transmitido através de doadores que tiveram metástases de melanoma cerebral e foram erroneamente diagnosticados como tumor cerebral primário ou hemorragia cerebral.[22,27] Pacientes com diagnóstico de melanoma cutâneo e realizaram transplante de órgãos apresentaram recidiva em 20% dos casos, mesmo quando o diagnóstico de melanoma ocorreu 10 anos antes do transplante.[22,27]

Pacientes diagnosticados com melanoma previamente ao transplante, o tempo de espera para o procedimento foi proposto de acordo com a extensão da doença. Pacientes com doença *in situ* não precisam esperar pelo transplante, aqueles que apresentam Breslow inferior 1 mm e/ou biópsia de linfonodo sentinela negativa devem esperar por 2 anos para o transplante, com avaliações frequentes para recorrências nesse período. Os pacientes com Breslow igual ou acima de 2 mm o tempo de espera ideal é de 5 anos, devido o aumento do risco de recorrência e comportamento imprevisível do mesmo em imunossuprimidos. Pacientes que apresentam envolvimento linfonodal e doença metastática geralmente não devem receber transplante de órgão sólidos.[1,29]

2. REFERÊNCIAS BIBLIOGRÁFICAS

1 Dufrechou L, Borges AL. Dermatologic Manifestations Among Transplant Recipients. In: Bonamigo RR, Dornelles SIT (eds). *Dermatology in Public Health Environments: A Comprehensive Textbook*. Springer International Publishing: Cham, 2018, pp 987–1009.

2 Euvrard S, Kanitakis J, Claudy A. Skin cancers after organ transplantation. *N Engl J Med* 2003; **348**: 1681–1691.

3 Dimensionamento dos Transplantes no Brasil e em cada estado. Associação Brasileira de Transplante de Orgãos. http://www.abto.org.br. Acesso em: 2019. 2018.http://www.abto.org.br. Acesso em: 2019 (accessed 2019).

4 Sorensen A, Norsen L, Chen L, Palermo E, Martens J. A Multimodal Skin Cancer Prevention Program for Heart Transplant Patients. *Prog Transplant* 2018; **28**: 263–266.

5 Dados Númericos da doação de órgãos e transplantes realizados por estado e instituição no período: Março 2019. Associação Brasileira de Transplante de Orgãos 2019. São Paulo. http://www.abto.org.br. http://www.abto.org.br (accessed 2019).

6 Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ *et al.* The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report—2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant* 2017; **36**: 1037–1046.

7 Petter Jensen, Ole P. F. Clausen, Odd Geiran, Svein Simonsen, Anne Relbo, Svein Hansen, Tor Langeland. Cutaneous Complications in Heart Transplant Recipients in Norway 1983-1993. *Acta Derm Venereol* 1995; : 400–403.

8 Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. *J Am Acad Dermatol* 1999; **40**: 27–34.

9 España A, Redondo P, Fernández AL, Zabala M, Herreros J, Llorens R *et al.* Skin cancer in heart transplant recipients. *J Am Acad Dermatol* 1995; **32**: 458–465.

10 Opelz G, Henderson R. Incidence of non-Hodgkin lymphoma in kidney and heart transplant recipients. *Lancet* 1993; **342**: 1514–1516.

11 Caforio AL, Fortina AB, Piaserico S, Alaibac M, Tona F, Feltrin G *et al.* Skin cancer in heart transplant recipients: risk factor analysis and relevance of immunosuppressive therapy. *Circulation* 2000; **102**: III222–7.

12 Bacal F, Souza Neto JD de, Fiorelli AI, Mejia J, Marcondes-Braga FG, Mangini S *et al.* II Diretriz Brasileira de Transplante Cardíaco. *Arq Bras Cardiol* 2010; **94**: e16–e76.

13 Ippoliti G, Rinaldi M, Pellegrini C, Viganò M. Incidence of cancer after immunosuppressive treatment for heart transplantation. *Crit Rev Oncol Hematol* 2005; **56**: 101–113.

14 Lindenfeld J, Miller GG, Shakar SF, Zolty R, Lowes BD, Wolfel EE *et al.* Drug therapy in the heart transplant recipient: part I: cardiac rejection and immunosuppressive drugs. *Circulation* 2004; **110**: 3734–3740.

15 Dressler DK. Hear transplantation: a review. *Journal of Transplant Coordination, Vol 9, Number 1* 1999.

16 Karia PS, Azzi JR, Heher EC, Hills VM, Schmults CD. Association of Sirolimus Use With Risk for Skin Cancer in a Mixed-Organ Cohort of Solid-Organ Transplant Recipients With a History of Cancer. *JAMA Dermatol* 2016; **152**: 533–540.

17 C. L. Pimentel, J. Dalmau, L. Puig, M. Gilaberte, E. Roé, L. Peramiquel, A. Alomar. Manifestaciones cutáneas en pacientes trasplantados: estudio de 63 pacientes Cutaneous manifestations of post-trasplanted patients. A study of 63 cases. https://www.researchgate.net/publication/237232185.

18 Wisgerhof HC, Edelbroek JRJ, de Fijter JW, Feltkamp MCW, Willemze R, Bouwes Bavinck JN. Trends of skin diseases in organ-transplant recipients transplanted between 1966 and 2006: a cohort study with follow-up between 1994 and 2006. *Br J Dermatol* 2010; **162**: 390–396.

19 Galimberti R, Parra IH, Malieni D, Galimberti y Alicia Kowaiczuk G. Infecciones cutáneas en pacientes con trasplante de órganos sólidos. .

20 Ho WL, Murphy GM. Update on the pathogenesis of post-transplant skin cancer in renal transplant recipients. *Br J Dermatol* 2008; **158**: 217–224.

21 Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, Van de Beek D *et al.* Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol* 2009; **145**: 1391–1396.

22 Euvrard S, Kanitakis J, Claudy A. Neoplastic skin diseases in organ transplant recipients. *Am J Cancer* 2002; **1**: 109–120.

23 Jensen P, Møller B, Hansen S. Skin cancer in kidney and heart transplant recipients and different long-term immunosuppressive therapy regimens. J. Am. Acad. Dermatol. 2000; **42**: 307.

24 Ulrich C, Arnold R, Frei U, Hetzer R, Neuhaus P, Stockfleth E. Skin changes following organ transplantation: an interdisciplinary challenge. *Dtsch Arztebl Int* 2014; **111**: 188–194.

25 de Carvalho AVE, Bonamigo RR, da Silva CM, Pinto ACDZ. Positivity for HLA DR1 is associated with basal cell carcinoma in renal transplant patients in southern Brazil. *Int J Dermatol* 2012; **51**: 1448–1453.

26 Lindelöf B, Sigurgeirsson B, Gäbel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol* 2000; **143**: 513–519.

27 Penn I. Malignant melanoma in organ allograft recipients. *Transplantation* 1996; **61**: 274–278.

28 Robbins HA, Clarke CA, Arron ST, Tatalovich Z, Kahn AR, Hernandez BY *et al.* Melanoma Risk and Survival among Organ Transplant Recipients. *J Invest Dermatol* 2015; **135**: 2657–2665.

29 Stoff B, Salisbury C, Parker D, O'Reilly Zwald F. Dermatopathology of skin cancer in solid organ transplant recipients. *Transplant Rev* 2010; **24**: 172–189.

3. JUSTIFICATIVA

O transplante cardíaco é uma medida que salva a vida de pacientes. A imunossupressão utilizada nesses pacientes, principalmente durante o primeiro ano após o transplante, é considerada intensa e o balanço entre os riscos causados por ela e os riscos de rejeição do órgão transplantado configura um desafio no manejo clínico desses pacientes.

Apesar de uma longa experiência com transplantados de órgão sólidos (em especial, renais), as equipes de dermatologia consideram que há poucos estudos na literatura avaliando doenças infecciosas cutâneas e cânceres cutâneos na população de transplantados cardíacos; particularmente não são encontrados pesquisas na população brasileira, com suas nosologias específicas.[7,9,30] Além disso, e especialmente relacionado a este estudo, a alta incidência de cânceres cutâneos nessa população específica destaca a necessidade de uma avaliação cuidadosa e criteriosa desta associação. A participação do dermatologista na vigilância da saúde cutânea após transplante cardíaco pode ser primordial no seguimento desse paciente.
Devido a essa forte suposição realizamos essa revisão sistemática.

4. OBJETIVOS

4.1 Objetivo geral

Verificar a frequência de câncer de pele em pacientes transplantados cardíacos a partir de dados da literatura.

4.2 Objetivos específicos

a) Realizar uma revisão de literatura para avaliar a frequência de câncer de pele não melanoma, melanoma e sarcoma de Kaposi em pacientes transplantados cardíacos.
b) Avaliar possíveis fatores clínicos e medicamentosos associados ao câncer de pele em pacientes transplantados cardíacos, a partir de dados da literatura.
c) Avaliar a qualidade dos artigos e a metodologia utilizada nos trabalhos que incluem a população de transplantados cardíacos.
d) Organizar os dados encontrados com base na literatura a fim de oferecer estratégias e equidade em cuidados dermatológicos para essa população específica de pacientes.

5. ARTIGO CIENTÍFICO REDIGIDO EM INGLÊS

Title of the paper: Skin cancer after heart transplantation: a systematic review.

Authors:

1. Nathalia Hoffmann Guarda Aguzzoli (Aguzzoli, NHG)[1]
2. Ana Laura Bueno (Bueno, AL)[1]
3. Yağmur Halezeroğlu (Halezeroğlu, Y)[2,3] 4. Renan Rangel Bonamigo (Bonamigo, RR)[1,4]

Filiations Institutions each authors:

1. Federal University of Health Sciences of Porto Alegre (UFCSPA), Porto Alegre, Brazil
2. University of California - San Francisco (UCSF), California, USA
3. University of California Berkeley School of Public Health and University of California San Francisco School of Medicine, United States.
4. Federal University of Rio Grande do Sul, (UFRGS), Porto Alegre, Brazil

Corresponding Author:

Nathalia Hoffmann Guarda Aguzzoli, MD

Federal University of Health Sciences of Porto Alegre nathaliahoff@gmail.com

Phone number: +1 628 688 5686

Address: 236 South Negley Avenue, Pittsburgh, Pennsylvania, United States.

Manuscript word count: 9280
Tables: 2
Figures: 1

Conflict of interest: None.

Funding source: None.

O artigo será enviado para Revista **Internacional Journal of Dermatology.**

ABSTRACT

Background: Malignancies are an important cause of morbidity and mortality after solid organ transplants. Skin cancer is the most prevalent non-lymphoid malignancy occurring in heart transplantation follow-up. Due to the complexity of immunosuppressive therapy and the high prevalence and incidence of skin cancer in this population, dermatologists play an important role in the short and long-term follow-up of heart transplant patients. **Methods:** We conducted a systematic review of the literature on the prevalence and incidence of skin cancer in heart transplant patients. **Results:** Based on the search strategy, we found 2589 studies, out of which 37 were eligible for the inclusion in this study. Provided data are from 20 different countries, over the period of 1974 to 2015. Frequency of non-Melanoma skin cancer (NMSC) ranges from 52,8% to 0,97% and frequency of Melanoma ranges from 4,6% to 0,94%.
Conclusion: Although gathering methodologically heterogeneous data, this systematic review was able to demonstrate the epidemiological importance of skin cancer in heart transplant patients. This study reinforces the important role dermatologists play in the short and long-term follow-up of heart transplant patients. (205 words)

INTRODUCTION

Malignancies are an important cause of morbidity and mortality after solid organ transplant[1]. The correlation between immunosuppression and the development of malignancies is well documented[2,3]. Overall transplant recipients have an increased risk of developing a malignancy when compared with the general population, and heart transplants are described among those with highest risk[2,3]. Malignancy incidences after heart transplantation is two to threefold higher compared to renal transplantation[3]. This fact can be attributed to aggressive immunosuppression that these patients require[3,4].

The skin is affected in 45–100% of patients who undergo an organ solid transplant[5]. Skin cancer is the most prevalent non-lymphoid malignancy occurring in heart transplantation follow-up[6]. NMSC, such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), are among the most prevalent[2,5].

The risk of development of SCC is known to be increased 10-16 times in transplant patients compared to the general population[5]. Studies estimate the incidence of SCC to be 65 to 250 times higher in solid organ transplant recipients (OTRs) when compared with the general population[7]. The incidence ratio of SCC to BCC in the general population is about 1:4. Conversely, among OTRs, this ratio is 5:1, therefore SCC is more frequent than BCC in transplanted patients[5,8].

Melanoma is the most aggressive type of skin cancer and is also increased in OTRs. The risk of developing melanoma after a solid organ transplant is two to eight-fold compared with the general population[5]. Additionally, this population may have a worse melanoma prognosis[9].

Despite the medication therapeutic arsenal, heart transplantation is a life-saving treatment in patients with advanced heart failure. It provides better survival rates than clinical therapy alone, since advanced heart failure is a severe and life-threatening condition [10].

The association of solid organ transplant and skin cancer is well established, mainly in renal transplants[5]. Currently, there are few studies focused specifically on patients with heart transplant and development of skin tumors.

According to the United Network for Organ Sharing (UNOS), the percentage of heart transplantation in the USA increased 4,3% between 2020 and 2021[11]. This increase was maintained even during the Sars-Cov 2019 pandemic[11]. Considering the increased number of heart transplants performed in recent years, the long-term survival after this procedure, and the association of immunotherapy with malignancies, we believe that understanding thoroughly

the epidemiology of skin cancer following heart transplantation is paramount to deliver adequate care for these patients and foster skin health equity.

The aim of this study is to present data from a systematic literature review on the presence of skin cancer among heart transplant patients. For this study, we divided skin cancer into squamous cell carcinoma, basal cell carcinoma, Kaposi sarcoma and melanoma.

MATERIALS AND METHODS

Search strategy

This study consisted of a systematic review of the literature on the prevalence, incidence and the frequency of skin cancer in heart transplant patients.

The comprehensive search strategy was performed on Pubmed on July 1st, 2021, and on EMBASE and Scopus platforms on August 27th, 2021. We used the following search strings to identify relevant papers: *Neoplasms, basal cell carcinoma, squamous Cell, squamous cell carcinoma, nonmelanoma, melanoma, skin neoplasms, skin cancer and transplant recipient, organ transplantation, solid organ transplant, Immunosuppression, immunocompromised host and heart or cardiac*. Our strategy also included searching for those terms in the bibliographic references of the selected articles.

Selection of the studies

Selected articles were analyzed by two independent evaluators who critically reviewed the main characteristics of each study, such as population and sample size, casuistic of patients, country, dermatology evaluations and overall epidemiologic analysis. A third examiner evaluated and reviewed this work when disagreement was present.

Titles were read first, and then the titles and the abstracts. Finally, the articles that were within the scope of this research were read entirely. After reading the full text, the articles that met the inclusion criteria were selected. Studies that qualified for full text revision were further analyzed by the following criteria: author, year of publication, study design, country, data/period evaluated, size of the study population, immunosuppressant medications, results, and other relevant information.

Inclusion and exclusion criteria

We included original articles written in English concerning the prevalence and incidence of skin cancer in patients who received heart transplantation. We divided skin cancer into SCC, BCC, kaposi sarcoma (KS) and melanoma. In the selected articles, the frequency of skin cancer in the population studied had to be directly mentioned and easily calculated.

The exclusion criteria were review articles, clinical trial studies, articles with no individual evaluation per organ transplant type (evaluation only of the general cohorts), case reports, and studies that don't evaluate the frequency of skin cancer in the specific population. When institutions published duplicate cohort studies with accumulating numbers of patients, only the most complete reports were included.

Quality assessment

We assessed the selected articles for methodological quality using the Newcastle Ottawa Scale (NOS) Quality Assessment Form for cohort studies. Studies with NOS scores 0–3, 4–6, and 7–9 were considered as low, moderate and high quality, respectively [12].

We add sun exposure calculation as a comparability variable criteria, because it is an important risk factor to skin cancer development in any population. We considered the evaluation of the exposure to radiation UV and the calculation of the time that this exposure represents.

The quality and relevance of the articles were investigated by two independent reviewers. In the avaliaton, 23 (62%) studies were classified as good quality, 2 (5,4%) studies were classified as fair quality and 12 (32,4%) studies were classified as poor quality.

The quality of the studies could be compromised because most of them are composed by cohorts of organ solid transplants, including all the solid organ transplant patients. Our study focuses only on the heart transplant patients; therefore, this can represent a bias in the analysis of the study quality, since studies with a good final score may overestimate the heart transplant studies quality interpretation.

RESULTS

A total of 2589 records were initially identified through the literature search. We performed the first screening by reading the titles. From the selected titles, we screened the abstracts, and 2123 articles were excluded in this process. We identified 175 duplicated articles. In the end, a total of 291 articles were read to the full extent and after screening for eligibility and inclusion criteria, 37 studies were included in this systematic review. Figure 1 summarizes the search strategy and articles selection.

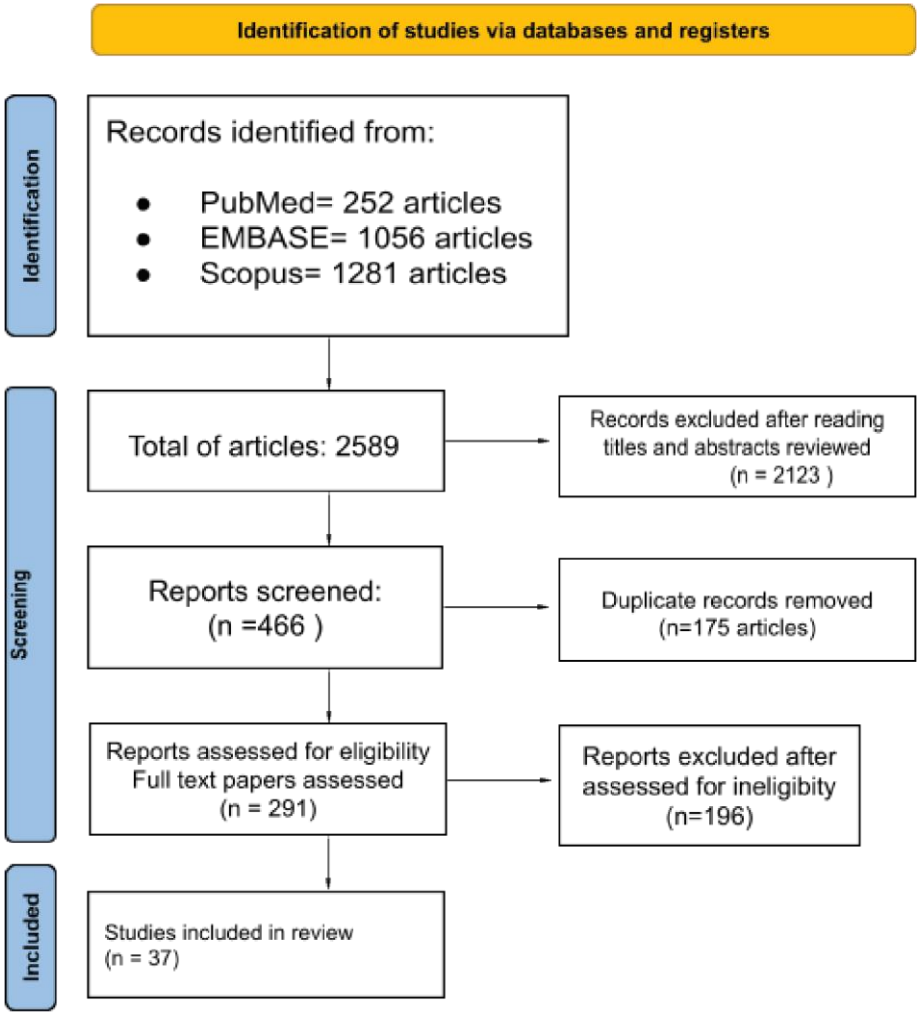


Figure 1. Results of the search strategy.

The selected articles and their clinical characteristics are summarized in Table 1. These studies were conducted in 21 different countries: United States 7 studies, Italy 6 studies, Germany 3 studies, Spain 3 studies, Belgium 1 study, Taiwan 2 studies, Japan 1 studY, Canada 2 studies, Finland 1 study, Brazil 1 study, England 1 study, Norway 1 study, Korea 1 study, China 1 study, Australia 2 studies, Ireland 1 study, Czech Republic 1 study, Denmark 1 study, Scotland, 1 study. Provided data are from 20 different countries, over the period of 1974 to 2015. Table 1 summarizes the results.

The methodological quality of the studies varied with a range of scores between 1-9, using the tool Newcastle Ottawa Scale (NOS) Quality Assessment Form for cohort studies. Table 2 shows the quality control for each of the selected articles.

Herein we provide a comprehensive overview on the frequency of skin cancer among patients following heart transplantation.

Table 1. Summary of all the articles of the study

First Author/ Year	Study Design	Country	Evaluated period	Sample Size (heart transplant)	Immunosuppressant medications	Results: Skin Cancer in heart transplantation	Study design: prevalence or incidence and relevant other informations
Jensen et al 1995 [13]	Cohort	Norway	1983 to 1992 (9y)	140 (M: 113 F: 27) Mean Age*: 47.7 (2-67)	CsA, AZA and prednisolone. No cytolytic induction therapy was used.	**Total of patients with Skin Cancer:** 18 (12,8%) **Total of skin lesions:** 27 lesions (0,19 lesions/patient) **Squamous Cell Carcinoma:** 10 (7.1%) **Basal Cell Carcinoma:** 9 (6.4%) **Melanoma:** 1 (0.7%) **Morbus Bowen:** 13 (9.3%) **Solar Keratosis:** 18 **Keratoacantoma**: 8 (5.7%) None of the patients died of malignant skin tumors. No metastatic lesions were diagnosed.	Incidence
Espanã et al 1995 [14]	Cohort	Spain	1984 to 1993 (9y)	111 (M&F) Mean Age: 49.5 (2-69)	1984 to 1986 and 1989 to 1993: CsA, 6-methylprednisolone and equine antithymocytic y-globulin. 1986 to 1989: CsA, AZA and corticosteroid. 1986 to 1989. In patients Cr > 1.5, CsA was substituted for OKT3.	**Total of patients with Skin Cancer:** 14 (12.6%) **Total of skin lesions:** 26 (0.53 lesions/patient) **Squamous Cell Carcinoma:** 9 patients (64.2%) **Basal Cell Carcinoma:** 8 patients (57.1%)	Incidence SCC ratio was 1:1.5 for the first malignancy. BCC to SCC ratio was 1:1.3. Skin cancer appeared an average of 31.5 months after transplantation. BCC appeared at an average of 25.3 months, and the SCC appeared at 36 months. Most cancers appeared in the first 4 years after transplantation.
Sigfusson et al 1996 [15]	Cohort (Children)	United States	1975 to 1989 (14y)	68 (M&F) Mean Age: NP (<18y) Pediatric heart transplantation	1975 to 1980: AZA and corticosteroids 1980 to 1989: CsA, AZA and corticosteroids	**Total of patients with Skin Cancer:** 1 **Total of skin lesions:** 1 **Squamous Cell Carcinoma:** 1 **Basal Cell Carcinoma: NP**	Prevalence

Ong et al 1999 [16]	Cohort	Australia	1984 to 1998 (14y)	400 (M&F) Sex: NP Median age: 47.9 (6.6 - 67)	AZA and CsA with or without prednisolone. Rejection episodes: IV pulsed methylprednisolone, OKT-3, antithymocyte globulin, total lymphoid irradiation, tacrolimus, MMF	**Total of patients with Skin Cancer:** 152 (38%) **Total of skin lesions:** 1436 **Squamous Cell Carcinoma:** 113 patients (28,2%) - 849 lesions (2,1 lesions/patient) **Basal Cell Carcinoma:** 92 patients (23%) - 285 lesions (32.2%) **Melanoma:** 7 patients (4.6%) - 7 lesions **Actine Keratosis:** 19 patients - 28 lesions **Bowen`s Disease:** 79 - 263 lesions	Incidence Crude cumulative incidence rates of skin cancer: 1 y: 8.5%; 3 y: 21%; 5 y: 31%; 10 y: 43%. NSCC/BCC ratio of 3:1; a larger proportion of SCC in male than in female patients was found (3.2:1 vs 1.3:1). Most lesions occurred on the head and neck. Metastases developed in 9 male patients with SCC and 4 with melanoma. Eleven deaths from skin cancer (6 from SCC, 4 from melanoma, 1 from Merkel cell carcinoma) accounted for 27% of deaths occurring after the fourth year after transplantation.
Fortina et al 2000 [17]	Cohort	Italy	Mean follow-up period: 4.7 years (1 month - 12 years)	252 (M: 219 F:33) Mean age: 49 +/- 14	CsA and AZA (double therapy, n= 67), or with CsA, AZA and oral prednisone (triple therapy, n= 185). Induction immunosuppression: CsA or of AZA administered 6 hours before operation, and a bolus of methylprednisolone during cardiopulmonary bypass. Rejection episodes: IV methylprednisolone, OKT3 or ATG.	**Total of patients with Skin Cancer:** 40 (15.8%) **Total of skin lesions:** 72 (1.8 lesions/patient) **Squamous Cell Carcinoma:** 17 patients (42%) - 36 lesions. **Basal Cell Carcinoma:** 20 patients (50%) - 24 lesions **Melanoma:** 1 patient (2.5%) - 1 lesion **Bowen`s Disease:** 8 patients - 9 lesions **Kaposi Sarcoma:** 1 **Merkeloma:** 1	Incidence SCC/BCC ratio in the transplant population was 1.17 :1. A higher number of HT patients (40, 16%) developed at least One skin cancer compared to Kidney Transpant patients (16, 7%, p = 0.004). The mean interval between transplantation and detection of the first skin cancer was lower in HT (4.5 years) than in KT (6.7 years, p = 0.05).
Caforio et al 2000 [18]	Cohort	Italy	NP	300 (M: 258 F:42) Mean age: 49 +/- 15	Receiving standard double (CsA plus AZA) or triple (CsA plus AZA plus prednisone) therapy. HT recipients were treated with CsA and AZA (double therapy, n=62) or with CsA, AZA and oral prednisone (triple therapy, n=238). Postoperatively, the majority (83%) of patients received antilymphocyte globulin (ALG) or antithymocyte globulin (ATG), or both, for 3 to 5 days.	**Total of patients with Skin Cancer:** 48 (16%) **Total of skin lesions:** 104 (2.1 lesion/patient) **Squamous Cell Carcinoma:** 22 patients - 53 lesions (45.8%) **Basal Cell Carcinoma:** 24 patients (50%) - 37 lesions **Melanoma:** 2 patients (4.1%)- 2 lesions **Bowen`s Disease:** 9 patients - 9 lesions **Kaposi Sarcoma:** 1 patient - 1 lesion **Merkeloma:** 1 patient - 1 lesion	Incidence SCC/BCC ratio was 1.43:1. Large majority of lesions occurred on the head and neck (73, or 70%). Mean interval between HT and detection of the first skin cancer correlated with age at transplantation (P=0.01). HT patients aged > 50 years had an earlier onset of skin cancer lesions than those aged <50 (4+-3 versus 6+-3 years, P<0.001). 3 patients died of early metastasis of melanoma (n=1), merkeloma (n=1), and Kaposi's sarcoma (n=1).
Catena et al 2001 [19]	Cohort	Italy	Underwent transplantation until 1997	124 (M:124) Meand age: 55 (44 - 62)	All patients received triple immunosuppression, and all showed rejection episodes.	**Total of patients with Skin Cancer: NP** **Total of skin lesions:** NP **Squamous Cell Carcinoma: NP**. **Basal Cell Carcinoma: NP** **Melanoma:** 2 (1.6%)	Incidence When cancer diagnosis was made, all patients had already metastatic disease. Marked disparity in the interval to De Novo Malignancy between KT and HT recipients (69 versus 24 months); this is probably related to the higher level of Immunosuppression therapy.

Caforio et al 2001 [20]	Cohort	Italy		304 (M: 261 F:43) Mean age: 49 ± 15	Standard double (CsA, AZA) or triple (CsA, AZA, prednisone therapy).	**Total of patients with Skin Cancer:** 57 (18.75%) **Total of skin lesions:** 104 lesions (1.82 lesions per patient) **Squamous Cell Carcinoma:** 26 patients (45.6%) **Basal Cell Carcinoma:** 27 patients (47.3%) **Melanoma: NP**	Incidence The SCC/BCC ratio was 1.43:1, and most lesions were on head and neck. HT >49 years (P = .008; RR = 3.0), skin type II (P = .0001; RR = 3.5), solar keratosis (P = .0007, RR = 2.8), and sunlight exposure > 30000 hours (P = .01; RR = 2.1) were risk factors for skin tumors of any type.
Fortina et al 2004 [21]	Cohort	Italy	At least 3 years of follow-up	230 (M: 198 F: 32) Mean age: 50.2 ± 11.0	CsA and AZA (double therapy; n=37) or with CsA, AZA , and oral prednisone (triple therapy; n=193). Oral prednisone was added to the double therapy regimen of CsA and AZA in cases of repeated or persistent rejection or of CsA nephrotoxic effects.	**Total of patients with Skin Cancer:** 48 patients (20.8%) **Total of skin lesions:** 120 lesions (just NMSC`s) **Squamous Cell Carcinoma:** 26 patients (54.1%) - 83 lesions (3.19 lesions/patient) **Basal Cell Carcinoma:** 13 patients (27%)- 37 lesions(2.84 lesions/patient) Melanoma: Not evaluated (NP)	Incidence **Cumulative incidence of NMSCs in HT recipients:** **SCC: 5y:** 6.5% (95% CI, 3.2%-9.7%); **10y:** 19.7% (95% CI, 13.3%-26.1%) **BCC: 5y:** 6% (95% CI, 2.9%-9.1%); **10y:** 12% (7%-17%) The cumulative risk of SCCs and BCCs increased steeply with increasing age at transplantation. The SCC/BCC ratio
							was 2.2:1. Most lesions occurred on the head and neck (n = 91; 69.5%). No metastatic or fatal tumors occurred. Median time between transplantation and appearance of the first NMSC was 5.2 years (3.5-7.8 years, 25th-75th percentile)..
Shiba et al 2004 [6]	Cohort	United States	1980 to 1991 (11y)	142 (M:109 F: 33) Mean age: 51.4 +- 9.9	**Initial immunosuppressive regimens of 10 year survivors:** CsA/P/RATAG: 6 (4.2%); CsA/P: 23 (16.2%); CsA/AZA: 8 (5.6%); CsA/AZA/P/ATGAM: 12 (8.5%); CsA/AZA/P: 30 (21.1%); CsA/AZA/P/PKT3: 63 (44.4%); CsA was administered in all cases as part of the initial immunosuppressive regimen. **Maintenance regimens at 10 years included the following:** CsA AZA and prednisone: 70 (49.3%); CsA, AZA: 19 (13.4%) received; CsA, prednisone: 18 (12.7%); CsA, MMF and prednisone: 10 (7.0%); CsA and MMFI: 5 (3.5%); TCA and AZA: 2 (1.4%); TAC, MMF, and prednisone: 2 (1.4%); CsA only: 1 (0.7%); Unknown regimens: 14 (9.9%); Single drug regimen (only CsA): 2 (because of refractory malignancies.	**Total of patients with** Skin cancer: 2 (1.4%) **Total of skin lesions:** 1 **Squamous Cell Carcinoma:** **Basal Cell Carcinoma:** Melanoma: 4 patients (2.8%) Fifty-four patients (38.0%) had skin cancers at 8.1 +- 3.7 y (1.6–16.6 years) after HTx. Most lesions were recurrent squamous cell carcinoma or basal cell carcinoma;	Incidence

El-hamamsy et al 2005 [22]	Cohort	Canada	1982 to 2002 (20y)	207 (M:172 F:35) Age: 46 +/- 11	1988 and 2002: 154 patients received IV thymoglobuline. Oral prednisone, AZA or MMF, which has replaced AZA since 1997 were started after patient extubation. CsA was initiated on postoperative day 2 to day 5 after transplantation.	**Total of patients with Skin Cancer:** 84 patients (42%) **Squamous Cell Carcinoma:** 1 patient (1.19%) **Basal Cell Carcinoma:** 16 patients (19.0%) Melanoma: NP **Kaposi Sarcoma:** 2% **Bowel:** 5%	Incidence Patients were divided into two groups: with a post-transplant neoplasm (n= 43) and cancer-free (n= 165). No differences between both groups regarding recipient age, sex, the underlying pathology, smoking history, and the number of treated rejection episodes in the first year. When examined separately, no significant association was found between the administration of any drug and the development of a neoplastic lesion.
Mello Júnior et al 2006 [23]	Cohort	Brazil	1986 to 2002 (16y)	106 (M: 87 F:19) Mean age: 43.7 (12 - 64)	All patients were submitted to CsA, AZA and a corticosteroid agent. Two patients also received orthoclone (OKT3) for treating rejection. The protocol of the immunosuppressive regimen consisted of CsA, AZA and corticosteroid.	**Total of patients with Skin Cancer:** 13 patients (12.26%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 8 (34.80%) **Basal Cell Carcinoma:** 5 (21.70%) **Melanoma:** not avaliated (NP)	Incidence
Geusau et al 2008 [24]	Cohort	Austria	1984 to 2003 (19y)	322 (M: 260 F:62) Median age: 54.02	Post-operatively: RATG, monoclonal murine antibodies muromonab OKT3 and monoclonal anti-IL-2 receptor antibodies. Maintenance therapy: triple drug regimen consisting CsA or Tac; Aza or MMF, and prednisolone. From the beginning of 1998: all patients had been routinely switched from AZA to MMF.	**Total of patients with Skin Cancer:** 73 (23%) **Total of skin lesions (NMSC):** 263 (3.6 lesions/patient) **Squamous Cell Carcinoma:** 27 patients (36.9%) - 64 lesions (2.3 lesions/patient) **Basal Cell Carcinoma:**46 patients (63%) - 104 lesions (2.2 lesions/patient) **Bowen`s Disease:** 25 patients (7.7%) - 61 lesions (2.44 lesions/patient) **Bowen Carcinoma:** 16 patients (4.9%) - 34 lesions (2.1 lesions/patient) **Melanoma:** NP	Incidence SCC (including BD and BowCa) to BCC ratio was 1.6 : 1. 33 patients had only a single skin tumor, 40 patients developed more than one tumor (28 had 2–5 skin malignancies, 12 more than 5). Cumulative incidence rates for NMSC: **5y:** 7.3%; **10y:** 26.9%; **15y:** 56.5% Overall incidence rate of NMSC: 33.1 cases per 1000 post-transplant person- years. 32 of the patients (44%) with at least one tumor had AK (vs. 10% without tumor) (P <

							0.0001). Average time from transplantation until diagnosis of the first NMSC: 79.56 months.

Brewer et al 2009 [25]	Cohort	United States	1988 to 2006 (18y)	All heart transplant recipients at Mayo Clinic from 1988 to 2006. (n=NP) 312 (M: 227 F:85) had skin cancer. Mean age:47.4 ± 16.37	NP number of patients with the indivuadlly immunosuppressive therapy. Medications that were not significantly associated with the development of SCC included AZA, CsA, MMF, sirolimus, corticosteroids, and TAC. MMF was significantly associated with an increased risk of BCC (HR, 2.32; P = 0.005) Medications that were not significantly associated with the development of BCC included CsA, sirolimus, corticosteroids, and TAC. AZA was significantly associated with a decreased risk of BCC development (HR, 0.56; P < .05)	**Total of patients with Skin Cancer:** 312 **Total of skin lesions:** 1395 (9.6 lesions/patient) **Squamous Cell Carcinoma:** Patients NP - 1236 lesions (89%) **Basal Cell Carcinoma:** Patients NP - 151 lesons (11%) **Melanoma:** 5 lesions (<1%) **Angiosarcoma:** 1 patient **Atypical fibroxanthoma:** 1 patient **Pilomatrix carcinoma:** 1 patient **Patients had an SCC:** **5y:** 15.4% / **10y:** 32.3% / **15y:** 38.2% **Patients had an BCC:** **5y:** 10.3% / **10y:** 19.2% / **15y:** 31.6% **Skin Cancer of any kind:** **5y:** 20.4% / **10y:** 37.5% / **15y:** 46.4% **Cumulative incidence rates of a second SCC:** **1y:** 44% / **3y:** 67.4% / **5y:** 75.9% **Cumulative incidence rates of having an SCC:** **1y:** 36.7% / **3y:** 54.7% / **5y:** 65.9% **Cumulative incidence rates of a second BCC:** **1y:** 32.1% / **3y:** 48.6% / **5y:** 51.4% **Cumulative incidence rates of a BCC developing:** **1y**: 16.3% / **3y**: 31.8% / **5y**: 45.7%	Incidence **Cumulative Incidence of death:** **5y:** 18.4% (95% CI, 13.6%-23.0%); **10y:** 37.9% (95% CI, 30.5%-44.5%); **15y:** 63.5% (95% CI, 51.5%- 72.5%); **18y:** 78.7% (95% CI, 57.7%-89.3%) Posttransplant SCC tumor burden of the 312 patients: 76 patients (24.4%) had at least 1 SCC, 24 patients (7.7%) had only 1 SCC, and 19 (6.1%) had 10 or more SCC. Evaluation of the BCC tumor burden of heart transplant recipients showed that 54 patients (17.3%) had at least 1 BCC, 23 patients (7.4%) had only 1 BCC, and 2 patients (0.6%) had 10 or more BCCs.
Chen et al 2009 [26]	Cohort	Taiwan	1987 to 2008 (21y)	66 (M&F)	All patients were treated with standard calcineurin inhibitor based triple immunosuppressive agent therapy (CsA or Tac; Aza or MMF, and prednisolone) After 1999, MMF gradually replaced AZA, and TAC replaced CsA as first-line immunosuppressive agents	**Total of patients with Skin Cancer:** 1 (1.5%) **Total of skin lesions:** 1 **Squamous Cell Carcinoma: 1** (1.5%) **Basal Cell Carcinoma:** NP **Melanoma:** NP	Incidence
Molina et al 2010 [27]	Cohort	Spain	1984 to 2003 (19)	3393 (M: 2874 F: 519) Mean age: 51.4 ± 11	**Patients receiving each kind of Immunosuppresor (percentages) by Period Post-HT (at any time):** CsA: 2863 (84.4%); AZA: 2334 (68.8%); Prednisone: 3365 (99.2%) TCA: 743 (21.9%); MMF:1628 (48.0%); Sirolimus: 223 (6.6%); Everolimus: 27 (0.8%); OKT3: 1503 (44.3%); RATG: 580 (17.1%); Basiliximab: 227 (6.7%); Daclizumab:139 (4.1%)	**Total of patients with Skin Cancer:** 204 (6%) **Total of skin lesions:** 324 (1.58 lesion per patient) **Squamous Cell Carcinoma:** patients NP - 169 lesions (52%) **Basal Cell Carcinoma:** patients NP - 104 lesions (32%) **Melanoma:** patients NP - 9 lesions (2.7%) **Kaposi Sarcoma:** patients NP - 4 lesions **Undifferentiated malignant tumors:** patients NP - 23 lesions	Incidence RR of developing SCC in patients who were transplanted in a high sunshine zone (>2500 hours/year) was 8.7 (95% CI, 4.3–17.8; P= .0001) in relation to patients who were transplanted in a low sunshine zone, and in BCC the RR was 3 (95% CI, 1.7–5.4; P= .0001). AZA was associated with an increased SCC risk (RR, 1.8; 95% CI, 1.2–2.7; *P*=.003). Induction therapy was a risk factor for NMSC (RR, 2.1; 95% CI, 1.6–2.7; P= .0001), SCC (RR, 2.3; 95% CI, 1.6 –3.4; P= .0001) and BCC (RR, 2.6; 95% CI, 1.6 – 4.2; P= .0001), but only OKT3 was associated with both SCC and BCC.

Hsu et al 2010 [28]	Cohort	China	1987 to 2008 (21y)	291 (M: 244 F: 47) Mean age: 45.1+/- 16.1	All patients received triple drug immunosuppressive therapy. Since 1995, RTAG was used for induction therapy.	**Total of patients with Skin Cancer:** 3 (1%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** NP **Basal Cell Carcinoma:** NP **Melanoma:** patients NP - 9 lesions (2.7%) No Kaposi's sarcoma.	Incidence Incidence of skin cancers has slightly increased. It resulted probably from a relative rarity of skin cancers in the Chinese population.
Doesch et al 2010 [29]	Cohort	Germany	1989 and 2005	211 (M: 175 F: 36) Mean age: 51.4 +- 10.5	All 211 transplant recipients received RATG intravenously. 1989 - 2001: CsA combined with azathioprine 2001 - 2003: CsA and MMF 2003 - onward: mTOR inhibitors (everolimus/sirolimus)	**Total of patients with Skin Cancer:** 36 (17.1%) **Squamous Cell Carcinoma:** 9 patients (4.2%) - lesions NP **Basal Cell Carcinoma:** 24 patients (11.3%) - lesions NP **Melanoma: NP** **Pre cancerous lesions:** 3 patients (1.4%)	Incidence Mean interval from transplantation until initial diagnosis of a cutaneous malignancy was 7.6 +- 3.5 years.
Jensen et al 2010 [30]	Cohort	Denmark	1977 to 2006 (29y)	459 (M: 368 F:91) Median age: 50 (2 - 89)	High dose induction therapy up to one year after transplantation Maintenance therapy: AZA, CsA, prednisolone	**Total of patients with Skin Cancer:** 40 patients (8.7%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 26 patients (65%) **Basal Cell Carcinoma:** 14 patienst (35%) **Melanoma:** NP	Incidence **Heart transplantation:** **BCC:** SIR of 5.6 (95% CI: 3.1-9.5); **SCC**: SIR of 113 (95% CI: 74-166) Highest risk of SCC among heart recipients, who are maintained on the highest dose regimen of immunosuppressive medication.
Hamour et al 2011 [10]	Cohort	England	1995 to 2007 (12y)	399 (M: 318 F:81) Mean age: 48 +-12	All patients received CsA and corticosteroids with either MMF or AZA. Maintenance therapy: MMF and AZA Rejections: high-dose corticosteroids	**Total of patients with Skin Cancer:** NP **Total of skin lesions:** NP **Squamous Cell Carcinoma:** NP **Basal Cell Carcinoma:** NP **Melanoma:** NP	Incidence **Cumulative incidence of skin malignancy:** **1y =** 2%**; 3y =** 4%; **5y =** 6%; **7y =** 8%; **10y =** 13%

Alam et al 2011 [31]	Cohort	United States	1993 to 2003 (10y)	6271 (M: 4202 F:2069)	NP imunossupressive therapy protocol. Relative risk of skin cancer was 1.5 for higher dosages of CsA measured at the 1-year follow-up (6 vs. 2 mg/kg/d, p = 0.01), 1.4 for higher dosages of AZA (2.5 vs. 1 mg/kg/d, measured at 1-year follow-up, p = 0.007) and 1.4 for higher dosages of MMF (40 vs. 10 mg/kg/d, at one-year follow-up, p = 0.04).	**Total of patients with Skin Cancer:** 545 (8.6%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 289 patients (53%) - lesions NP **Basal Cell Carcinoma:** 228 patients (41%) - lesions NP **Melanoma:** 22 patienst (4%) - lesions NP **Other skin Cancer:** 6 patients	Incidence Lower latitude had a RR of skin cancer of 1.2 (p = 0.03). Pretransplantation history of skin cancer was associated with a 2.0 RR of skin cancer (p = 0.001). All-cause mortality after post transplant skin cancer varied by type of skin cancer. For BCC, 5-year survival was 83% (95% CI: 73–90%). For SCC, 5-year survival was 80% (95% CI: 74–86%). For melanoma, 3-year survival was 50% (95% CI: 27–73%). White patients were more susceptible to skin cancer than nonwhite patients (p < 0.0001), with 10- year freedom from skin cancer at 83% (95% CI: 81–85%).
Chivukula et al 2014 [32]	Cohort	United States	2000 to 2011 (11y)	402 patients (M: 310 F: 92) Mean age: 54.0 +/- 12.4	Subgroups: -185 (46.0%) received alemtuzumab (M:140) -56 (13.9%) thymoglobulin (M:46) -161 (40.0%) no induction.(M:124) 2000 - 2006: calcineurin inhibitor and steroids typically 2006 - onward: all patients received routine induction therapy with alemtuzumab and were subsequently treated with a CNI and a secondary agent with no postoperative steroid use.	**<u>Alemtuzumab:</u>** **Total of patients with Skin Cancer:** 15 (8.1%) - lesion NP **Squamous Cell Carcinoma:** 10 patients (5.4%)- lesion NP **Basal Cell Carcinoma:** 4 patients (2.2%) - lesion NP **Melanoma:** 1 patient (0.5%) - lesion NP **<u>Thymoglobulin:</u>** **Total of patients with Skin Cancer:** 4 (71%) - lesion NP **Squamous Cell Carcinoma:** 1 patient (1.8%) - lesion NP **Basal Cell Carcinoma:** 2 patients (3.6%) - lesion NP **Melanoma:** 1 (1.8%) - lesion NP **<u>No induction:</u>** **Total of patients with Skin Cancer:** 11 (6.8%) - lesion NP **Squamous Cell Carcinoma:** 5 patients (3.1%) - lesion NP **Basal Cell Carcinoma:** 5 patients (3.1%) - lesion NP **Melanoma:** 1 patients (0.6%) - lesion NP	Incidence Skin cancers were the most common malignancies after cardiac transplantation: SCC followed by BCC. Neither alemtuzumab nor thymoglobulin was associated with enhanced rates of early skin malignancy. At 4 years after cardiac transplantation, induction with alemtuzumab showed similar rates of cancer-free survival, both overall and for nonskin cancers, compared with thymoglobulin and noninduced historical control subjects.
Fuchs et al 2014 [33]	Cohort	Germany	2003 to 2007 (4y)	145 (M&F) CSA group = mean age:58.8 ± 11.4 TAC group mean age: 49.1 ± 13.0	Patients were divided into a CSA group (n=25) and a TAC group (n=120). Initial immunosuppressive therapy was performed in all patients with CSA, using AZA and methylprednisolone. Maintenance therapy: CSA or TAC or in combination with a DNA synthesis-inhibitor like AZA or MMF.	**Total of patients with Skin Cancer:** 7 (4.8%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 2 patients (1.3%) - lesions NP **Basal Cell Carcinoma:** 3 patients (2%) - lesions NP **Melanoma:** 2 patients (1.3%) - lesions NP	Incidence **Metastasis:** 1 malignant melanoma with metastases in lymph nodes. There was no significant difference between the 2 CNIs CSA and TAC regarding tumor incidence, overall survival, and important postoperative com- plications in HT patients.

Park et al 2014 [34]	Cohort	Korea	1990 to 2008 (18y)	207 (M&F)	NP imunossupressive therapy protocol.	**Total of patients with Skin Cancer:** 7 (3.3%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** NP **Basal Cell Carcinoma:** NP **Melanoma:** NP	Incidence Association between the indicated factors and the risk of skin cancer including carcinoma in situ in organ transplant recipients (heart only) : Hazard ratio: 3.5 (1.3 - 10.0) p = 0.01
Rivinius et al 2015 [3]	Cohort	Germany	1989 to 2014 (25y)	381 **(**M: 300 F:81) Mean age: 51.2 ± 10.5	**Initial immunosuppressive:** CsA and AZA was replaced by CsA and MMF in 2001, and by TAC and MMF in 2006. mTOR inhibitors (everolimus/ sirolimus) were used from 2003.	**Total of patients Skin Cancer:** 74 (19.4%) **Squamous Cell Carcinoma:** 28 patients (37,8%) - lesions NP **Basal Cell Carcinoma:** 30 (40,6%) lesions NP **Melanoma:** 2 (2.7%)- lesions NP **Kaposi Sarcoma:** NP	Incidence
Secnikova et al 2015 [35]	Cohort	Czech Republic	1993 to 2010 (17y)	603 (M: 493 F: 110)	Standard initial regimen: steroids, calcineurine inhibitors (CsA or tacrolimus) and antimetabolites (MMF or AZA). 2004/2005 onward: mTOR inhibitors (sirolimus, everolimus)	**Total of patients with Skin Cancer:** 119 patients (19.7%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 62 patients (52.1%) - lesions NP **Basal Cell Carcinoma:** 37 patients (31.1%) - lesions NP **Melanoma:** 3 patients (2.5%) - lesions NP **Actine Keratosis:** 11 patients (9.2%) - lesions NP **Morbus Bowen:** 4 patients (3.3%) - lesions NP **Merkell Cell Carcinoma:** 1 patient (0.84%) - lesions NP	Incidence The median time to develop non-melanoma skin malignancy was 10 years.

Keer et al 2016 [4]	Cohort	Belgium	1987 to 2013 (26y)	541 (M: 431 F:110) Mean age: 50 ± 14	Before 2000: CsA, AZA and methylprednisolone After 2000: MMF replaced AZA and AZA and TAC replaced CsA. All patients received induction therapy with polyclonal rabbit antithymocyte globulin. CsA: 272 (50%); TAC: 269 (50%); AZA: 237 (44%); MMF**:** 304 (56%)	**Total of patients with Skin Cancer:** 112 (20.7%) **Total of skin lesions:** 294 (2.6 lesions per patient) **Squamous Cell Carcinoma:** 58 patients (51.7%) - lesions NP **Basal Cell Carcinoma:** 51 patients (45.5%) - lesions NP **Melanoma:** 2 patients (1.7%) - lesions NP **Kaposi Sarcoma:** 1 patients(0,89%) lesions NP	Incidence
Delgado et al 2016 [36]	Cohort	Spain	1984 to 2010	4561(M: 3808 F: 753) Mean Age: NP	The cohort was classified in PT ((PT/malignant non cardiac neoplasia): 77 (1.7%) and no previous tumor (NPT);4484 (98.3%) with previous tumor. (No Previous Tumor group: 84% and Previous Tumor group: 62%)	**Total of patients with Skin Cancer:** 637 patients **Squamous Cell Carcinoma:** 382 (PT: 8 NPT:374) - lesion NP **Basal Cell Carcinoma:** 228 (PT: 2 , NPT:226) - lesion NP **Melanoma: 1**5 patients (PT:2 , NPT:13) - lesion NP **Kaposi Sarcoma:** 12 (PT:0 NPT:12) - lesion NP	Incidence This was the only study to report heart transplant recipients with previous neoplasia history

Mcpherson et al 2017 [37]	Cohort	Scotland	1992 to 2016 (24y)	363 (M: 285; F: 78)	Most common regime: CyA and MMF. 116 patients were given additional OKT3 induction between 1995 and 1998 and 72 patients were given r-ATG between 2010 and 2016 CyA + MMF: 216 patients; CyA + AZA: 111 patients	**Total of patients with Skin Cancer:** 60 (16.5%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 26 (7.1%) - lesion NP **Basal Cell Carcinoma:** 34 (9.3%) - lesion NP **Melanoma:** NP	Incidence
Bhatt et al 2018 [1]	Cohort	United States	1987 to 2015 (28y)	44.162 (M: 33.767; F: 10395) Mean age: 52.0 ± 12.0	91.4% of HT recipients were using 3 or more immunosuppressant medications.	**Total of patients Skin Cancer:** 5060 (11.4%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 3218 patients (63.5%) - lesion NP **Basal Cell Carcinoma:** 1175 patients (23,2%) - lesion NP **Melanoma:** 48 (0,94%) - lesion NP **Kaposi Sarcoma:** 19 (0,37%) - lesion NP	Incidence **Cumulative Incidence of Cancer at Various Time Points: Heart (%[95%CI])** 1y = 1.4 (1.3-1.5); 5y = 10 (9.6-10.3); 10y = 21 (20.5-21.4); 15y = 28.2 (27.5-28.7); 20y = 32 (31.3-32.6) Duration of follow up (y), mean +-SD (range): 5.8 (0-24.3)
Jäämaa-Holmberg et al 2019 [38]	Cohort	Finland	1985 to 2014 (29y)	479 (M: 381; F: 98) Median age: 52	All patients: received immunosuppression based on calcineurin inhibitors (CsA or TAC) combined with either AZA or MMF Until the end of 2010: polyclonal anti-thymocyte antibodies were administered during the first three days for all patients.	**Total of patients Skin Cancer:** 145 (30.2%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 56 patients (38.6%) - lesion NP **Basal Cell Carcinoma:** 83 patients (57.2%) - lesion NP **Melanoma:** 5 patients (3.4%) - lesion NP **Kaposi Sarcoma:** 1 patients (0.68%) - lesion NP	Incidence **Expected/Standardized Incidence ratio/95%CI /pvalue** **Squamous Cell Carcinoma:** 1.1 / 51.9 / 39.2-67.4 / p=<.001 **Basal Cell Carcinoma:** 7.9 / 10.5 / 8.4-13.0 / p=<.001 **Melanoma:** 1.3 / 3.8 / 1.2-8.8 / p=<.01 **Kaposi's Sarcoma:** 0 / 365.0 / 9.2 - 2033 / p=<.01
Kimura et al 2019 [39]	Cohort	Japan	1999 to 2017 (18y)	103 (M: 79; F: 24) Malignancy group (n = 7) and a no-malignancy group (n = 96). Mean age:	**Initial maintenance therapy** **Prednisolone:** 103 (100%) **CsA:** 20 (19%) / **TAC:**83 (81%) / **MMF:** 100 (97%) / **AZA:** 2 (1.9%) / **Sirolimus:** 1 (1%) **Maintenance therapy at the end point:** **Prednisolone:** 27 (26%) / **CsA:** 8 (7.8%) / **TAC:** 88 (85%) / **MMF:** 38 (37%) / **Everolimus:** 67 (65%) **Induction therapy:** 41 (40%)	**Total of patients with Skin Cancer:** 1 patient (0.97%) **Bowen's disease:** 1 patient **Squamous Cell Carcinoma:** NP **Basal Cell Carcinoma:** NP **Melanoma:** NP	Incidence PTLD and colon cancer were more common than skin cancer in Japanese recipients. These differences might be caused by differences in ethnicity, diet, environment, and viral status. For example, skin type II and sunlight exposure >30,000 h, are not common in Japan and may explain the low prevalence of
				39.6 ± 12.6	**Basiliximab:** 33 (32%) / **OKT3:** 7 (6.8%) / **Daclizumab:** 1 (1%)		skin cancer.

Park et al 2019 [40]	Cohort	Canadá	1994 to 2013 (19y)	684 (M: 530; F: 144) Median age: 53 (44-59)	NP	**Total of patients with Skin Cancer:** NP **Bowen's disease:** NP **Squamous Cell Carcinoma:** NP **Basal Cell Carcinoma:** NP **Melanoma:** NP	Incidence **Cumulative incidence of Keratinocyte Carcinoma (95% CI) - heart transplantation** **2 y:** 5.68 (4.10-7.61) **5 y:** 15.04 (12.32-18.02) **10 y:** 26.67 (22.73-30.76) **15 y:** 34.27 (29.37-39.23) **19 y:** 37.18 (31.48-42.87)
Asleh et al 2019 [41]	Cohort	United States	1994 to 2016 (22y)	523 (M: 354; F: 169) Mean age: 50.0 ± 13.6	All patients received induction therapy with RATG, and a minority of patients received muromonab-CD3 (OKT3) Maintenance: CNI (tacrolimus or cyclosporine), an antimetabolite (MMF or AZA), and tapering doses of prednisone.	**Distribution of Cancer Events While on CNI or SRL Therapy** **Squamous Cell Carcinoma:** **Overall:** 123 (23.5%) / **While on CNI:** 70 (13.3%) / **While on SRL:** 53 (10.1%) **Basal Cell Carcinoma:** **Overall:** 46 (8.7%) / **While on CNI:** 22 (4.2%) / **While on SRL:** 24 (4.5%) **Total number of subsequent primary occurrences of NMSC** **Squamous Cell Carcinoma:** **Overall:** 276 (52.7%)/ **While on CNI:** 179 (34.2%) **/ While on SRL:** 97 (18.5%) **Basal Cell Carcinoma:** **Overall:** 41 (7.8%) / **While on CNI:** 19 **(3.6%) / While on SRL:** 2 (0.3%) **Melanoma: NP**	Incidence Most malignancies were NMSCs (n= 169; 92 in the CNI and 77 in the SRL groups). SRL conversion was associated with a significantly decreased risk of subsequent primary occurrences of NMSC compared with CNI therapy (unadjusted HR: 0.44; 95% CI: 0.27 to 0.71; p < 0.001; adjusted HR: 0.44; 95% CI: 0.28 to 0.69; p < 0.001)
O'neill et al 2019 [42]	Cohort	Irelând	1994 to 2014 (20y)	214 (M: 166; F:48) Median age: 47.1	-	**Total of patients with Skin Cancer:** 59 patients (27%) **Total of skin lesions:** NP **Squamous Cell Carcinoma:** 36 patients (16.8%) **Basal Cell Carcinoma:** 40 patients (18.6%) **Melanoma:** 0	Incidence Standardized incidence ratios (**SIR**) for All Skin in Heart transplant: 9.26 (7.05-11.94) Total Incident cases: 59 **SIR** for NMSC (keratinocyte carcinoma) in Heart transplant: 9.87 (7.51-12.73) Total Incident cases: 59 **SRI** for NMSC BCC in Heart transplant: 8.7 (6.22-11.85) Total Incident cases: 40 **SRI** for NMSC SCC in Heart transplant:19.05 (13.34-26.37) Total Incident cases: 36

Infusino et al 2020 [43]	Cohort	Italy	1974 to 2014 (40y)	133 (M&F)	Patients were treated with immunosuppressant drugs in accordance with the specific guidelines Alone or in association, cyclosporine, tacrolimus or sirolimus, while sodium mycophenolate, mycophenolate mofetil and everolimus were always administered in association with other drugs.	**Total of patients with Skin Cancer:** 70 (52,6%) **Total of skin lesions:** NP **Squamous Cell Carcinoma + Keratosis Actinic:** 91 (68.4%) **Basal Cell Carcinoma:** 21 (15,7%) **Melanoma:** 0	Incidence The heart transplant patients showed statistically significant higher rates of nmSC and aK compared with other organ transplants (52.6%, P=0.0352).
Yeh et al 2020 [44]	Cohort	Taiwan	1997 to 2011 (14y)	687 (M: 548; F: 139)	**TCA:** 188 (27.4%); **CSA:** 445 (64.3%); **MMF:** 433 (63.0%); **AZA:** 111 (16.2) **Everolimus:** 47 (6.8%) **Sirolimus:** 0 (0%) **Steroid: 638** (92.9%) Approximately 79% of heart transplant recipients used thymoglobulin	**Total of patients with Skin Cancer:** 2 (0,29%) **Total of skin lesions:** NP **Melanoma:** 0 **Squamous Cell Carcinoma:** NP **Basal Cell Carcinoma:** NP	Incidence Significantly higher incidences of nonmelanoma skin cancer SIR (95% CI): 5.8 (1.5-23.3) **Standardized incidence ratio** Significantly higher incidences of nonmelanoma skin cancer (SIR = 5.8; 95% CI, 1.5-23.3; P < .05)

AK = Actinic keratosis; AZA = Azathioprine; BCC= Basal cell carcinoma;**CNI: calcinerin inhibitor;** CsA = Cyclosporine; HT / HTx = Heart transplant; KT = Kidney transplant; MM = Malignant melanoma; MMF = Mycophenolate mofetil; mTOR = Mammalian target of rapamycin; NMSC = Non-melanoma skin cancer; RATG = Rabbit antithymocyte immunoglobulin; SCC= Squamous cell carcinoma; SRL = SIrolimus; TAC = Tacrolimus; M&F: male and female; * age unit in years; CI: Confidence interval; RR: relative risk;

Table 2: **Summary of the quality analysis using the Newcastle-Ottawa Quality Assessment Form for Cohort Studies modified.**

	Selection				Comparability		Outcome			Quality
	Representativeness of cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis		Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
					Age and Sex	Sun exposure calculation				
Jensen 1995	☆	-	☆	☆	-	-	☆	☆	☆	🟠
España 1995	☆	-	☆	☆	-	-	☆	☆	☆	🟠
Sigfusson 1996	☆	-	☆	☆	☆	-	☆	☆	☆	🟢
Ong 1999	☆	-	☆	☆	☆	-	☆	☆	☆	🟢
Fortina 2000	☆	☆	☆	☆	☆	☆	☆	☆	☆	🟢
Caforio 2000	☆	-	-	☆	☆	☆	☆	☆	☆	🟡
Catena 2001	☆	-	☆	☆	-	-	☆	☆	☆	🟠
Caforio 2001	☆	-	-	☆	- -	-	-	☆	☆	🟠
Fortina 2004	☆	-	-	☆	☆	☆	☆	☆	☆	🟡
Shiba 2004	☆	-	☆	☆	-	-	☆	☆	☆	🟠
El-hamamsy 2005	☆	☆	☆	☆	☆	-	☆	☆	☆	🟢
Mello Júnior et al 2006	☆	-	☆	☆	-	-	☆	☆	☆	🟢

Geusau 2008	☆	-	☆	☆	☆	☆	☆	☆	☆	
Brewer 2009	☆	-	☆	☆	☆	-	☆	☆	☆	
Chen 2009	☆	-	☆	☆	-	-	☆	☆	☆	
Molina 2010	☆	-	☆	☆	☆	☆	☆	☆	☆	
Hsu 2010	☆	-	☆	☆	☆	-	☆	☆	☆	
Doesch 2010	☆	-	☆	☆	☆	-	☆	☆	☆	
Jensen 2010	☆	-	☆	☆	☆	-	☆	☆	☆	
Hamour 2011	☆	-	☆	☆	-	-	☆	☆	☆	
Alam 2011	☆	-	☆	☆	-	-	☆	☆	☆	
Chivukula 2014	☆	☆	☆	☆	☆	-	☆	☆	☆	
Fuchs 2014	☆	-	☆	☆	☆	-	☆	☆	☆	
Park 2014	☆	-	☆	☆	☆	-	☆	☆	☆	
Rivinius 2015	☆	-	☆	☆	☆	-	☆	☆	☆	
Secnikova 2015	☆	-	☆	☆	☆	-	☆	☆	☆	
Keer 2016	☆	-	☆	☆		-	☆	☆	☆	
Delgado 2016	☆	☆	☆	☆	☆	-	☆	☆	☆	
Mcpherson 2017	☆	-	☆	☆	-	-	☆	☆	☆	

Bhad 2018	☆	-	☆	☆	☆	-	☆	☆	☆	
Jäämaa-Holmberg 2019	☆	-	☆	☆		-	☆	☆	☆	
Kimura 2019	☆	-	☆	☆	☆	-	☆	☆	☆	
Park 2019	☆	-	☆	☆	☆	-	☆	☆	☆	
Asleh 2019	☆	-	☆	☆	☆	-	☆	☆	☆	
O'neill et al 2019	☆	-	☆	☆	☆	-	☆	☆	☆	
Infusino 2020	☆	-	☆	☆	-	-	☆	☆	☆	
Yeh 2020	☆	-	☆	☆	☆	-	☆	☆	☆	

Legend: Quality : Good Quality Fair Quality Poor Quality

Good quality= 3 or 4 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain. **Fair quality=** 2 stars in selection domain and 1 or 2 stars in comparability domain and 2 or 3 stars in outcome/exposure domain. **Poor quality**= 0 or 1 star in selection domain or 0 stars in comparability domain or 0 or 1 stars in outcome/exposure domain.

DISCUSSION

The impact of skin cancer in heart transplant patients

We conducted a comprehensive systematic review on skin cancer among patients who underwent heart transplantation, summarizing data from 39 studies. To our knowledge, this is the first systematic review focusing specifically on the frequency of skin cancer in this specific population of patients.

The incidence of NMSC in this systematic review ranges from 52,8% in an Italian cohort to 0,97% in a cohort from Taiwan.

The highest incidence of NMSC in the Italy study (Infusino et al 2020) could possibly be attributed to the good size of the sample, long term follow-up, analysis

performed by type of organ transplant, predisposition of white skin in Italian patients, UV light exposure, and high immunosuppression prescription among heart transplant patients[43].

The lowest incidence of NMSC in Taiwan (Yeh et al) could be influenced by genetic factors that lowers the prevalence of such cancer in the Asian population[44].

Considering melanoma, the highest incidence was 4,6% in a study conducted in Australia (Ong et al). This study confirms significant associations between skin cancer and HLA antigens among heart transplant patients. It also reinforces the importance of regular skin examinations in the follow-up.

The lowest incidence of melanoma was 0,94% in a cohort from United States (Bhat et al). Limitations of this study include the underreporting of skin cancers in the registry and individual risk factors for skin cancer.

All articles that provide the gender on the demographic characteristics of the sample had predominance of male in the population in analysis.

Skin cancer is the most common malignancy among solid organ transplant recipients[21]. Among the skin cancer subtypes, non-melanoma is the most prevalent in this population[21,27,43]. It is also well established that heart transplant patients require higher doses of immunosuppressive therapy before and after the surgical procedure in comparison to other solid organ transplantation[27 21].

Many studies from the literature have addressed the prevalence of skin cancer in the kidney transplantation follow-up. Although it is a more common procedure than heart transplant, patients generally need lower doses of immunosuppressive therapy following the procedure. Therefore, it is paramount to understand the effect of immunosuppressive therapy in different solid organ transplants in the outcome of skin cancer [1,3,5].

Several factors contribute to the development of malignancies, including older age at transplantation, retransplantation, type and degree of the immunosuppression therapy, sunlight exposure, skin type, and male sex[1,17,25,27,45]. Accordingly, we highlight that heart transplant patients are particularly susceptible to developing skin cancer because of the intense immunosuppression required, as well as older age at the time of the transplant [1,25]. Furthermore, we emphasize that beyond its high prevalence, SCC appears to be more aggressive in ORTs, with a higher risk of metastasis. These patients are on average 10 times at a greater risk of metastasis when compared to the general population, which is associated with increased morbidity and mortality of these patients [5,18,46]

Solid organ transplant recipients have an increased risk of developing malignant melanoma [5,46]. It is estimated that they have up to 2-8-fold increased risk compared to the general population, with an average time to development of 5 years post-transplant [5,46]. Studies show that the likelihood of developing melanoma after heart

transplantation is higher when compared with other organ transplant recipient subgroups, which can be attributed to more intensive immunosuppressive therapy in those patients[47]. These data are controversial in the literature, since some studies don't show a substantial risk of melanoma among these patients[48]. There are many articles showing an increased risk of melanoma in ORTs, and considering that melanoma is a potentially fatal malignancy, health care providers need to proceed with caution [5,9,46,47,49]. Another important fact to highlight is that the incidence of malignant melanoma has been increasing in the general population, which should be an alarm to susceptible groups, such as the population in this study [9,47,50].

Our review is in accordance with the literature regarding skin cancer as the most common malignancy between solid organ transplants. Associated with this fact, among solid organ transplants, patients with heart transplants are considered a vulnerable population because they need intense and strong immunosuppressive therapy. Since the risk of rejection of the transplanted organ can be fatal, these patients usually receive 3 different types of immunosuppressive drugs. This fact can be one of the main reasons why these patients have even more rates of skin cancer, as our study suggests. Our review shows that most of the studies found an increased frequency of skin cancer in this population.

Interestingly, our analysis confirms that the incidence of skin cancer is reported to be lower in Asian countries, including studies in Taiwan, Japan, Korea and China [26,28,34,39,44]. Yeh 2020 et al mention that predominant genetic influence could justify this phenomenon[44]. Kimura 2018 et al cite that this lower incidence might be caused by different ethnicity, diet, environment, viral status, phototype and sunlight exposure [39]. Park 2014 et al speculate that the low absolute incidence results in his study can correlate with the rarity of skin cancer in the Korean general population. Hsu 2010 et al attributes the low incidence to the relative rarity of skin cancer and Kaposi sarcoma in the Chinese population, and also cite that the ethnic, skin type, and possible virus status can contribute to this observation. Chen 2009 et al hypothesize that probably this phenomenon can be attributed to the paucity of skin cancer and Kaposi's sarcoma in the Chinese general population.

Generally, it was difficult to determine if the skin neoplasms existed before the transplant or if these lesions developed after the immunosuppression therapy, because this information is not provided by the papers. The patients were not examined by a dermatologist before the heart transplantation, so there are no data to support that pre-existing lesions were absent and that all the skin cancer was a consequence of the immunosuppressive therapy, although we presume it is probably true for most of the cases. A thorough dermatologic evaluation prior to the solid organ transplant is also important because one of our difficulties was to establish the correct classification of terms: incidence, prevalence and frequency rates.

The studies have different study designs, statistical analysis, and different datasets. Moreover, immunosuppression protocols vary according to the different centers and protocols. The study design of an authentic cohort study is compromised when there is not a comparison cohort, which derives from the same center, and which matches with demographic characteristics. This fact does not invalidate or diminish the importance of the data collected, but is important to evaluate the scientific rigors of the articles.

We also highlight that most of the papers did not mention if the diagnosis of skin cancer was confirmed by cutaneous biopsy and if these patients sought dermatological services outside their heart transplant centers. Both hypothetical situations can be a risk of bias in the outcome.

Most of the studies analyze their cohorts with all types of solid organ transplants and the immunosuppression that involve each procedure. We reinforce the importance of focusing on each population of organ transplant, each immunosuppression therapy and each malignancy, separately, providing the statistical analysis in a more precise and less generalized way.

Immunosuppression therapy

Focusing on the immunosuppressive medications in heart transplant and skin cancer, Bhat 2018 et al show that a lower number of immunosuppression medications is associated with a decreased incidence of skin cancer and no significant changes were found for Kaposi's Sarcoma [1]. Many studies suggest that mTOR may have a slightly protective effect in preventing skin cancer in solid organ transplant [1,3,51].

Fortina *et al* (2004) found that no association between cumulative doses of each single immunosuppressive drug used in the maintenance or acute rejection immunosuppression, and the risk of development of BCC`s and SCC`s, in heart transplant patients[21]. They also suggest that SCC`s, but not BCC`s, are related to global immunosuppression levels after 3 years rather than to specific immunosuppressive drugs. Another point in this study is that SCC was increased substantially by high occupational sunlight exposure, but not BCC[21]. On the other hand, Fortina 2000 et al in another study found that the type of immunosuppressive regimen did not affect the risk of skin cancer in heart transplant patients[17].

The results of Molina 2010 et al, suggest that SCC in heart transplant depends on the type of immunosuppressive therapy that is prescribed, and not just the duration and the dose of the immunosuppression[27]. They found that MFF was a protective factor against SCC, azathioprine was a risk factor and tacrolimus and cyclosporine had no effect[27]. In this study, no immunosuppressive drugs were associated with BCC and high sunlight exposure was a risk factor for both tumors, BCC and SCC[27].

Brewer 2009 et al show an increased risk of BCC in patients using MMF compared to those using Azathioprine, while tacrolimus and sirolimus had no significant effects to decrease the risk of BCC and SCC, respectively[25]. Asleh 2019 et al shows that the substitution of calcineurin inhibitor by sirolimus had a positive impact on susceptible patients with non-melanoma skin cancer history in the post heart transplant period[41]. Fuchs 2014 et al, in a comparison study between cyclosporine and tacrolimus after heart transplant, did not see significant difference between the groups, including skin cancer analysis[33].

Geusau 2008 et al found that an increased number of NMSC correlates with the duration of the immunosuppressive therapy, and regimens containing Azathioprine seemed influential on the development of NMSC, however this effect was not statistically significant[24]. This group concluded that the induction therapy does not appear to be associated with higher incidences of NMSC[24].

During our review, to draw conclusions about the association between the immunosuppressive therapy and skin cancer was a challenge, because most of the studies included patients with solid organ transplant in general, and they don't evaluate organs, immunosuppression therapy and the malignancies separately.

Clearly, we see the importance and the necessity of an evaluation of the heart transplant patients, focusing only on the skin cancer outcome and the association of this outcome with the induction and maintenance immunosuppression therapy. Furthermore, we also need to better characterize the correlation of immunosuppressive therapy and the other risk factors for skin cancer, which is complex but necessary to evaluate individually each patient. We believe this gap in knowledge needs to be addressed to advance precision medicine in this specific population. Although skin cancer is the most common malignancy in transplant patients, and it influences directly on mortality and morbidity rates, we emphasize the necessity of an accurate evaluation of this outcome.

Pediatric Heart Transplantation

The first pediatric heart transplantation was performed in 1967, right after the first human heart transplantation [15,52]. In this systematic review, just one study analyzed the pediatric heart transplant population.

Sigfússon et al evaluated all the heart transplants in a small center in patients under the age of 18[15]. Most of the articles provide the mean age at the time of the transplantation and the standard deviation. Many articles do not provide the range of age, so we cannot determine which age is the youngest in the cohort. Therefore, the papers that cite the age range have a wide variance.

Strengths and limitations of study

Our study has some limitations. First, most of the studies are cohorts of patients that underwent a solid organ transplant. They analyzed all the cohorts and they didn't focus specifically on heart transplantation and its peculiarities. This can be a risk of bias because the heart transplant population has unique features. We selected the analysis that involved only heart transplant patients. In this way statistical analysis of the sample may have been hampered.

Difficulties in the analysis occurred, mainly due to the heterogeneity of the studies; we reinforce this point because it was the most notable challange during the analysis of the results. Future studies with rigorous methodology are necessary, ideally considering prospective and synchronous international multicenter studies, with the same methodology. Additionally, the retrospective nature of the studies in analysis carries the limitations of all such study design.

Additional coments

Fifty-five years have passed since the first human heart transplant was performed. During this period we are able to draw a general overview of these patients in regard to skin neoplasm development[52]. This systematic review shows that future research studies need to analyze exclusively heart transplant patients and specifically the outcome of skin cancer. It also reinforces the importance of taking care of this population in a multidisciplinary approach, where the dermatologist plays a key role.

Due to the complexity of the tailored immunosuppressive therapy and the environmental and individual risk factors, more studies are needed to understand this interaction, focusing especially on heart transplant patients and the immunosuppression therapy that they are exposed to. We emphasize the importance of understanding ethnicity, accurately evaluating sunlight exposure, viral status, family history, comorbidities, and sunscreen use in the studies, and judiciously analise the different types of skin cancer, mainly SCC, BCC, Melanoma and Kaposi`sarcoma. It is important to screen and identify which patients are at risk to develop skin cancer, and to act accordingly.

Moreover, considering the difficulties in this study, we highlight that it is necessary to conduct prospective, international multi-center and synchronous studies, with the same methodology and design. More homogenous methodology will be helpful to understand the complexity of this cohort of patients.

Conclusion

In conclusion, the risk of post-transplant NMSC and melanoma has increased universally, and heart transplant patients have a high frequency of skin cancer and

other skin conditions. Such measures and well comprehension may prevent many skin cancers in this population.

Healthcare professionals should be highly familiarized with each regional organ transplant program and its demographic characteristics to improve the outcome of skin cancer among transplant patients.

This study reinforces that the dermatologist play an important role in the short and long-term follow-up of heart transplant patients. This population require a careful and continuous evaluation from the dermatologist. This approach can change morbidity, mortality and the quality of life of many patients after the heart transplant. This study demonstrates that improving the communication between transplant's surgeons and dermatologists is a crucial and essential action in the care of heart transplant patients.

ACKNOWLEDGMENTS

We are very grateful for all the anonymous patients that allow the follow up in every single paper of this multinational analysis. We deeply appreciate the help and tireless review of Cristiano Schaffer Aguzzoli. Furthermore, we also appreciate the scientific rigor and patience of Guilherme Brodt.

REFERENCES:

1 Bhat M, Mara K, Dierkhising R, Watt KDS. Immunosuppression, Race, and Donor-Related Risk Factors Affect De novo Cancer Incidence Across Solid Organ Transplant Recipients. *Mayo Clin Proc* 2018; **93**: 1236–1246.

2 Michael J. Veness, David I. Quinn, Colin S. Ong, Anne M. Keogh, Peter S. Macdonald, Stephen G. Cooper, Graeme W. Morgan. Aggressive Cutaneous Malignancies following Cardiothoracic Transplantation. *American Cancer Society* 1999; **85**: Number 8.

3 Rivinius R, Helmschrott M, Ruhparwar A, Schmack B, Klein B, Erbel C *et al.* Analysis of malignancies in patients after heart transplantation with subsequent immunosuppressive therapy. *Drug Des Devel Ther* 2015; **9**: 93–102.

4 Van Keer J, Droogné W, Van Cleemput J, Vörös G, Rega F, Meyns B *et al.* Cancer After Heart Transplantation: A 25-year Single-center Perspective. *Transplant Proc* 2016; **48**: 2172–2177.

5 Dufrechou L, Borges AL. Dermatologic Manifestations Among Transplant Recipients. In: Bonamigo RR, Dornelles SIT (eds). *Dermatology in Public Health Environments: A Comprehensive Textbook*. Springer International Publishing: Cham, 2018, pp 987–1009.

6 Shiba N, Chan MCY, Kwok BWK, Valantine HA, Robbins RC, Hunt SA. Analysis of survivors more than 10 years after heart transplantation in the cyclosporine era: Stanford experience. *J Heart Lung Transplant* 2004; **23**: 155–164.

7 Karia PS, Azzi JR, Heher EC, Hills VM, Schmults CD. Association of Sirolimus Use With Risk for Skin Cancer in a Mixed-Organ Cohort of Solid-Organ Transplant Recipients With a History of Cancer. *JAMA Dermatol* 2016; **152**: 533–540.

8 Coghill AE, Johnson LG, Berg D, Resler AJ, Leca N, Madeleine MM. Immunosuppressive Medications and Squamous Cell Skin Carcinoma: Nested Case-Control Study Within the Skin Cancer after Organ Transplant (SCOT) Cohort. *Am J Transplant* 2016; **16**: 565–573.

9 Fattouh K, Ducroux E, Decullier E, Kanitakis J, Morelon E, Boissonnat P *et al.* Increasing incidence of melanoma after solid organ transplantation: a retrospective epidemiological study. *Transpl Int* 2017; **30**: 1172–1180.

10 Hamour IM, Khaghani A, Kanagala PK, Mitchell AG, Banner NR. Current outcome of heart transplantation: a 10-year single centre perspective and review. *QJM* 2011; **104**: 335–343.

11 Organ transplant trends. UNOS. 2019.https://unos.org/data/transplant-trends/ (accessed 18 May2022).

12 Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M *et al.* Newcastle-Ottawa quality assessment scale cohort studies. *University of Ottawa* 2014.https://www.ncbi.nlm.nih.gov/books/NBK99082/bin/appb-fm4.pdf.

13 Petter Jensen, Ole P. F. Clausen, Odd Geiran, Svein Simonsen, Anne Relbo, Svein Hansen, Tor Langeland. Cutaneous Complications in Heart Transplant Recipients in Norway 1983-1993. *Acta Derm Venereol* 1995; : 400–403.

14 España A, Redondo P, Fernández AL, Zabala M, Herreros J, Llorens R *et al.* Skin cancer in heart transplant recipients. *J Am Acad Dermatol* 1995; **32**: 458–465.

15 Sigfússon G, Fricker FJ, Bernstein D, Addonizio LJ, Baum D, Hsu DT *et al.* Long-term survivors of pediatric heart transplantation: a multicenter report of sixty-eight children who have survived longer than five years. *J Pediatr* 1997; **130**: 862–871.

16 Ong CS, Keogh AM, Kossard S, Macdonald PS, Spratt PM. Skin cancer in Australian heart transplant recipients. *J Am Acad Dermatol* 1999; **40**: 27–34.

17 Fortina AB, Caforio AL, Piaserico S, Alaibac M, Tona F, Feltrin G *et al.* Skin cancer in heart transplant recipients: frequency and risk factor analysis. *J Heart Lung Transplant* 2000; **19**: 249–255.

18 Caforio AL, Fortina AB, Piaserico S, Alaibac M, Tona F, Feltrin G *et al.* Skin cancer in heart transplant recipients: risk factor analysis and relevance of immunosuppressive therapy. *Circulation* 2000; **102**: III222–7.

19 Catena F, Nardo B, Liviano d'Arcangelo G, Stefoni S, Arpesella G, Faenza A *et al.* De novo malignancies after organ transplantation. *Transplant Proc* 2001; **33**: 1858–1859.

20 Caforio AL, Belloni Fortina A, Gambino A, Piaserico S, Feltrin G, Tona F *et al.* High rejection score in the first year and risk of skin cancer in heart transplantation. *Transplant Proc* 2001; **33**: 1608–1609.

21 Fortina AB, Piaserico S, Caforio ALP, Abeni D, Alaibac M, Angelini A *et al.* Immunosuppressive level and other risk factors for basal cell carcinoma and squamous cell carcinoma in heart transplant recipients. *Arch Dermatol* 2004; **140**: 1079–1085.

22 El-Hamamsy I, Stevens L-M, Carrier M, Pelletier G, White M, Tremblay F *et al.* Incidence and prognosis of cancer following heart transplantation using RATG induction therapy. *Transpl Int* 2005; **18**: 1280–1285.

23 de Mello Junior WT, Branco JNR, Catani R, de Figueiredo Aguiar L, Paez RP, Buffolo E. Cardiac Transplantation and Neoplasms: Experiences at Escola Paulista de Medicina of. .

24 Geusau A, Dunkler D, Messeritsch E, Sandor N, Heidler G, Rödler S *et al.* Non-melanoma skin cancer and its risk factors in an Austrian population of heart transplant recipients receiving induction therapy. *Int J Dermatol* 2008; **47**: 918–925.

25 Brewer JD, Colegio OR, Phillips PK, Roenigk RK, Jacobs MA, Van de Beek D *et al.* Incidence of and risk factors for skin cancer after heart transplant. *Arch Dermatol* 2009; **145**: 1391–1396.

26 Chen P-L, Chang H-H, Chen I-M, Lai S-T, Shih C-C, Weng Z-C *et al.* Malignancy after heart transplantation. *J Chin Med Assoc* 2009; **72**: 588–593.

27 Molina BD, Leiro MGC, Pulpón LA, Mirabet S, Yañez JF, Bonet LA *et al.* Incidence and risk factors for nonmelanoma skin cancer after heart transplantation. *Transplant Proc* 2010; **42**: 3001–3005.

28 Hsu R-B, Chang C-I, Tsai M-K, Lee P-H, Chou N-K, Chi N-H *et al.* Low incidence of malignancy in heart-transplant recipients in Taiwan: an update and comparison with kidney-transplant recipients. *Eur J Cardiothorac Surg* 2010; **37**: 1117–1121.

29 Doesch AO, Müller S, Konstandin M, Celik S, Kristen A, Frankenstein L *et al.* Malignancies after heart transplantation: incidence, risk factors, and effects of calcineurin inhibitor withdrawal. *Transplant Proc* 2010; **42**: 3694–3699.

30 Jensen AO, Svaerke C, Farkas D, Pedersen L, Kragballe K, Sørensen HT. Skin cancer risk among solid organ recipients: a nationwide cohort study in Denmark. *Acta Derm Venereol* 2010; **90**: 474–479.

31 Alam M, Brown RN, Silber DH, Mullen GM, Feldman DS, Oren RM *et al.* Increased incidence and mortality associated with skin cancers after cardiac transplant. *Am J Transplant* 2011; **11**: 1488–1497.

32 Chivukula S, Shullo MA, Kormos RL, Bermudez CA, McNamara DM, Teuteberg JJ. Cancer-free survival following alemtuzumab induction in heart transplantation. *Transplant Proc* 2014; **46**: 1481–1488.

33 Fuchs U, Klein S, Zittermann A, Ensminger SM, Schulz U, Gummert JF. Incidence of malignant neoplasia after heart transplantation--a comparison between cyclosporine a and tacrolimus. *Ann Transplant* 2014; **19**: 300–304.

34 Park G-H, Chang SE, Won CH, Lee MW, Choi JH, Moon KC *et al.* Incidence of primary skin cancer after organ transplantation: An 18-year single-center experience in Korea. *J Am Acad Dermatol* 2014; **70**: 465–472.

35 Secnikova Z, Gopfertova D, Hoskova L, Hercogova J, Dzambova M, Jirakova A *et al.* Significantly higher incidence of skin cancer than other malignancies in patients after heart transplantation. A retrospective cohort study in the Czech Republic. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2015; **159**: 648–651.

36 Delgado JF, Alonso-Pulpón L, Mirabet S, Almenar L, Villa FP, González-Vílchez F *et al.* Cancer Incidence in Heart Transplant Recipients With Previous Neoplasia History. *Am J Transplant* 2016; **16**: 1569–1578.

37 McPherson I, Kirk A. The incidence of non-melanoma skin cancer and post-transplant lympho-proliferative disorders in the Scottish cardiac transplant population and the provision of specialist dermatological follow-up. *Scott Med J* 2018; **63**: 3–10.

38 Jäämaa-Holmberg S, Salmela B, Lemström K, Pukkala E, Lommi J. Cancer incidence and mortality after heart transplantation – A population-based national cohort study. *Acta Oncol* 2019; **58**: 859–863.

39 Kimura Y, Yanase M, Mochizuki H, Iwasaki K, Toda K, Matsuda S *et al.* De novo malignancy in heart transplant recipients: A single center experience in Japan. *J Cardiol* 2019; **73**: 255–261.

40 Park CK, Fung K, Austin PC, Joseph Kim S, Singer LG, Baxter NN *et al.* Incidence and Risk Factors of Keratinocyte Carcinoma After First Solid Organ Transplant in Ontario, Canada. *JAMA Dermatol* 2019; **155**: 1041–1048.

41 Asleh R, Clavell AL, Pereira NL, Smith B, Briasoulis A, Alnsasra H *et al.* Incidence of Malignancies in Patients Treated With Sirolimus Following Heart Transplantation. *J Am Coll Cardiol* 2019; **73**: 2676–2688.

42 O'Neill JP, Sexton DJ, O'Leary E, O'Kelly P, Murray S, Deady S *et al.* Post-transplant malignancy in solid organ transplant recipients in Ireland, The Irish Transplant Cancer Group. *Clin Transplant* 2019; **33**: e13669.

43 Infusino SD, Loi C, Ravaioli GM, Piraccini BM, Bardazzi F, Patrizi A. Cutaneous complications of immunosuppression in 812 transplant recipients: a 40-year single center experience. *G Ital Dermatol Venereol* 2020; **155**: 662–668.

44 Yeh C-C, Khan A, Muo C-H, Yang H-R, Li P-C, Chang C-H *et al.* De Novo Malignancy After Heart, Kidney, and Liver Transplant: A Nationwide Study in Taiwan. *Exp Clin Transplant* 2020; **18**: 224–233.

45 Kellerman L, Neugut A, Burke B, Mancini D. Comparison of the incidence of de novo solid malignancies after heart transplantation to that in the general population. *Am J Cardiol* 2009; **103**: 562–566.

46 Tufaro AP, Azoury SC, Crompton JG, Straughan DM, Reddy S, Prasad NB *et al.* Rising incidence and aggressive nature of cutaneous malignancies after transplantation: An

update on epidemiology, risk factors, management and surveillance. *Surg Oncol* 2015; **24**: 345–352.

47 Green AC, Olsen CM. Increased risk of melanoma in organ transplant recipients: systematic review and meta-analysis of cohort studies. *Acta Derm Venereol* 2015; **95**: 923–927.

48 Lindelöf B, Sigurgeirsson B, Gäbel H, Stern RS. Incidence of skin cancer in 5356 patients following organ transplantation. *Br J Dermatol* 2000; **143**: 513–519.

49 Zwald FO, Christenson LJ, Billingsley EM, Zeitouni NC, Ratner D, Bordeaux J *et al.* Melanoma in solid organ transplant recipients. *Am J Transplant* 2010; **10**: 1297–1304.

50 Arnold M, Holterhues C, Hollestein LM, Coebergh JWW, Nijsten T, Pukkala E *et al.* Trends in incidence and predictions of cutaneous melanoma across Europe up to 2015. *J Eur Acad Dermatol Venereol* 2014; **28**: 1170–1178.

51 Knoll GA, Kokolo MB, Mallick R, Beck A, Buenaventura CD, Ducharme R *et al.* Effect of sirolimus on malignancy and survival after kidney transplantation: systematic review and meta-analysis of individual patient data. *BMJ* 2014; **349**: g6679.

52 Sutaria N, Sylvia L, DeNofrio D. Immunosuppression and Heart Transplantation. *Handb Exp Pharmacol* 2021. doi:10.1007/164_2021_552.

6. CONSIDERAÇÕES FINAIS

O presente estudo foi realizado foi realizado como alternativa ao projeto inicial, que consistia em um estudo longitudinal e transversal a ser realizado no Hospital de Clínicas de Porto Alegre, por um período de dois anos, com vistas a avaliar dermatologicamente os pacientes que já haviam sido foram submetidos a transplante cardíaco e mantém acompanhamento no serviço, a partir disso identificar a prevalência das dermatoses nos pacientes já transplantados. Além disso seriam avaliados também os pacientes com plano de serem submetidos a transplante cardíaco antes e após o procedimento e acompanhando-os ao longo do primeiro ano, a partir dessas avaliações, realizaremos a identificação da incidência e da prevalência das dermatoses em pacientes transplantados cardíacos.

Entretanto, devido a pandemia e a intensa imunossupressão a que esses pacientes são submetidos, o projeto não poderia ser realizado em tempo hábil para finalização do mestrado. Ao escrever o projeto inicial, percebemos uma grande heterogeneidade dos estudos e artigos publicados nessa área, assim como ausência

de um olhar acurado sobre essa população específica. Dessa forma, optou-se por realizar uma revisão sistemática sobre o tema, para que dessa forma conseguissemos analisar o que há na literatura sobre o tema.

Com a publicação desse trabalho, pretendemos ressaltar a complexidade da terapia imunossupressora e da análise dos fatores de risco ambientais e individuais, focando estudos em pacientes transplantados cardíacos e na terapia imunossupressora a que estes estão expostos, visto que há diferenças consideráveis nessa subpopulação.

Também pretendemos enfatizar a importância do cuidado multidisciplinar dessa população, reforçando que os Dermatologistas desempenham um importante papel fundamental no seguimento de curto e longo prazo dos pacientes transplantados cardíacos. Essa população merece uma avaliação acurada e cuidados contínuos do Dermatologista. Essa prática clínica pode alterar a morbimortalidade e a qualidade de vida após o transplante cardíaco. Assim, ressaltamos que melhorar a comunicação entre os cardiologistas especialistas em transplantes e os dermatologistas é uma ação crucial e essencial no atendimento ao paciente transplantado cardíaco.

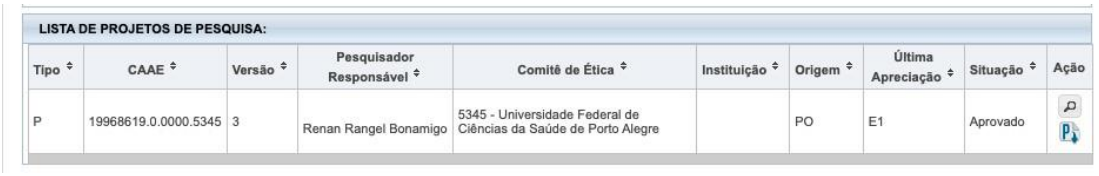
7.ANEXOS

Anexo 1. Aprovação do projeto original

O projeto foi avaliado pelo Comitê de Ética e Pesquisa da UFCSPA e aprovado.

Devido a pandemia COVID19, o projeto inicial foi impossibilitado de ser realizado em período hábil para a conclusão do Mestrado. Dessa forma, foi optado por realizar uma revisão sistemática sobre a associação de neoplasias cutâneas em pacientes transplantados cardíacos, mudança realizada em setembro de 2021. Após a aprovação da Comissão

Coordenadora do PPG em Patologia da UFCSPA



LISTA DE PROJETOS DE PESQUISA:

Tipo	CAAE	Versão	Pesquisador Responsável	Comitê de Ética	Instituição	Origem	Última Apreciação	Situação	Ação
P	19968619.0.0000.5345	3	Renan Rangel Bonamigo	5345 - Universidade Federal de Ciências da Saúde de Porto Alegre		PO	E1	Aprovado	

Anexo 2. Alteração do projeto para a Revisão Sistemática

REPÚBLICA FEDERATIVA DO BRASIL
MINISTÉRIO DA EDUCAÇÃO

UFCSPA
UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE
Rua Sarmento Leite, 245 - Fones: 0 xx 51 3303 9000 - Fax: 0 xx 51 3303.8810
CEP 90050-170 - Porto Alegre - RS - www.ufcspa.edu.br
PROGRAMA DE PÓS-GRADUAÇÃO EM PATOLOGIA

Porto Alegre, 09 de setembro de 2021

Para

Comissão Coordenadora do PPG em Patologia

UFCSPA

Venho por meio deste comunicar a alteração do projeto de Mestrado da aluna Nathalia Hoffmann Guarda, Matrícula 201S30118014, originalmente denominado "Doenças Dermatológicas em Pacientes Transplantados Cardíacos em Hospital Terciário".

A alteração foi necessária devido ao contexto de pandemia pelo Coronavírus, pois o projeto inicial foi impossibilitado de ser realizado em período hábil para a conclusão do estudo

Para substituir o projeto acima será realizado um estudo de Revisão Sistemática sobre a associação de neoplasias cutâneas em pacientes transplantados cardíacos.

Dr. Renan Bonamigo
Chefe Dermatologia
Santa Casa de Porto Alegre
CREMERS 18722

Prof. Renan R Bonamigo (Orientador) _____

Dra. Nathália H Guarda (Aluna) Nathalia Hoffmann Guarda

Rua Sarmento Leite, 245, centro histórico, Porto Alegre (RS), 90050-170 – Tel. (51) 3303 8700 – www.ufcspa.edu.br